FINAL PROGRAMME & ABSTRACTS

18TH INTERNATIONAL CONFERENCE ON CACHEXIA, SARCOPENIA & WASTING DISORDERS

ROME

11-13 DECEMBER 2025

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SCWD
SOCIETY ON SARCOPENIA, CACHEXIA & WASTING DISORDERS

Journal of Cachexia, Sarcopenia and Muscle

Open Access

Presenting research and clinical topics on the typical aging progression and disease related changes.

EDITED BY

Stefan D. Anker
& Stephan von Haehling

Impact Factor 9.1

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Faculty 222

ORGANIZATION

Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD)
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Richard Skipworth, UK
Florian Strasser, Switzerland
Stephan von Haehling, Germany
Hidetaka Wakabayashi, Japan

CONFERENCE LOCATION

Hotel A.Roma Lifestyle
Via Giorgio Zoega 59
00164 Rome
Italy

OPENING HOURS OF THE ON-SITE REGISTRATION DESK

Thursday, 11 December 2025
8:00-18:30 hrs

Friday, 12 December 2025
8:00-18:30 hrs

Saturday, 13 December 2025
8:00-16:00 hrs

POSTER EXHIBITION

Thursday, 11 December 2025
09:30-20:00 hrs

Friday, 12 December 2025
8:00-19:00 hrs

Saturday, 13 December 2025
8:00-14:00

POSTER SESSIONS

Thursday, 11 December 2025
15:50-16:40 hrs

Friday, 12 December 2025
10:20-11:10 hrs
15:05-15:55 hrs

Saturday, 13 December 2025
10:50-11:40 hrs

BREAKS

Thursday, 11 December 2025
10:45-11:00 hrs
14:15-14:30 hrs
15:45-16:45 hrs

Friday, 12 December 2025
10:15-11:15 hrs
15:00-16:00 hrs
17:15-17:30 hrs

Saturday, 13 December 2025
09:15-09:30 hrs
10:45-11:45 hrs
13:45-14:00 hrs

LUNCH BREAKS

Thursday, 11 December 2025
12:15-13:15 hrs

Friday, 12 December 2025
12:30-13:45 hrs

Saturday, 13 December 2025
13:00-14:00 hrs

A
09:30 – 10:45 **HALL A**

BASIC SCIENCE
New and established mouse models for the study of cancer cachexia

(each talk 15 minutes)

Chairs: Elke Dworatzek (Germany)
Jochen Springer (Germany)

1. 09:30 – 09:45
Atrophy-independent mechanisms of muscle weakness during ovarian cancer
Christopher Perry (Canada)
2. 09:45 – 10:00
Bedside to bench: modeling cachexia in different cancer patient trajectories
Fabio Penna (Italy)
3. 10:00 – 10:15
Mouse models of pancreatic cancer cachexia: investigating sex-dependent tissue loss
Erin Talbert (USA)
4. 10:15 – 10:30
Ovarian cancer cachexia: new insights from clinical studies and animal models
Andrea Bonetto (USA)

10:30 – 10:45
Discussion

10:45 – 11:00

BREAK

B
11:00 – 12:15 **HALL B**

BASIC SCIENCE

The role of the liver in cancer cachexia

(each talk 15 minutes)

Chairs: Mauricio Berriel Diaz (Germany)
Andrew Judge (USA)

1. 11:00 – 11:15
Leukemia inhibitory factor (LIF) suppresses hepatic de novo lipogenesis and induces cachexia
Wenwei Hu (USA)
2. 11:15 – 11:30
Vagal blockade of the brain-liver axis deters cancer-associated cachexia
Xiling Shen (USA)
3. 11:30 – 11:45
Genomic liver profiling identifies hepatokines promoting tissue wasting in cancer cachexia
Doris Kaltenecker (Germany)
4. 11:45 – 12:00
Regulation of hepatic amino acid metabolism
Anne-Catherine Maurin (France)

12:00 – 12:15
Discussion

C
11:00 – 12:15 **HALL A**

GENERAL CACHEXIA AND SARCOPENIA

Muscle wasting and osteosarcopenia: the role of the immune system

(each talk 15 minutes)

Chairs: Paul Titchenell (USA)
Henning Wackerhage (Germany)

1. 11:00 – 11:15
RAGE expressed by myofibers sustains hallmarks of cancer cachexia
Guglielmo Sorci (Italy)
2. 11:15 – 11:30
Shaping the immune landscape by IL-4: relevance to cancer-induced muscle wasting
Paola Costelli (Italy)
3. 11:30 – 11:45
Fat infiltration in muscle and bone in osteosarcopenia
Kamal Awad (USA)
4. 11:45 – 12:00
The geroscience framework for osteosarcopenia: mechanistic insights and clinical implications
Gustavo Duque (Canada)

12:00 – 12:15
Discussion

12:15 – 13:15

LUNCH BREAK

D
13:15 – 14:15 **HALL A**

OPENING SESSION

(Welcome: 5 minutes, talk 2 and 3: 20 minutes + 5 minutes discussion each, talk 4: 5 minutes)

Chairs: Stefan Anker (Germany)
Maurizio Muscaritoli (Italy)

1. 13:15 – 13:20
Welcome
Stefan Anker (Germany)
2. 13:20 – 13:45
"Prometheus" basic science key note lecture:
GDF15 from bench to bedside
Samuel Breit (Australia)
3. 13:45 – 14:10
"Hippocrates" clinical science key note lecture:
"Sooner or later, this has gotta work," Garibaldi (Michael), as paraphrased
Aminah Jatoi (USA)
4. 14:10 – 14:15
JCSM lecture
Stephan von Haehling (Germany)

14:15 – 14:30

BREAK

E
14:30 – 15:45 **HALL B**

BASIC SCIENCE

Titin and cachexia – organs specific regulation and genetics

(each talk 15 minutes)

Chairs: Volker Adams (Germany)
Doris Kaltenecker (Germany)

1. 14:30 – 14:45
The myocardium
Katja Gehmlich (UK)
2. 14:45 – 15:00
The skeletal muscle
Beatrice Vahle (Germany)
3. 15:00 – 15:15
The diaphragm
Marloes van den Berg (USA)
4. 15:15 – 15:30
Titin (and similar) as biomarker
Simone Agostini (Italy)

15:30 – 15:45
Discussion

F
14:30 – 15:45 **HALL A**

GENERAL SARCOPENIA

Multidimensional biomarkers of aging: molecular, functional, and social hallmarks of frailty

(each talk 15 minutes)

Chairs: Hidenori Arai (Japan)
Marcello Maggio (Italy)
Emanuele Marzetti (Italy)

1. 14:30 – 14:45
Physical performance metrics as biomarkers of frailty phenotypes
Stephan von Haehling (Germany)
2. 14:45 – 15:00
Sociobiological pathways linking psychosocial stressors to frailty: social determinants as emerging biomarkers
Jürgen Bauer (Germany)
3. 15:00 – 15:15
Blood-based signatures of frailty
Riccardo Calvani (Italy)
4. 15:15 – 15:30
GDF-15 as biomarker: state of the art
Kai Wollert (Germany)

15:30 – 15:45
Discussion

15:45 – 16:45

COFFEE BREAK

15:50 – 16:40 **POSTER AREA**

POSTER VIEWING 1

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 1.1
Muscle Wasting & Sarcopenia (posters 4-25 to 4-36)
Chairs: Monty Montano, Stephan von Haehling

Poster session 1.2
Cachexia – animal models (posters 2-01 to 2-12)
Chairs: Xiling Shen, Jochen Springer

Poster session 1.3
Cancer Cachexia (posters 3-13 to 3-21)
Chairs: Mauricio Berriel Diaz, Paola Costelli

Poster session 1.4
Muscle Wasting & Sarcopenia (posters 4-37 to 4-48)
Chairs: Guilherme Fonseca, Joerg Schefold

Poster session 1.5
Nutrition & Appetite (posters 5-01 to 5-10)
Chairs: Alessandro Laviano, Paula Ravasco

15:50 – 16:40 **HALL A**

RAPID FIRE ABSTRACTS SESSION 1

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Elke Dworatzek (Germany)
Katja Gehmlich (UK)

15:50 – 15:55
Accelerometer-determined physical activity and sarcopenic obesity risk in older European men and women (3-29)
Andreas Nilsson (Sweden)

15:55 – 16:00
Localized chemotherapy drives tumor regression and halts cancer-associated cachexia (3-05)
Franciska Telebar, Vito Telebar-Žbulj (Austria)

16:00 – 16:05
Impaired cAMP/PKA/CREB1 signaling drives mitochondrial dysfunction in skeletal muscle in cancer cachexia (3-11)
Andrea Graziani (Italy)

16:05 – 16:10
Effects of multicomponent interventions on physical function for people with cancer cachexia (3-12)
Megan Bowers (UK)

16:10 – 16:15
An assessment of the healthcare resource use and cost impacts of cachexia among cancer patients in the United States: a Medicare claims study (3-28)
Joshua Roth (USA)

16:15 – 16:20
Local TGF-β signaling causes impaired contractability and low-response to exercise in human skeletal muscle (4-18)
Simon Dreher (Germany)

16:20 – 16:25
Myofiber aryl hydrocarbon receptor is essential for maintaining skeletal muscle integrity (4-19)
Charlotte Claeyssen (Norway)

16:25 – 16:30
Unravelling metabolic dysregulation in heart failure with frailty: insights from plasma metabolomics (4-87)
Konstantinos Prokopidis (UK)

16:30 – 16:35
Ultrasound assessment of quadriceps muscle architecture as a diagnostic and prognostic tool in hospitalized older adults with sarcopenia (4-49)
Zahira Zohari (Malaysia)

16:35 – 16:40
Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-07258669, a small-molecule MC4R antagonist: Results from first-in-human Phase 1 studies (8-08)
John Groarke (USA)

G
16:45 – 18:00 **HALL B**

NUTRITION & METABOLISM

Targeting metabolic storm: from nutrients to clinical practice

(each talk 15 minutes)

Chairs: Maurizio Muscaritoli (Italy)
Paula Ravasco (Portugal)
Ashish Singh (India)

1. 16:45 – 17:00
Targeting metabolic storm: from nutrients to clinical practice
Carolina Trabulo (Portugal)
2. 17:00 – 17:15
Nutrition as a co-therapy in pharmacological cancer cachexia trials: a must?
Barry Laird (Norway)
3. 17:15 – 17:30
Sustaining the muscle, sustaining the environment: is plant protein the key?
Gianni Biolo (Italy)
4. 17:30 – 17:45
New insights into DHA supplementation in breast cancer
Alessio Molfino (Italy)

17:45 – 18:00
Discussion

H
16:45 – 18:00 **HALL A**

GENERAL SARCOPENIA

Update on clinical muscle research 2025

(each talk 15 minutes)

Chairs: Francesco Landi (Italy)
Hidetaka Wakabayashi (Japan)

1. 16:45 – 17:00
What is the role of body composition in diagnosing obesity and sarcopenic obesity?
Manfred James Müller (Germany)
2. 17:00 – 17:15
Is there a "gold standard" method for measuring skeletal muscle mass
Steve Heymsfield (USA)
3. 17:15 – 17:30
What have we learned from measuring D3Cr muscle mass in older men and women?
William Evans (USA)
4. 17:30 – 17:45
Why do we need muscle / fat biopsies in 2025?
Mitja Lainscak (Slovenia)

17:45 – 18:00
Discussion

18:15 – 19:00 **HALL A**

Muscle wasting and cachexia: new multidisciplinary approach

(each talk 8 minutes)

Chairs Stefan Anker (Germany)
Andrew Coats (Australia)
Ashok K. Vaid (India)

An innovative approach to cancer cachexia: role of S-pindolol
Andrew Coats (Australia)

GLP1 therapy in obesity and loss of skeletal muscle: a new therapeutic target?
Markus Anker (Germany)

Amyotrophic lateral sclerosis (ALS) and muscle wasting: what can s-oxprenolol do about it?
Jochen Springer (Germany)

Panel discussion

(Symposium supported by Actimed Therapeutics)

19:15 – 20:00 **POSTER AREA**

WELCOME RECEPTION

08:00 – 08:50 **FOYER**

KEN FEARON CAREER CAFÉ - MEET THE MENTOR

(attendance upon application and confirmation)

I
09:00 – 10:15 **HALL B**

CANCER CACHEXIA

Cancer cachexia: new insights

(each talk 15 minutes)

Chairs: Paola Costelli (Italy)
Maria Rohm (Germany)

1. 09:00 – 09:15
Sex differences in the skeletal muscle-aging trajectory of energy metabolism
Jaap Keijer (The Netherlands)
2. 09:15 – 09:30
The role of the exosome in cancer cachexia
Marilia Seelaender (Brazil)
3. 09:30 – 09:45
Chronological vs biological age: implications for cachexia
Alessandro Laviano (Italy)
4. 09:45 – 10:00
Mitochondrial dysfunction in colon cancer: already occurring in the primary-stage to further worsen in liver metastasis
Klaske van Norren (The Netherlands)

10:00 – 10:15
Discussion

J
09:00 – 10:15 **HALL A**

THERAPEUTICS / GENERAL CACHEXIA

A short history of trial endpoints that could be approvable for cancer cachexia indications

(each talk 15 minutes)

Chairs: Stefan Anker (Germany)
John Borg (Malta)
Jeffrey Crawford (USA)
Dominik Modest (Germany)
Prabrajya Narayan Mohapatra (India)

1. 09:00 – 09:15
EORTC QLQ 30 and its physical functioning domain and EORTC-QLQ-C15-PAL
Markus Anker (Germany)
2. 09:15 – 09:30
EORTC QLQ-CAX24
Richard Skipworth (UK)
3. 09:30 – 09:45
Stair Climb Power Test and 6 Minute Walk Test
Andrew Coats (Australia)
4. 09:45 – 10:00
Morbidity & mortality outcomes
Tim Friede (Germany)

10:00 – 10:15
Discussion

10:15 – 11:15

COFFEE BREAK

10:20 – 11:10 **POSTER AREA**

POSTER VIEWING 2

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 2.1
Therapeutic Development (pre-clinical) (posters 7-01 to 7-12)
Chairs: James Carson, Mitja Lainscak

Poster session 2.2
Muscle Wasting & Sarcopenia (posters 4-80 to 4-90)
Chairs: Gustavo Duque, Andreas Fischer

Poster session 2.3
Physical Activity & Training (posters 6-01 to 6-13)
Chairs: Volker Adams, Andrew Judge

Poster session 2.4
Muscle Wasting & Sarcopenia (posters 4-01 to 4-12)
Chairs: Philip Atherton, Henning Langer

10:20 – 11:10 **HALL A**

RAPID FIRE ABSTRACTS SESSION 2

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Wenwei Hu (USA)
Jaap Keijer (The Netherlands)

10:20 – 10:25
Role of growth hormone resistance in IGF-I deficient sarcopenic patients (4-44)
Michael Drey (Germany)

10:25 – 10:30
Low relative muscle power in patients on haemodialysis: poor health outcomes of the SARC-HD (4-56)
Maryanne Zilli Canedo Silva (Brazil)

10:30 – 10:35
Trajectories of skeletal muscle index in patients with endometrial cancer after surgery: A group-based trajectory modeling analysis (4-66)
Kiriko Abe (Japan)

10:35 – 10:40
DNA methylation as a driver of long-term muscle transcriptome alterations in critical illness survivors (4-71)
Ceren Uzun (Belgium)

10:40 – 10:45
The burden of malnutrition in patients with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF): a systematic literature review (5-06)
Reshma Merchant (Singapore)

10:45 – 10:50
The anti-inflammatory effects and safety of omega-3 fatty acids regarding dose, active ingredients, ratio and source in patients receiving haemodialysis: a systematic review and meta-analysis (5-01)
Joanne Reid (UK)

10:50 – 10:55
Risk of sarcopenia in people with long-term conditions and multimorbidity: a prospective UK Biobank study (4-36)
Marion Guerrero Wyss (UK)

10:55 – 11:00
Single-cell transcriptomics reveals cellular drivers of human skeletal muscle regeneration: implications for sarcopenia (4-27)
Joshua Price (UK)

11:00 – 11:05
The impact of EWGSOP2-defined sarcopenia on treatment tolerance and survival in patients with lung cancer – preliminary data from a prospective cohort study (4-63)
Gunn Ammitzbøll (Denmark)

11:05 – 11:10
Mitochondrial protein modulation as a therapeutic approach to counteract muscle wasting in cancer cachexia, steroid use, and disuse conditions (4-70)
Ibotombi Singh Sinam (Republic of Korea)

K
11:15 – 12:30 **HALL B**

BASIC SCIENCE

Novel insights into muscle atrophy and hypertrophy mechanisms

(each talk 15 minutes)

Chairs: Andrea Bonetto (USA)
Denis Guttridge (USA)

1. 11:15 – 11:30
Do hypertrophying muscles reprogram their metabolism like cancer cells?
Henning Wackerhage (Germany)
2. 11:30 – 11:45
Tumor-derived ADAMTSL4 drives muscle atrophy and fibrosis in cancer cachexia
Mauricio Berriel Diaz (Germany)
3. 11:45 – 12:00
Integration of single nucleus multi-omics with spatial transcriptomics identifies the molecular signature of muscle wasting in cancer cachexia
Marco Sandri (Italy)
4. 12:00 – 12:15
The role of skeletal muscle fibrosis in cancer cachexia
Andrew Judge (USA)
12:15 – 12:30
Discussion

L
11:15 – 12:30 **HALL A**

GENERAL CACHEXIA

Recent advances in cachexia. Research in chronic illness – update 2025

(each talk 12 minutes)

Chairs: Lars Larsson (Sweden)
Robert Mak (USA)

1. 11:15 – 11:27
COPD cachexia
Annemie Schols (The Netherlands)
2. 11:27 – 11:39
CKD cachexia
Angela Wang (Singapore)
3. 11:39 – 11:51
Heart failure with cachexia
Wolfram Doehner (Germany)
4. 11:51 – 12:03
Cancer cachexia
Egidio Del Fabbro (USA)
5. 12:03 – 12:15
Cachexia in neurological diseases
Fabrizio Stocchi (Italy)
12:15 – 12:30
Discussion

12:30 – 13:45

LUNCH BREAK

12:45 – 13:30 **HALL A**

Defining meaningful endpoints in cancer cachexia: a patient-to-regulatory perspective

Moderator:
Richard Dunne, University of Rochester, USA

Panel Discussants:
Carole Motycka, Fight CRC, USA
Abigail Newell, Cancer Support Community, USA
Susan Martin, Research Triangle Institute, USA

(Symposium supported by Pfizer)

M
13:45 – 15:00 **HALL B**

BASIC SCIENCE

Signaling pathways in cachexia

(each talk 15 minutes)

Chairs: Pim Pijnappel (The Netherlands)
Jochen Springer (Germany)

1. 13:45 – 14:00
Emerging signaling mediators in cancer cachexia
Denis Guttridge (USA)
2. 14:00 – 14:15
The NLRP3 inflammasome signaling pathway in CKD cachexia
Robert Mak (USA)
3. 14:15 – 14:30
Markers and mediators of cachexia in pancreatic cancer
Teresa Zimmers (USA)
4. 14:30 – 14:45
Novel insights in molecular and cellular mechanisms of pulmonary cachexia
Ramon Langen (The Netherlands)

14:45 – 15:00
Discussion

N
13:45 – 15:00 **HALL A**

GENERAL SARCOPENIA

GLP1-based therapy and skeletal muscle wasting

(each talk 15 minutes)

Moderators:
Stefan Anker (Germany)
Ken Attie (USA)
John Borg (Malta)
Andrew Coats (Australia)
Fabio Dorigotti (Switzerland)
Mitchell Steiner (USA)

1. 13:45 – 14:00
Changes to muscle mass during weight cycling
Paul Titchenell (USA)
2. 14:00 – 14:15
Muscle function during pharmacological and physiological weight loss in humans
Philip Atherton (UK)
3. 14:15 – 14:30
The effect of GLP-1RA on muscle loss during immobilization
Henning Langer (Germany)
4. 14:30 – 14:45
Pharmacological improvements in weight regain
David Glass (USA)

14:45 – 15:00
Discussion

15:00 – 16:00

COFFEE BREAK

15:05 – 15:55 **POSTER AREA**

POSTER VIEWING 3

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 3.1
Muscle Wasting & Sarcopenia (posters 4-49 to 4-60)
Chairs: Guglielmo Sorci, Florian Strasser

Poster session 3.2
Therapeutic Development (clinical) (posters 8-01 to 8-10)
Chairs: Mitja Lainscak, Emanuele Marzetti

Poster session 3.3
Muscle Wasting & Sarcopenia (posters 4-70 to 4-79)
Chairs: Christopher Perry, Erin Talbert

Poster session 3.4
Cancer Cachexia (posters 3-22 to 3-31)
Chairs: Paige Arneson-Wissink, Egidio Del Fabbro

15:05 – 15:55 **HALL A**

RAPID FIRE ABSTRACTS SESSION 3

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Faisal Beg (Canada)
Marilia Seelaender (Brazil)

15:05 – 15:10
Using a proximity labeling approach to investigate lung-secreted proteins in an inflammatory weight loss model (2-06)
Jack Sanford (USA)

15:10 – 15:15
Adipose tissue macrophages and IL-4 receptor signaling under hypercatabolic conditions (2-09)
Michaela Lang (Austria)

15:15 – 15:20
MyoRep: a novel reporter system to detect early muscle atrophy in vitro and in vivo (3-10)
Rosanna Piccirillo (Italy)

15:20 – 15:25
Territorial differences in vitamin d status and gait performance among chilean older people: a multi-regional analysis across 30 degrees of latitude (5-07)
Barbara Angel (Chile)

15:25 – 15:30
Optimising amino acid availability in older adults: contrasting the effects of essential amino acid supplementation and a standard protein-content breakfast in a randomised crossover trial (5-08)
Theocharis Ispoglou (UK)

15:30 – 15:35
Association between cardiovascular health metrics and self-reported walking difficulty in community-dwelling middle-aged and older adults: results from the Longevity Check-up 8+ (6-06)
Stefano Cacciatore (Italy)

15:35 – 15:40
Associations of long-term physical activity levels with sarcopenia in older adults: the HUNT study (6-09)
Karina Tommerdal (Norway)

15:40 – 15:45
UCN2 treatment enhanced fat mass loss while increasing muscle mass and function in preclinical models (7-08)
Pablo Vidal Souza (USA)

15:45 – 15:50
Glycerol kinase mediated lipid cycling contributes to fat loss in cancer associated cachexia (1-01)
Pia Benedikt-Kühnast (Germany)

15:50 – 15:55
Body composition abnormalities and their association with physical function in patients with idiopathic pulmonary fibrosis (6-07)
Felipe Machado (Belgium)

O
16:00 – 17:15 **HALL B**

GENERAL SARCOPENIA

Neuromuscular disorders: from acute to chronic conditions

(each talk 15 minutes)

Chairs: Marcello Maggio (Italy)
Reshma Merchant (Singapore)
Teresa Zimmers (USA)

1. 16:00 – 16:15
Neuromuscular disorders in the ICU in 2025
Joerg Schefold (Switzerland)
2. 16:15 – 16:30
ICU-acquired weakness: are we creating survivors or victims?
Stefan Schaller (Austria)
3. 16:30 – 16:45
Muscle and brain dysfunction associated with long-term mechanical ventilation
Lars Larsson (Sweden)
4. 16:45 – 17:00
Sarcopenia of uncertain pathogenesis: the case of systemic sclerosis (SSc)
Maurizio Muscaritoli (Italy)

17:00 – 17:15
Discussion

P
16:00 – 17:15 **HALL A**

THERAPEUTICS

Weight loss drugs and cardiovascular health

(each talk 15 minutes)

Chairs: David Glass (USA)
Henning Langer (Germany)

1. 16:00 – 16:15
GLP1-based therapy and cardiac wasting
Stefan Anker (Germany)
2. 16:15 – 16:30
Impact of resistance exercise on muscle wasting in obesity therapy
Signe Torekov (Denmark)
3. 16:30 – 16:45
The Veru experience
Mitchell Steiner (USA)
4. 16:45 – 17:00
The Actimed experience
Andrew Coats (Australia)

17:00 – 17:15
Discussion

17:15 – 17:30

BREAK

Q
17:30 – 18:45 **HALL B**

BASIC SCIENCE

Organ crosstalk in metabolic disease and across the life course

(each talk 15 minutes)

Chairs: Jose Medina Echeverz (Germany)
Monty Montano (USA)

1. 17:30 – 17:45
Muscle-brain axis, exercise and nutrition
Emanuele Marzetti (Italy)
2. 17:45 – 18:00
Mechanism regulating energy expenditure and potential role of GDF15
Gregory Steinberg (Canada)
3. 18:00 – 18:15
Cancer cachexia: miRNAs, inflammation and beyond
Federica Tambaro (Italy)
4. 18:15 – 18:30
Immuno-metabolic crosstalk in cancer cachexia
Maria Rohm (Germany)

18:30 – 18:45
Discussion

R
17:30 – 18:45 **HALL A**

GENERAL SARCOPENIA

Hot issues in clinical research

(talks 1 and 2: 10 minutes each; talk 3: 15 minutes)

Chairs / Panel:
Stefan Anker (Germany)
Andrew Coats (Australia)
Fabio Dorigotti (Switzerland)
David Glass (USA)
Richard Skipworth (UK)

How to use AI as a tool in cachexia research?

1. 17:30 – 17:40
AI in imaging
Faisal Beg (Canada)
2. 17:40 – 17:50
Using AI to develop drugs against muscle wasting
Wei Lu (USA)

17:50 – 18:10
Panel discussion
3. 18:10 – 18:25
Unifying the sarcopenia terminology – primary / secondary / tertiary sarcopenia
Stephan von Haehling (Germany)

18:25 – 18:45
Panel discussion

S
08:15 – 09:15 **HALL A**

YOUNG INVESTIGATORS AWARD SESSION

(each presentation: 5 minutes + 3 minutes discussion)

Chairs / Judges:
Andrew Coats (Australia)
Wolfram Doehner (Germany)
Jose Garcia (USA)
Mitja Lainscak (Slovenia)
Reshma Merchant (Singapore)
Marilia Seelaender (Brazil)
Klaske van Norren (The Netherlands)
Hidetaka Wakabayashi (Japan)

08:15 – 08:23
DNA methylation–based liquid biopsy for cachexia risk stratification in glioma via Transformer-enabled muscle transcriptome inference (1-09)
Yan Sun (The Netherlands)

08:23 – 08:31
Muscle-targeted OPA1 overexpression confers sex-specific protection against pancreatic cancer cachexia (3-06)
Ruqaiza Muhyudin (USA)

08:31 – 08:39
Obesity reprograms adipose extracellular vesicles to induce muscle atrophy via miR-150-5p-mediated transcriptional silencing (4-22)
Joshua Price (UK)

08:39 – 08:47
Taste and smell changes and quality of life among ambulatory cancer patients receiving systemic treatment. (5-04)
Doireann Ní Chonaill (Ireland)

08:47 – 08:55
AntimiR therapy improves muscle mass and function in in vivo models of muscle wasting (7-10)
Andrea Garcia (Spain)

08:55 – 09:03
Change in skeletal muscle mass among patients with cancer undergoing chemotherapy or immunotherapy: a systematic review and meta-analysis (4-53)
Lukas Svendsen (Denmark)

09:03 - 09:11
The meaning of the EORTC Physical Functioning domain as a potential clinical endpoint in trials of patients with cancer cachexia: the association to direct physical assessments (3-31)
Jonathan Hella (Germany)

T
08:00 – 09:15 **HALL B**

BASIC SCIENCE

Progress in modelling skeletal muscle biology and pathology

(each talk 15 minutes)

Chairs: Pauline Henrot (France)
Ramon Langen (The Netherlands)

1. 08:00 – 08:15
A 3D-tissue-engineering toolbox to model skeletal muscle pathology
Pim Pijnappel (The Netherlands)
2. 08:15 – 08:30
Incorporation of macrophages into engineered skeletal muscle models
Nenad Bursac (USA)
3. 08:30 – 08:45
Human neuromuscular organoids mimic cancer-induced muscle cachexia
Anna Urciuolo (Italy)
4. 08:45 – 09:00
Role of substrate composition in muscle cell biology
Stephan Matecki (France)

09:00 – 09:15
Discussion

09:15 – 09:30

BREAK

U
09:30 – 10:45 **HALL A**

THERAPEUTICS

Novel strategies to address sarcopenia while treating obesity – round table discussion

(each talk 15 minutes)

Chairs / Panel:
Stefan Anker (Germany)
John Borg (Malta)
David Glass (USA)

1. 09:30 – 09:45
Myostatin and activin inhibitors as a treatment for sarcopenia in obese patients
Ken Attie (USA)
2. 09:45 – 10:00
GHSR1a antagonism for sarcopenic obesity
Jose Garcia (USA)
3. 10:00 – 10:15
Enobosarm
Mitchell Steiner (USA)
4. 10:15 – 10:30
Impact of the ACTA s-pindolol on muscle mass during and after GLP1-RA therapy
Andrew Coats (Australia)
5. 10:30 – 10:45
Panel discussion

V
09:30 – 10:45 **HALL B**

GENERAL SARCOPENIA

Organ and cell crosstalk in cancer cachexia

(each talk 15 minutes)

Chairs: Marco Sandri (Italy)
Xiling Shen (USA)

1. 09:30 – 09:45
Contribution of the endothelium to adipose tissue loss in cancer cachexia
Andreas Fischer (Germany)
2. 09:45 – 10:00
The tumor-bone-muscle axis in cancer cachexia
Fabrizio Pin (USA)
3. 10:00 – 10:15
The RNA-binding protein HuR impairs adipose tissue anabolism in pancreatic cancer cachexia
Paige Arneson-Wissink (USA)
4. 10:15 – 10:30
The critical role of the ovary in colorectal cancer and treatment-induced cachexia
James Carson (USA)

10:30 – 10:45
Discussion

10:45 – 11:45

COFFEE BREAK

10:50 – 11:40 **POSTER AREA**

POSTER VIEWING 4

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 4.1
Muscle Wasting & Sarcopenia (posters 4-61 to 4-69)
Chairs: Gustavo Duque, Andreas Fischer

Poster session 4.2
Cancer Cachexia (posters 3-01 to 3-12)
Chairs: Mauricio Berriel Diaz, Paola Costelli

Poster session 4.3
Cachexia (posters 1-01 to 1-11)
Chairs: Andrea Bonetto, Denis Guttridge

Poster session 4.4
Muscle Wasting & Sarcopenia (posters 4-13 to 4-24)
Chairs: Christopher Perry, Erin Talbert

W
11:45 – 13:00 **HALL A**

LATE BREAKING SCIENCE

(each talk 8 minutes + 4 minutes discussion)

Chairs: Stefan Anker (Germany)
John Borg (Malta)
Andrew Coats (Australia)
Manish Singhal (India)

1. 11:45 – 11:57
Phase 1 trial in healthy participants of KER-065, modified activin receptor ligand trap, supports development in sarcopenia and neuromuscular disorders (8-03)
Harveen Natarajan (USA)
2. 11:57 – 12:09
Efficacy and safety of ponsegromab in patients with cancer-associated cachexia: results from the open-label extension of a randomized, placebo-controlled, phase 2 study (8-07)
John Groarke (USA)
3. 12:09 – 12:21
Efficacy and safety of ponsegromab in patients with pancreatic cancer, cachexia, and elevated growth differentiation factor: insights from the Phase 2 PROACC-1 trial (8-05)
John Groarke (USA)
4. 12:21 – 12:33
Biophytis: BIO101 (20E) as a drug candidate targeting the reduction of GLP1-RA-induced muscle mass or function loss in patients with obesity (8-09)
Waly Dioh (France)
5. 12:33 – 12:45
S-pindolol protects lean body mass and skeletal muscle during incretin-induced weight loss and regain in obese mice
Henning Langer (Germany)
6. 12:45 – 12:57
Insights from the BELIEVE phase 2b trial of bimagrumab and semaglutide
Ken Attie (USA)

12:57 – 13:00
Closing remarks

13:00 – 14:00

LUNCH BREAK

13:05 – 13:35 **HALL A**

MEET THE EDITOR

Chair: Stephan von Haehling (Germany)

Journal of Cachexia, Sarcopenia and Muscle
Stefan Anker (Germany)

Journal of Gerontology: Biological Sciences
Gustavo Duque (Canada)

Nutrition
Alessandro Laviano (Italy)

Aging Cell
Monty Montano (USA)

13:05 – 13:45 **HALL B**

COACH-ED: CROSS-TALKS ON DIAGNOSIS AND MANAGING CANCER CACHEXIA: SHAPING THE FUTURE STANDARD OF CARE FOR CANCER CACHEXIA

Moderator:
Maurizio Muscaritoli (Italy)

Panel: Bharat Bhosale (India)
Jeffrey Crawford (USA)
José Garcia (USA)
Dominik Modest (Germany)
Paula Ravasco (Portugal)
Richard Skipworth (UK)
Florian Strasser (Switzerland)
Hidetaka Wakabayashi (Japan)

(Supported by an independent medical education grant provided by Pfizer and Actimed Therapeutics)

13:45 – 14:00

BREAK

X
14:00 – 15:15 **HALL A**

THERAPEUTICS

Cachexia care in the last year of life

(each talk 15 minutes)

Chairs: Randeep Singh (India)
Florian Strasser (Switzerland)

1. 14:00 – 14:15
Optimising nutrition during systemic anti-cancer therapy (SACT)
Alessandro Laviano (Italy)
2. 14:15 – 14:30
Holistic impact of cachexia on patients and informal caregivers
Joanne Reid (UK)
3. 14:30 – 14:45
Corticosteroids in cachexia care: who, where, when?
Dominik Modest (Germany)
4. 14:45 – 15:00
Nutritional impact symptoms: elephants in the room
David Blum (Switzerland)

15:00 – 15:15
Discussion

Y
14:00 – 15:15 **HALL B**

NUTRITION & METABOLISM

Update on substrates in muscle-wasting conditions

(each talk 15 minutes)

Chairs: Anja Bosy-Westphal (Germany)
Alessio Molfino (Italy)

1. 14:00 – 14:15
Integrated evaluation of body composition in the oncology setting: paradigm change
David Dias (Portugal)
2. 14:15 – 14:30
Nutrition, microbiome and cancer response to treatments
Paula Ravasco (Portugal)
3. 14:30 – 14:45
Immunonutrition in cancer: body of evidence, feasibility and limits
Marco Cintoni (Italy)
4. 14:45 – 15:00
NutrimiRomics: how close we are?
Maurizio Muscaritoli (Italy)

15:00 – 15:15
Discussion

15:15 – 16:00 **HALL A**

HIGHLIGHTS SESSION

Chairs: Mitja Lainscak (Slovenia)
Reshma Merchant (Singapore)
Maurizio Muscaritoli (Italy)

Basic Science
Joshua Huot (USA)

Nutrition
Guilherme Fonseca (Brazil)

Sarcopenia
Hidetaka Wakabayashi (Japan)

Cancer Cachexia
Jeffrey Crawford (USA)

Poster Award
Young Investigator Award
Farewell

ABSTRACTS OF ORAL PRESENTATIONS

A1 *(15 minutes)*

Atrophy-independent mechanisms of muscle weakness during ovarian cancer

Christopher Perry, Canada

While there is an urgent need to develop therapies that preserve muscle mass during cancer, understanding the causes of muscle weakness that occur independent of muscle atrophy could guide additional therapeutic directions focused on improving muscle quality. This presentation will provide an overview of discoveries of how muscle strength can decrease prior to muscle wasting as well as how muscle strength has been partially preserved in late-stage cancer models without preserving muscle mass. The objective is to stimulate discussion of atrophy-independent mechanisms of muscle weakness in relation to the progression of both muscle wasting and cancer itself. New opportunities for examining how early onset muscle weakness prior to muscle wasting might predict cancer progression will also be discussed.

A2 *(15 minutes)*

Bedside to bench: modeling cachexia in different cancer patient trajectories

Fabio Penna
Dept. of Clinical and Biological Sciences, University of Torino, Torino, Italy

The occurrence of cachexia in cancer (CC) patients is featured by muscle wasting, adipose tissue depletion, and systemic metabolic dysregulation, severely impacting patients' quality of life. The most commonly adopted experimental models to study CC in rodents implement injectable cancer cells expanded in vitro or inducible spontaneous cancers in genetically engineered mice[1], studying mostly active and acute cachexia, i.e. the rapid loss of body weight and muscle mass. The C26 colon carcinoma mouse model represents the prototypical, more widely used one. However, the rapid tumor growth and the lack of metastatic progression strongly limit its clinical relevance. In the clinical setting, intestinal cancer patients generally undergo medical (chemo- or radio- or immuno-therapy) and surgical interventions, with a chronic trajectory that may last for years with different waves of cachexia onset, followed by recovery and/or relapse when the primary tumor relapses and/or progresses to metastatic growth.

Current research in my laboratory aims to set up refined experimental protocols in C26-bearing mice in order to investigate tissue-specific metabolic alterations present in distinct stages of the long and variegated journey of cancer hosts experiencing chemotherapy, surgical resection and eventually cancer progression to a metastatic disease. This presentation will show results from an ongoing project modelling distinct CRC patient trajectories along with metabolomic data characterizing the alterations occurring in either skeletal muscle or liver.

Overall, dissecting the complexity and the multisystemic pathogenesis of cachexia, affecting relevant metabolic organs beyond the skeletal muscle, will help defining new and effective prospective therapeutic approaches[2].

References:

[1] Animal models for cancer cachexia. Ballarò R, Costelli P and Penna F. Curr Opin Support Palliat Care. 2016. PMID: 27454355
[2] NAD+ repletion with niacin counteracts cancer cachexia. Beltrà M, …and Penna F. Nat Commun. 2023. PMID: 37012289

A3 *(15 minutes)*

Mouse models of pancreatic cancer cachexia: investigating sex-dependent tissue loss

Erin Talbert
Department of Health and Human Physiology, and the Holden Comprehensive Cancer Center, University of Iowa, Iowa, USA

Cachexia is highly prevalent in people with pancreatic ductal adenocarcinoma (PDAC) and therefore animal models of pancreatic cancer are often used to understand mechanisms underlying cachexia. Previous work has demonstrated sex differences in cancer cachexia, particularly in regards to the role of activin signaling [1]. We sought to use the *Kras*$^{LSL\text{-}G12D}$, *Ptf1a*$^{Cre\text{-}ER/+}$, *Pten*$^{flox/flox}$ (KPP) model to further explore these differences. This model utilizes an inducible Cre recombinase to initiate tumor development by tamoxifen administration. In our previous work, tumors were induced in KPP mice at 4 weeks of age [2]. However, because mice are rapidly growing at this age, a portion of the body weight differences seen between control and KPP mice is likely due to slowed growth of KPP mice rather than cachexia alone. To address this, pancreatic tumors were induced to develop with tamoxifen in KPP mice after rapid postnatal growth has slowed at 10 weeks of age (KPP10) [3]. Similar to our previous findings, KPP10 mice had lower body, muscle, and adipose tissue weights compared to non-tumor mice, and these differences were similar between male and female mice. However, male mice experienced greater relative weight loss. Unexpectedly, we identified that survival was significantly shorter in female KPP10 mice compared to KPP10 males. Greater body weight at tumor induction was associated with longer survival, suggesting that the sex difference in survival may be related to differences in body weight between male and female mice at tumor induction, which resulted in female mice receiving higher tamoxifen dosages.

References:

1. Zhong, X., et al., Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: role of Activin. J Cachexia Sarcopenia Muscle, 2022. 13(4): p. 2146-2161. PMC9397557.
2. Talbert, E.E., et al., Modeling Human Cancer-induced Cachexia. Cell Rep, 2019. 28(6): p. 1612-1622 e4. PMC6733019.
3. Weinzierl, N.M., et al., Sex-specific survival but not tissue wasting in the KPP mouse model of pancreatic cancer-induced cachexia. J Appl Physiol (1985), 2025. 139(5): p. 1189-1194. PMC12590564.

A4 *(15 minutes)*

Ovarian cancer cachexia: new insights from clinical studies and animal models

Caleb J. Gammon[1], Esehoi Ehimiaghe[1,2], Patrick D. Livingston[1], Stephanie M. Wang[1,2], Nicholas A. Jamnick[1], Natalia M. Weinzierl[1], Elizabeth R. Woodruff[2], Benjamin G. Bitler[2,3], Leah J. Novinger[1,3], Andrea Bonetto[1,3]

[1]Department of Pathology, School of Medicine, University of Colorado Anschutz, Aurora, CO, USA;[2]Department of Obstetrics & Gynecology, Division of Reproductive Sciences ;[3]Comprehensive Cancer Center, University of Colorado Anschutz, CO, USA

Ovarian cancer (OC) is a leading cause of death from gynecologic malignancies, with most patients presenting at an advanced stage. Up to one-third of patients with OC show metabolic and body composition changes consistent with cancer cachexia (CC). Cachexia, marked by unintentional weight loss, muscle depletion, metabolic dysfunction, and inflammation, impairs quality of life and survival [1]. Despite its clinical relevance, cachexia in OC remains understudied, also due to limited preclinical models [2].
In a 10-month prospective study conducted at University of Colorado Hospital, 32 patients were enrolled, with 20 having confirmed epithelial OC. About 47% of patients with high-grade serous (HGS)-OC, accounting for up to ~90% of epithelial OC cases, showed signs of cachexia at diagnosis, including weight loss, sarcopenia, or low BMI, thus further highlighting the need for translational models. Cachectic patients were generally older, had higher comorbidity scores, and had elevated CA-125 levels. Most were non-hispanic white with advanced-stage disease. Rectus muscle biopsies showed high-quality preservation for molecular analysis.
To model these findings, immunocompetent mice were implanted with HGSOC cells. FVB mice implanted with BR-Luc cells [3] (mutant p53, BRCA1, Myc, Akt) developed ascites, muscle and fat wasting, and reduced strength. Ascites cytokines showed elevated IL-6, MCP-1, and VEGFA. In a second experiment, C57BL6J mice injected with ID8 cells ($p53^{-/-}$ or $p53^{-/-}$/$BRCA2^{-/-}$) showed similar cachexia features and altered plasma cytokines (elevated IP-10, Eotaxin, and reduced IL-5). Muscle tissue showed a typical cachexia signature, with proteasome/ubiquitin activation, mitophagy, mitochondrial dysfunction, and inflammation. Interestingly, by using rank-rank hypergeometric overlap analysis, we also found that the patients with OC exhibit suppression of muscle key processes, including mitochondrial homeostasis and respiration.
In conclusion, cachexia affects half of epithelial OC patients at cytoreductive surgery. Murine models recapitulate human cachexia features and offer platforms for identifying biomarkers and testing interventions.

References:

1 Fearon, K. C., Voss, A. C., Hustead, D. S. & Cancer Cachexia Study, G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *The American journal of clinical nutrition* 83, 1345-1350 (2006). https://doi.org:10.1093/ajcn/83.6.1345

2 Pin, F. *et al.* Growth of ovarian cancer xenografts causes loss of muscle and bone mass: a new model for the study of cancer cachexia. *Journal of cachexia, sarcopenia and muscle* 9, 685-700 (2018). https://doi.org:10.1002/jcsm.12311

3 Xing, D. & Orsulic, S. A mouse model for the molecular characterization of brca1-associated ovarian carcinoma. *Cancer research* 66, 8949-8953 (2006). https://doi.org:10.1158/0008-5472.CAN-06-1495

B1 *(15 minutes)*

Leukemia inhibitory factor (LIF) suppresses hepatic de novo lipogenesis and induces cachexia

Xue Yang [1], Juan Liu [1], Yiyun Shen [1], Jianming Wang [1], Wei-Xing Zong [1, 3], Xiaoyang Su [1], Eileen White [1], Zhaohui Feng [1], and Wenwei Hu[1]
1. Rutgers Cancer Institute, Rutgers University, New Brunswick, USA; 2. Department of Pharmacology and Toxicology, Rutgers University, Piscataway, USA;3. Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, USA.

Many cancer patients exhibit cachexia, a systemic disorder characterized by involuntary weight loss and the wasting of muscle and adipose tissues. Cachexia leads to reduced tolerance and responses to cancer treatments, reducing the survival of cancer patients. Cancer cachexia is partly fueled by the metabolic competition for nutrients between tumor and host tissues. In addition, metabolic and signaling communications across multiple organs mediated by a group of tumor- and host-derived cytokines and other factors plays a crucial role in driving this systemic wasting syndrome.
Leukemia inhibitory factor (LIF), a multi-functional cytokine, is frequently overexpressed in many human cancers and has been suggested as a cachexia-inducing factor. We investigated the role and mechanism of LIF in cancer cachexia using several mouse models, including a transgenic LIF knock-in line with conditional systemic or tumor-specific LIF overexpression, and conditional LIF receptor (LIFR) knockouts to block LIF signaling in either tumor cells or the host. We found that LIF overexpression downregulates hepatic PPARα signaling, leading to disrupted hepatic lipid homeostasis characterized by suppressed *de novo* lipogenesis and β-oxidation, ultimately contributing to cachexia. Activation of PPARα with fenofibrate, a PPARα agonist, restored hepatic lipid balance and substantially alleviated LIF-induced cachexia. These results reveals a key role of the LIF-hepatic PPARα axis in cachexia, and suggest potential therapeutic strategies to treat cancer cachexia.

References:
1. Yang X., et al. (2024) Leukemia inhibitory factor suppresses hepatic de novo lipogenesis and induces cachexia in mice. *Nature Communications* **15**:627.
2. Wang J., et al. (2023) Leukemia inhibitory factor, a double-edged sword with therapeutic implications in human diseases. *Mol Ther.* **31**: 331-343.

B2 *(15 minutes)*

Vagal blockade of the brain-liver axis deters cancer-associated cachexia

Xiling Shen
Terasaki Institute for Biomedical Innovation, Los Angeles, CA 90024, USA; Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

This talk will demonstrate a vagal liver-brain neuroinflammatory axis that plays an important role in cachexia progression. Based on the finding, a transcutaneous block device has been shown to be efficacious and safe in animal models. A randomized clinical trial to test this novel non-invasive vagal treatment to prevent cachectic progression in pancreatic cancer patients is slated start at MD Anderson Cancer Center in February, 2025.

B3 *(15 minutes)*

Genomic liver profiling identifies hepatokines promoting tissue wasting in cancer cachexia

Doris Kaltenecker[1,2,3], Søren Fisker Schmidt[1,4], Peter Weber[1,2,3], Anne Loft[1,4], Pauline Morigny[1,2,3], Juliano Machado[1,2,3], Julia Geppert[1,2,3], Kerstin Saul[5], Pia Benedikt[1,2,3], Claudia-Eveline Molocea[1,2,3], Rachel Scott[6], Kerstin Haase[6], Marc E. Martignoni[7], Ana Jimena Alfaro[1,2,3], Kan Kau Chow[1,2,3], Estefania Simoes[8], José Pinhata Otoch[8], Joanna D. C. Lima[8], Charles Swanton[9], Nadine Spielmann[10], Martin Hrabé de Angelis[10], Markus Elsner[11], Ali Ertürk[11], Kenneth A. Dyar[1,2,3], Maria Rohm[1,2,3], Olga Prokopchuk[7], Mariam Jamal-Hanjani[6], Marilia Seelaender[8], Johannes Backs[5], Stephan Herzig[1,2,3], Mauricio Berriel Diaz[1,2,3]

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Cancer cachexia (CCx) is a complex metabolic syndrome characterized by unintended weight loss and increased mortality. While muscle and adipose tissue wasting have been extensively studied, liver-mediated processes that shape or sustain the cachectic state have remained insufficiently understood.
Here, we applied hepatocyte-specific transcriptomic and epigenomic profiling across multiple weight-stable and cachectic cancer models to dissect the hepatic response in CCx. This approach revealed key transcriptional regulators of the cachexia-associated gene program, together with hepatocyte-secreted factors, also known as hepatokines, that were upregulated in CCx. A consistent hallmark of the hepatic response was the pronounced down-regulation of the circadian nuclear receptor REV-ERBα in hepatocytes. Notably, hepatocyte-specific reconstitution of REV-ERBα in cachectic C26 tumor-bearing mice ameliorated both muscle and adipose tissue wasting. Mechanistically, we found that REV-ERBα controlled the expression of specific hepatocyte-secreted factors that induced catabolic activity in target cells, including myotubes and cardiomyocytes *in vitro*. Furthermore, hepatocyte-specific knockdown of these hepatokines mitigated key features of CCx *in vivo*. Importantly, these hepatokines were also elevated in plasma of cancer patients with CCx across diverse tumor types, underscoring their translational relevance.
Together, our findings position the liver as an active driver of cachexia and reveal a circadian-hepatokine axis that represents a compelling therapeutic target to counteract systemic wasting.

B4 *(15 minutes)*

Regulation of hepatic amino acid metabolism

Anne-Catherine Maurin and colleagues
Proteostasis team, Human Nutrition Unit, INRAE/Clermont-Auvergne University, France

Marked changes in amino acid (AA) homeostasis have been associated with cachexia, due to high AA requirements related to tumor growth, immune response and associated metabolic changes. As the body does not have a dedicated system for storing AA, the adaptive breakdown of fibrillar proteins in skeletal muscles mobilizes AA to meet these requirements, contributing significantly to cachexia. The liver plays a central role in regulating protein/AA homeostasis, releasing many AA used by other organs and tissues and producing the majority of proteins secreted into the blood. In the liver during cachexia, highly AA-consuming processes are upregulated or induced, such as the massive production of positive acute phase proteins (APP)[1] in response to inflammatory cytokines.

Two major signaling pathways are involved in detecting intracellular AA levels and regulating AA utilization and supply accordingly[2]. The mTORC1 complex stimulates protein synthesis (notably via rpS6 phosphorylation) and inhibits autophagy when AA is abundant. Conversely, AA scarcity activates GCN2-dependent eIF2α phosphorylation, selectively reducing protein synthesis while upregulating the transcription factor ATF4, which stimulates the expression of genes involved in AA supply and utilization. Interestingly, these two pathways interact with each other. In addition, the eIF2α-ATF4 signaling pathway can be triggered by mitochondrial or endoplasmic reticulum stress, both of which have been reported in the liver during cachexia.

In our recent study using the C26 mouse model, we found that pre-cachectic stage of cancer progression was already associated with a strongly induced production of positive APP and reduced levels of most AA in systemic circulation. At the same time, the liver exhibited increased expression of positive APP, decreased albumin expression and upregulated autophagy[3]. At the onset of cachexia, we observed simultaneous activation of rpS6 and eIF2a signalings in the liver, as well as increased expression of ATF4 target genes involved in AA synthesis and transport, and autophagy.

This session will address the mechanisms regulating protein/AA metabolism and their potential involvement in hepatic adaptive changes associated with progression of cachexia.

References:

1. Pötgens, S.A., Thibaut, M.M., Joudiou, N., Sboarina, M., Neyrinck, A.M., Cani, P.D., Claus, S.P., Delzenne, N.M., and Bindels, L.B. (2021). Multi-compartment metabolomics and metagenomics reveal major hepatic and intestinal disturbances in cancer cachectic mice. J Cachexia Sarcopenia Muscle *12*, 456–475. https://doi.org/10.1002/jcsm.12684.

2. Wek, R.C., Anthony, T.G., and Staschke, K.A. (2023). Surviving and Adapting to Stress: Translational Control and the Integrated Stress Response. Antioxid Redox Signal *39*, 351–373. https://doi.org/10.1089/ars.2022.0123.

3. Chaouki, G., Parry, L., Vituret, C., Jousse, C., Leremboure, M., Bourgne, C., Mosoni, L., Delorme, Y., Djelloul-Mazouz, M., Hermet, J., et al. (2025). Pre-cachectic changes in amino acid homeostasis precede activation of eIF2α signaling in the liver at the onset of C26 cancer-induced cachexia. iScience *28*. https://doi.org/10.1016/j.isci.2025.112030.

C1 *(15 minutes)*

RAGE expressed by myofibers sustains hallmarks of cancer cachexia

Guglielmo Sorci
Department of Medicine and Surgery, University of Perugia, Perugia, Italy; Interuniversity Institute of Myology (IIM), Perugia, Italy

RAGE (receptor for advanced glycation end-products) is a multiligand receptor of the immunoglobulin superfamily involved in physiological and pathological processes. RAGE is expressed in several cell types, including immune cells, and sustains the inflammatory response. In skeletal muscle, RAGE is expressed during development but repressed in adult healthy myofibers [1]. However, RAGE is re-expressed in myofibers during the muscle regeneration process and in muscle atrophy conditions. We reported that RAGE-null (*Ager*$^{-/-}$) mice show reduced systemic inflammation, delayed body and skeletal muscle weight loss, and dramatically increased survival in cancer cachexia (CC) conditions [2]. However, the specific contribution of RAGE re-expressed at myofiber level to cancer-induced muscle wasting was still unknown. We generated a tamoxifen-inducible conditional *Ager*^{mKO} mouse model in which RAGE is selectively ablated in myofibers, using an HSA/Cre-Lox system. Tamoxifen-treated *Ager*$^{-/-}$, *Ager*^{mKO}, and control (*Ager*^{flox}) mice were subcutaneously injected with Lewis lung carcinoma (LLC) cells or vehicle, and analyses were performed at 25 dpi. LLC-*Ager*^{mKO} mice showed reduced body weight loss, maintenance of hind-limb muscle mass and strength and myofiber cross-sectional areas, restrained muscle and systemic inflammation, and increased survival, compared with LLC-*Ager*^{flox} mice. Muscles of tumor-bearing *Ager*^{mKO} mice maintain an active Akt-GSK-3β-PGC-1α pathway and undergo a fast-to-slow myofiber transition. The expressions of several antioxidant enzymes and enzymes involved in the glycolytic process were found to increase in muscles lacking RAGE, in cancer conditions, reminiscent of Warburg-like metabolism. Noteworthy, increased amounts of RAGE along with reduced activation of Akt and reduced amounts of PGC-1α were found in the *rectus abdominis* muscles of clinically diagnosed pancreatic carcinoma patients in both the pre-cachectic and cachectic stages, compared with healthy control subjects. This suggests that the overexpression of RAGE is an early event in muscles of cancer patients, and highlights a role of RAGE in the onset of CC. Thus, RAGE engagement at myofiber level drives CC, and the pharmacological inhibition of RAGE might be useful to counteract the cachectic syndrome in cancer patients.

References:
1. Riuzzi F., Sorci G., Sagheddu R., Chiappalupi S., Salvadori L., Donato R. (2018) RAGE in the pathophysiology of skeletal muscle. *J. Cachexia Sarcopenia Muscle*, 9, 1213–1234.
2. Chiappalupi S., Sorci G., Vukasinovic A., Salvadori L., Sagheddu R., Coletti D., Renga G., Romani L., Donato R., Riuzzi F. (2020) Targeting RAGE prevents muscle wasting and prolongs survival in cancer cachexia. *J. Cachexia Sarcopenia Muscle*, 11, 929–946.

C2 *(15 minutes)*

Shaping the immune landscape by IL-4: relevance to cancer-induced muscle wasting

Paola Costelli
Department of Clinical and Biological Sciences, University of Torino, Italy

While malignant tumors are well known on one side to evade the immune response, on the other to shape the immune system to their own advantage, the possibility that such a behavior could also impinge on the onset of cachexia has long been neglected. Indeed, most of the research on cachexia was focused on the relevance of cytokines and/or chemokines to the alterations of signaling pathways contributing to body wasting. At present, little is known about the interaction among cells of the immune system and the homeostasis of peripheral tissues, the more so when the picture is complicated by the presence of the tumor and/or of the anticancer treatments.

In the last years interleukin (IL) 4 was shown to improve muscle mass and function, body weight and survival in mice bearing the C26 colon carcinoma (1). The present study aimed to investigate the mechanisms underlying such effects, focusing on immunomodulation.

The results show that IL4 treatment counteracted the loss of body weight, muscle mass and strength in the C26 hosts. IL4 administration restored normal levels of circulating cytokines such as eotaxin, MCP-1, TNFα, IL6 and Jagged. As for the immune cells, no changes were observed in the blood, while reduction of myeloid-derived suppressor cells, T-regulatory lymphocytes, CD8+ T-cells and CTL occurred in the spleen. Single nuclei RNAseq revealed significant differences in tumors obtained by animals exposed to IL4 compared to the untreated hosts.

The data obtained demonstrate that IL-4 administration to the C26 hosts exerts a marked immunomodulatory activity, which revealed able to reduce the number of both MDSCs and Tregs, both features previously associated with the progression of cancer cachexia. Along this line, the reduction of Tregs and MDSCs positively correlated with improved body weight, muscle mass and strength. On the whole, the protective effect exerted by IL4 on the onset and progression of experimental cancer cachexia is associated with improvement of the host immunological milieu.

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C3 *(15 minutes)*

Fat Infiltration in muscle and bone in osteosarcopenia: mechanisms and therapeutic insights

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Osteosarcopenia, the combined degeneration of muscle and bone that occurs with aging, is characterized by fat infiltration in both tissues, which seems to replace the normal muscle and bone marrow. Current research aims to understand both the cause of fat accumulation with aging and whether it contributes to worsening regenerative capacity and the overall decline in bone-muscle function. Recent findings indicate that prostaglandin E2 (PGE_2), a signaling lipid mediator primarily secreted by osteocytes at levels significantly higher than those in skeletal muscle, plays a crucial role in regulating myogenesis and bone remodeling.[1, 2] Our research indicates that aging significantly lowers PGE_2 levels in both animal models and humans, primarily due to an increase in 15-Prostaglandin Dehydrogenase (15-PGDH), which degrades PGE_2. We and others have demonstrated that rescuing PGE_2 levels during aging improves muscle and overall tissue function, suggesting that PGE_2 could modulate bone-muscle fat infiltration during aging. [3, 4]

Building on these foundations, we developed a targeted nanoliposome delivery system[5] conjugated with a muscle-specific peptide to address the limited bioavailability of PGE_2, which is caused by its rapid degradation. In vitro studies confirmed the sustained release of encapsulated PGE_2 over 72 hours, enhanced myogenesis, increased expression of muscle regulatory genes, and Apelin, indicating PGE_2's major role in modulating lipid metabolism. In vivo experiments in aged mice (22-24 months old) demonstrated specific delivery to skeletal muscle, reducing off-target effects, sustained release of PGE_2, and enhanced muscle function (in vivo performance and muscle contractility function). These findings highlight the potential of modulating an osteokine, "PGE_2," signaling as an innovative therapeutic approach for nanomedicine to improve muscle and bone health and mitigate the progression of osteosarcopenia.

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C4 *(15 minutes)*

The geroscience framework for osteosarcopenia: mechanistic insights and clinical implications

Gustavo Duque
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Osteosarcopenia, the coexistence of osteoporosis and sarcopenia, represents a major geriatric syndrome that increases vulnerability to falls, fractures, disability, and mortality. Traditionally viewed as two parallel but independent musculoskeletal disorders, emerging evidence now supports a shared pathophysiological basis rooted in the biology of aging. The geroscience framework—linking the molecular mechanisms of aging to chronic disease—offers an integrative perspective to understand and intervene in osteosarcopenia. Hallmarks of aging, including cellular senescence, mitochondrial dysfunction, deregulated nutrient sensing, and chronic low-grade inflammation, are now recognized as common drivers of bone and muscle decline. These processes disrupt the bone–muscle crosstalk mediated by endocrine, paracrine, and mechanical pathways, leading to a self-perpetuating cycle of fragility.

This presentation will outline how geroscience-guided research has enhanced our mechanistic understanding of osteosarcopenia, highlighting recent discoveries about senescent cell buildup at bone–muscle interfaces, changes in myokine–osteokine signaling, and the influence of inflammatory stressors. It will also cover translational implications, including the potential of gerotherapeutic interventions to target shared aging mechanisms rather than isolated tissue endpoints.

Clinically, applying the geroscience framework allows a shift from disease-specific to system-wide assessment and management of musculoskeletal aging. It helps develop integrated diagnostic tools, combined biomarkers, and multimodal interventions that simultaneously maintain bone and muscle health. Ultimately, this approach redefines osteosarcopenia as a sign of accelerated biological aging—creating new opportunities for prevention, personalized therapy, and healthy longevity.

D2 *(25 minutes)*

GDF15 Research from Bench to Bedside

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Almost thirty years ago, GDF15 (then known as MIC-1), a member of the TGFb superfamily, was first described in PNAS (1997) as a cytokine induced in activated macrophages. Its circulating levels were later shown to rise markedly in many disease states, particularly cancer, but also in chronic cardiac and renal failure, and during. A decade later, a pivotal Nature Medicine paper (2007) demonstrated in murine models, supported by correlative human data, that GDF15 was a key driver of the anorexia/cachexia syndrome. Cell stress induced increases in GDF15 in serum act on brain regions regulations appetite and aversive behaviour, subsequently identified as the hindbrain area postrema (AP) and nucleus of the solitary tract (NTS), to elicit anorexic and aversive behaviours. This led to progressive loss of muscle and fat mass and eventually the cachexia. Ten years later, four Pharma research groups independently identified its receptor as GFRAL, a divergent member of the glial derived neurotrophic factor receptor alpha family (GDFRa) family thereby placing GDF15 within the GDNF subfamily of TGFb ligands. Consistent with earlier findings, this receptor is highly restricted to the AP/NTS.

After more than two decades of research, diagnostic assays for circulating GDF15 have entered clinical practice, and therapeutic blockade of the GDF15–GFRAL pathway has reached late stage clinical trials. Notably, Pfizer's anti-GDF15 antibody Ponsegromab produced favourable Phase II results in cancer cachexia (NEJM, 2024). Trials are also underway targeting GDF15 in hyperemesis gravidarum and in overcoming checkpoint-inhibitor resistance in cancer.

This talk will review the research science that led to the current clinical trials of GDF15 based therapeutics for anorexia cachexia syndromes

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D3 *(25 minutes)*

“Hippocrates” clinical science key note lecture:
“Sooner or later, this has gotta work,” Garibaldi (Michael), as paraphrased

Aminah Jatoi, USA

D4 *(5 minutes)*

JCSM lecture

Stephan von Haehling, Germany

E1 *(15 minutes)*

Titin and its role in the myocardium

Katja Gehmlich
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Titin is a giant protein spanning the sarcomere from the Z-disc to the M-band. It has crucial structural and signalling roles for striated muscle tissues, including the heart. Among other functions, it controls passive stiffness and relays hypertrophic signalling. Both processes are relevant e.g. for heart failure (with preserved and reduced ejection fraction). Numerous binding partners and posttranslational modifications have been reported [1].

Given the large size of the TTN gene, it was a challenge to interrogate the role of titin in genetic conditions historically. With the more recent roll-out of high throughput sequencing techniques in clinical practice, it has become apparent that up to 25 % of familial Dilated Cardiomyopathy cases (a form of heart failure with reduced ejection fraction) are associated with truncating variants in TTN [2]. The position of the variant within the TTN gene determines the risk and there is incomplete penetrance. The patho-mechanisms are discussed controversially, both haplo-insufficiency and 'poisonous' truncated protein have been suggested to contribute.

Truncating variants in TTN are also enriched in peripartum cardiomyopathy and alcohol-induced damage to the heart, prompting the idea of a 'second hit 'being needed for TTN truncating variants to become penetrant. TTN truncating variants are also associated with atrial fibrillation, a common cardiac arrhythmia. New data suggest that TTN truncating variants may predispose to atrial fibrillation even before the onset of structural cardiac remodelling.

The evaluation of missense variants in TTN is far more challenging, as rare missense variants also occur in normal control cohorts, due to the large size of the gene. Distinguishing the few pathogenic variants from the vast number of benign ones is a challenge for clinical geneticists and hence TTN missense variants are often ignored in genetic testing.

To gain insights into disease mechanisms of titin associated cardiac diseases, rodent in vivo models [3] and human induced pluripotent stem cell derived cardiomyocytes are valuable tools complementing investigation on patient samples.

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E2 *(15 minutes)*

The skeletal muscle

Beatrice Vahle
Heart Center Dresden, Laboratory of Molecular and Experimental Cardiology, TU Dresden, Germany

For proper muscle function a structured organization of the contractile proteins α-actin (thin filament), myosin (thick filament) and titin (elastic filament) in the sarcomere is essential. Titin, the largest known protein, that have been found in nature, spans half of the sarcomere and plays a fundamental role regarding passive elasticity and contractile regulation of striated muscles, serving as a central integrator of mechanical sensing, force transmission, and intracellular signaling.
Titin serves as a central integrator within the sarcomere, interacting with numerous sarcomeric proteins to regulate key mechanical properties of muscle at rest, as well as during contraction. Its structural and functional importance in muscle fibers is emphasized by the variety of known titinopathies and furthermore by animal models with complex rearrangements in the titin gene, all of them associated with severe muscle dysfunction. Titin undergoes a variety of posttranslational modifications like carbonylation, phosphorylation and ubiquitination impairing its proper function. Especially phosphorylation predominantly targeting the PEVK region (Serine (S)11878 and S12022) is described to negatively affect muscle compliance. The PEVK segment is a functionally relevant region of titin, contributing significantly to passive tension during muscle stretch. Titin modifications are often observed in conditions associated with muscle wasting like chronic heart failure, muscle denervation or tumor cachexia. Animal experiments, evaluating the effect of alcohol consumption and muscle unloading showed decreased titin content, and in some parts increased titin phosphorylation
Exercise intolerance and muscle wasting are well-established hallmarks of heart failure (HF), irrespective of etiology, extending beyond the heart's impaired function of pumping blood to the peripheral organs. Even though the heart's reduced cardiac output is a big factor, peripheral molecular alterations, particularly in SKM, also play a significant role.
Being aware that in cardiac muscle of HFpEF patients, increased titin stiffness—driven by isoform switching and post-translational modifications such as phosphorylation by protein kinases—is strongly associated with the development of diastolic dysfunction in heart failure, the question arises whether similar alterations occur in the skeletal muscle of heart failure patients.
In recent studies we detected a titin hyperphosphorylation in the skeletal muscle of female ZSF-1 obese rats, a metabolically-driven HFpEF model, driven by a S11878 phosphorylation. This hyperphosphorylation is associated with several muscle parameters predicting muscle function. In my presentation I will evaluate the effect of different therapeutical options on titin and muscular function and discuss the context of titin modification in different HFpEF etiologies, comparing the results with titin alterations in human muscle biopsies.
Furthermore, I will give an outlook to future experiments, aiming to identify the role of the two phosphorylation sites (S11878 and S12022) in the PEVK region, for the regulation of skeletal muscle function. Addressing this gap is essential to better understand the molecular mechanisms underlying skeletal muscle dysfunction in diseases such as HFpEF and to develop new treatment strategies.

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E3 *(15 minutes)*

The diaphragm

Marloes van den Berg
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The diaphragm, our primary respiratory muscle, is continuously active yet highly sensitive to unloading, with weakness developing within 24 hours of mechanical ventilation in critically ill patients. The mechanosensing protein titin, acting as a molecular spring, regulates sarcomere length and stiffness and may drive diaphragm fiber adaptations and weakness during ventilation with positive end-expiratory pressure (PEEP). Together, these findings underscore titin's central role in diaphragm adaptation and remodeling.

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E4 *(15 minutes)*

Titin (and similar) as biomarker

Simone Agostini
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Titin, encoded by the *TTN* gene, is the largest known human protein and a pivotal structural element of the striated muscle sarcomere [1]. Spanning from the Z-disk to the M-line, titin functions as a molecular spring, conferring passive elasticity, stabilizing sarcomeric architecture, and mediating mechanosensory signaling [2]. Its pronounced isoform heterogeneity—arising from extensive alternative splicing—allows muscle-type–specific tuning of compliance, stiffness, and contractile properties [3]. Beyond mechanical support, titin participates in intracellular signaling networks governing muscle protein turnover, hypertrophy, repair, and stress adaptation [4]. Under catabolic stress or damage, titin undergoes proteolytic cleavage, releasing soluble fragments—commonly N-terminal and M-line domains—into circulation and bodily fluids, thereby offering a minimally invasive readout of sarcomeric integrity [5].
Accumulating evidence positions titin and homologous sarcomeric proteins (e.g., nebulin, obscurin, myomesin) as candidate biomarkers for muscle wasting syndromes such as sarcopenia, cachexia, and generalized wasting disorders. In age-associated sarcopenia, the detection of elevated titin fragments in circulation correlates with reduced muscle strength and functional decline, reflecting chronic myofibrillar breakdown. In cachexia—driven by systemic inflammation, metabolic dysregulation, or cancer—titin-derived markers may more specifically indicate progressive muscle proteolysis compared to conventional markers (e.g., creatine kinase) that are less selective for chronic wasting. Structurally related giant proteins may complement titin in multiplex biomarker panels, by capturing distinct facets of sarcomeric disassembly.
Our 2025 study extends this paradigm by directly measuring serum TTN, N-terminal TTN (N-TTN), and miR-451a levels in older sarcopenic patients undergoing rehabilitation versus age-matched healthy controls [5]. Our findings show that baseline serum TTN and N-TTN concentrations are significantly increased in sarcopenic individuals and decline following a 30-day structured rehabilitation program, concomitant with functional improvement as measured by SPPB scores. Interestingly, circulating miR-451a—predicted *in silico* to target *TTN* mRNA—was also upregulated in sarcopenic patients, and its change (ΔmiR-451a) after rehabilitation exhibited predictive capacity (AUC ≈ 0.693) for functional recovery [5]. A negative correlation between miR-451a and N-TTN was observed, supporting a putative epigenetic regulatory axis. This work suggests that titin fragments in serum, in tandem with miRNA regulators, may serve as dynamic biomarkers for sarcopenia progression and treatment response.
To summarize, titin and titin-like proteins represent mechanism-based biomarkers bridging sarcomeric structural alterations with systemic muscle catabolism. Quantification of titin fragments in biofluids—especially when paired with regulatory miRNAs—holds promise for early detection, prognostic stratification, and therapeutic monitoring in sarcopenia, cachexia, and related wasting disorders.

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F1 *(15 minutes)*

Physical performance metrics as biomarkers of frailty phenotypes

Stephan von Haehling, Germany

F2 *(15 minutes)*

Sociobiological pathways linking psychosocial stressors to frailty: social determinants as emerging biomarkers

Jürgen M. Bauer
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Frailty represents a holistic, multi-dimensional concept. Its complex pathogenesis includes all factors that are relevant to the aging process. While the relevance of molecular aging mechanisms, diseases and life-style factors for the development of frailty has been analyzed thoroughly, psychological and social factors have been studied to a much lesser degree. As a consequence, the pathways that link the latter with the organic correlates of frailty have not been fully explored yet. It has also to be appreciated that the relationship between psychosocial factors and frailty is reciprocal, frailty affecting the psychological and social status of older person to a relevant degree. Psychosocial factors are multitude. Among the clinically most relevant are depression, loneliness and low socioeconomic status. The extent of these factors influences considerably the frailty risk. In a recent study social vulnerability which has been characterized by scarcity of adequate social connections, support or interaction was associated with more rapid progression of frailty and lower odds of improvement compared with its absence. In addition, negative health outcomes of frailty are mediated by psychosocial stressors. This has recently been shown for depression in the context of cardiovascular events and for overall mortality in the presence of loneliness and social isolation. Considering the pathways that link depression to frailty development sedentary behavior in depressive patients appears to be of special relevance. It is expected that in the near future functional MRI studies will provide valuable information on the basic mechanisms that underlie the interrelationship between these two entities.

In the years to come studies on frailty should reflect the relevance of psychosocial stressors to a much higher degree. Future therapeutic approaches in the field of frailty will include a wide array of options ranging from pharmaceutic compounds to life-style and psychosocial interventions. In most instances a combination therapy will still be indicated. Patient profiling including psychosocial biomarkers will be of special importance in this context.

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F3 *(15 minutes)*

Blood-based signatures of frailty

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Frailty is a condition of diminished physiological reserve arising from multisystem dysregulation and deeply intertwined with the biology of aging. Evidence indicates that frailty reflects disturbances across multiple hallmarks of aging, including chronic inflammation, mitochondrial dysfunction, epigenetic drift, altered nutrient sensing, and impaired proteostasis. Yet, single biomarkers often lack specificity, stimulating interest in multi-omic signatures and composite biological-aging scores. The validation and clinical applicability of these candidates are further constrained by the coexistence of different operational definitions of frailty, which capture only partially overlapping domains of vulnerability and often yield heterogeneous biological associations.
Within this complex landscape, the emerging concept of personalized biomarker setpoints offers a novel interpretative framework. Recent findings show that many routine blood parameters oscillate around highly stable, individual-specific homeostatic baselines that persist over decades and strongly predict morbidity and mortality. These deep phenotypes allow deviations from a person-specific “healthy state” to be detected, enabling a precision-medicine approach capable of revealing subtle shifts in biological aging long before population-based reference thresholds are exceeded. Such individualized trajectories may help disentangle early dysregulation in the core mechanisms underlying frailty.

Future work should prioritize the validation of multi-marker, personalized, and longitudinal biomarker architectures capable of capturing both inter-individual patterns of biological aging and intra-individual departures from homeostatic stability. These strategies hold considerable promise for transforming how frailty is identified, monitored, and managed in clinical research and practice.

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F4 *(15 minutes)*

GDF-15 as biomarker: state of the art

Kai Wollert
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GDF-15 is a distant member of the TGFbeta cytokine superfamily that is induced by cellular stress resulting from unhealthy lifestyle choices, reduced physical fitness, disease, and frailty. Plasma GDF-15 has emerged as a biomarker of biological age, increasing with chronological age and disease burden, but remaining at youthful levels in healthy centenarians.[1-3] Plasma GDF-15 is strongly and independently associated with future cardiovascular events, heart failure hospitalizations, and mortality in patients with coronary artery disease or heart failure. However, first attempts at using GDF-15 measurements for guiding treatment decisions in cardiovascular patients have not been successful.[4,5]

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G1 *(15 minutes)*

Targeting metabolic storm: from nutrients to clinical practice

Carolina Trabulo
Faculty of Health Sciences and Nursing, Universidade Católica Portuguesa, Lisbon; Medical Oncology Unit, Unidade de Saúde Local Arco Ribeirinho, Lisbon, Portugal

The concept of the *metabolic storm* encapsulates the complex metabolic dysregulation observed in cancer, driven by the interaction between tumor metabolism, host response, systemic inflammation, and treatment-related stress. This multifactorial disruption contributes to impaired treatment tolerance, cachexia, and reduced survival.

Recent clinical and translational evidence has reinforced the prognostic and therapeutic relevance of metabolic health in oncology. Early and systematic nutritional assessment, individualized macronutrient targets, and multimodal cachexia management are now considered core elements of comprehensive cancer care, as reflected in recent ESPEN and ESMO guidelines. Emerging research on metabolic modulation, including dietary timing strategies and metabolic drug combinations, shows promise but requires rigorous validation.

This presentation integrates current evidence from metabolism and clinical nutrition to propose practical, evidence-based strategies for mitigating the metabolic storm, improving patient performance, and enhancing outcomes through metabolic precision and multidisciplinary care.

G2 *(15 minutes)*

Nutrition as a co-therapy in pharmacological cancer cachexia trials: a must?

Barry Laird
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Cancer cachexia rests on three interconnected pillars: metabolic disruption, loss of physical function, and nutritional decline. Most drug trials have targeted the metabolic pillar, seeking to restore lean mass, appetite, and energy balance. Yet, by sidelining nutrition, we may be missing a crucial opportunity to strengthen the overall therapeutic response.

Evidence shows that structured nutritional support delivered through dietary counselling, high-protein oral supplements, or multimodal regimens combining nutrition with exercise and pharmacologic therapy can help maintain body weight, enhance intake, and improve quality of life. These effects are most consistent when nutrition is individualized, energy-dense, and led by dietitians as part of an integrated care strategy.

Simply adding calories is unlikely to reverse cachexia, but optimised nutritional therapy is safe, feasible, and may potentiate the benefits of metabolic and anti-inflammatory agents. Nutrition should therefore be viewed not as a secondary measure, but as a dynamic and essential platform within cachexia management.

Future cachexia trials should embed standardized, high-quality nutritional interventions alongside novel therapeutics to ensure real-world applicability and measurable patient benefit. Addressing only metabolism may be sub-optimal and rather true progress may come from rebuilding all three pillars together: metabolism, function, and nutrition.

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G3 *(15 minutes)*

Sustaining the muscle, sustaining the environment: is plant protein the key?

Gianni Biolo, Italy

G4 *(15 minutes)*

New insights into DHA supplementation in breast cancer

Alessio Molfino
Department of Translational and Precision Medicine, Sapienza University of Rome, Italy

Docosahexaenoic acid (DHA), a long-chain omega-3 polyunsaturated fatty acid, is increasingly recognized as a key modulator of the inflammatory microenvironment in cancer. Beyond its structural role in cell membranes, DHA represents a metabolic precursor for a family of bioactive lipid mediators—specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins—that actively promote inflammation resolution and tissue homeostasis. By these metabolites, DHA can regulate leukocyte trafficking, cytokine release, macrophage polarization, and angiogenesis, all processes intimately linked to tumor progression and immune escape.

Recent translational studies have clarified that the metabolism of DHA into D-series resolvins is altered in breast cancer, with circulating patterns reflecting disease subtype, proliferative index, and BRCA1/2 mutational status. In particular, baseline profiling of plasma resolvins in treatment-naïve breast cancer patients revealed a relevant reduction in their levels in biologically aggressive or genetically driven disease forms—specifically in those carrying BRCA1/2 mutations and in tumors characterized by high Ki-67 expression on immunohistochemical analysis[1]. Based on these observations, short-term oral DHA supplementation was shown to modulate circulating resolvins in vivo, selectively enhancing pro-resolving activity in BRCA1/2-mutated patients[2]. These findings suggest a possible genotype-related variability in the response to DHA supplementation, underscoring the need for further studies exploring SPMs as potential indicators of inflammation resolution and for a more precise phenotypic characterization to guide personalized nutritional and metabolic interventions in breast cancer.

Overall, current evidence highlights to a potential role of DHA beyond its nutritional value, as a modulator of inflammation resolution. These observations open new perspectives for integrating DHA-based approaches within precision nutritional and metabolic treatments aimed at improving immune regulation and nutritional status in breast cancer.

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H1 *(15 minutes)*

What is the role of body composition in diagnosing obesity and sarcopenic obesity?

Manfred J. Müller
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The definition and diagnostic criteria for clinical obesity have been published by the European Association for the Study of Obesity (1) and in a recent consensus statement by the Lancet Obesity Commission (2). After about 70 yrs of obesity research crude anthropometric characteristics (i.e., BMI and waist circumference) are still used to define obesity. By contrast, body composition analysis (BCA) was underestimated in both definitions. This can be seen as a missed opportunity, as there are different phenotypes of obesity (including sarcopenic obesity) and many therapies available for people with obesity that can have different effects on body composition resulting in specific indications or contraindications. Today, body composition assessment is widely used in both research and clinical practice leading to body composition standards, levels, models, assessment, comparison, and interpretation of the data (3). In general, BCA is about methods, models, reference values, risk assessment and interpretation of endocrine and metabolic fucntions. Here, we provide the rationale for a concise concept of targeted application of BCA in the diagnosis and staging of patients with obesity, which forms a basis for tailored treatment options and treatment monitoring.

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H2 *(15 minutes)*

Is there a "gold standard" method for measuring skeletal muscle mass

Steve Heymsfield, USA

H3 *(15 minutes)*

D_3Creatine dilution as an accurate measure of functional muscle mass

William J. Evans
University of California Berkeley, USA

The d_3-creatine dilution (D_3Cr) method provides a non-invasive and accurate measurement of functional muscle mass. In older men and women, lower D_3Cr muscle mass (but not DXA lean mass) is strongly linked to reduced strength, physical function, and performance, and in men higher risk of fractures, falls, disability, and mortality. New data in men and women between 30 and 90 years of age from the Study of Muscle Mobility and Aging show that age related decreases in functional muscle mass are strongly associated with reductions in strength and maximal aerobic capacity. Among the various types of mobility limitations, difficulty walking (34%), difficulty climbing stairs (23%), and difficulty rising from a chair (19%) are the most prevalent in community-dwelling older adults. Data[1] in older men show that low muscle mass is strongly associated with risk of mobility disability assess by reduced activities of daily living (ADL) and instrumental ADL. In overweight and obese older men, D_3Cr muscle mass is strongly associated with mobility limitations demonstrating that when an accurate assessment of muscle mass (rather than lean mass) is used, reduced muscle mass is highly associated with important outcomes and the negative effects of adiposity are minimal, suggesting that obesity has little relevance for the understanding of important outcomes of sarcopenia. "The term 'sarcopenic obesity' has few implications for physical function, injurious falls and mobility limitation."[2] In patients with Duchenne muscular dystrophy (DMD) from ages 4 – 24 years, D3Cr muscle is also strongly associated with strength and functional status. The data reveals a potential threshold of % muscle mass for a transition of ambulatory to non-ambulatory status suggesting that control of gain in body fatness in these patients may help to protect ambulatory status[3]. To date, this method has been used to assess muscle mass in neonates, infants, children, patients with cancer, DMD, malnutrition and in aging cohorts. Thus, accumulating evidence suggests that skeletal muscle mass, when assessed by the D_3Cr dilution method, is more strongly associated with strength and physical performance outcomes in older adults than previously recognized with proxy measures like DXA LST and muscle mass/body weight should be considered in any definition of sarcopenia[4].

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H4 *(15 minutes)*

Why do we need muscle / fat biopsies in 2025?

Mitja Lainscak, Slovenia

I1 *(15 minutes)*

Sex differences in the skeletal muscle-aging trajectory of energy metabolism

Physical weakness, but not Aging, displays sex-specific intramuscular changes associated in elderly

Jelle CBC de Jong[1,2], Marjanne D van der Hoek[1,4,5], Lars Verschuren[3], Martien PM Caspers[3], R van der Leij[4,6], Robert Kleemann[2], Anita M van den Hoek[2], Arie G Nieuwenhuizen[1] and Jaap Keijer[1]*
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Physical weakness is a key component of frailty, which is highly prevalent in older adults. Sex differences in muscle aging are understudied. Higher prevalence and earlier onset of frailty related physical weakness suggests sex specific effects. For insight in sex differences aging and physical weakness, we recruited young (23 ± 2 years, 13 males and 13 females) and old (80 ± 3.5 years, 28 males and 26 females) participants. Males and females were highly matched. To study muscle aging, *Vastus lateralis* parameters of old versus young participants were compared for each sex separately, focusing on gene expression. Top-ranked pathways differed between males (OXPHOS) and females (AKT), but were present and were altered in the same direction in both sexes as were the underlying experimentally confirmed gene/protein changes. Concluding: the same processes are associated with skeletal muscle aging in males and females, but the differential expression of those processes is sex specific. We next focused on intramuscular changes that differentiate fit and weak elderly, grouped on based on ranking according to three frailty related performance criteria. Transcriptome analysis of the *Vastus lateralis* muscle revealed an increased expression of inflammatory pathways and infiltration of NOX2 expressing immune cells, concomitant with an increased VCAM1 expression in weak females. Weak males were characterized by a shrinkage of type 2 (fast) myofibers and decreased expression of PRKN. In addition, weakness-associated transcriptome changes in the muscle were distinct from aging. We conclude that physical weakness associated changes in muscle are sex-specific, and frailty is distinct from aging. This may that frailty is an aging related disease, rather than a continuum of aging. We recommend that sex differences are taken into account in research on frailty, as these differences may impact the development of (pharmaceutical) interventions against frailty.

References:

doi: 10.1096/fj.202000493R; doi: 10.1007/s11357-023-00750-4; doi: 10.1186/s13293-023-00531-w; (related study:)doi: 10.1002/jcsm.12753.

I2 *(15 minutes)*

The role of the exosome in cancer cachexia

Marilia Seelaender
Cancer Metabolism Research Group, Department of Surgery and LIM26-HC, Faculdade de Medicina and CoMeta-HU, Universidade de São Paulo, Brazil

Cachexia remains an unsolved problem in the management of cancer and markedly impacts the success of patient treatment and survival. This syndrome is characterised by systemic chronic inflammation, associated with metabolic disruption and muscle wasting, among other symptoms. We have shown before (Matos-Neto et al., 2015) that the tumour of cachectic cancer patients (CC) actively expresses and secretes inflammatory factors to a significantly larger extent, when compared with biopsies from weight-stable counterparts (WSC). We now discuss the role of extracellular vesicles, particularly of exosomes (EXS:30-150 nm, CD63, *nanosight*), in the inflammatory inter-tissue/organ cross-talk in colorectal cancer patients (diagnosed as in Fearon et al., 2011). The data contrasting CC and WSC show cachexia decreases ($p<0.0001$) the number of circulating exosomes. We also examined the characteristics and number of EXS secreted by tumour explants (whole tissue) obtained from the patients, having found that CC tumours secrete augmented numbers of these vesicles, which also carry different inflammatory factors, as compared with those detected for WSC tumour explants. The EXS derived from CC tumours are enriched ($p<0.05$) with TNF α, IL-8, and Hsp 70 (the latter was found to be correlated with patient C-Reactive protein and BMI ($p<0.02$, $r= 0.68$). Proteomic analysis of EXS load also confirmed increased Hsp presence within EXS in CC, in regard to WSC. Finally, we shall address novel findings regarding the results of peptidomic analysis (semi-quantitative analysis by isotope-labelled electrospray mass spectrometry) of EXS load in the 2 groups, which demonstrates particular peptides to be present in cachexia.

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I3 *(15 minutes)*

Chronological vs biological age: implications for cachexia

Alessandro Laviano, Italy

I4 *(15 minutes)*

Mitochondrial dysfunction in colon cancer: already occurring in the primary-stage to further worsen in liver metastasis

Klaske van Norren
Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

Background: Colon cancer (CC), the third most common cancer worldwide, is accompanied by cachexia in 30% of patients. Its associated muscle loss directly impairs therapeutic response and survival. Early intervention is crucial, yet the underlying mechanisms of early-stage muscle dysfunction remain unclear. We (see Li et al) investigated mitochondrial function in skeletal muscle across different CC stages to identify early metabolic alterations.
Methods: In rectus abdominus muscle biopsies from primary CC patients, colorectal cancer patients with liver metastasis, and age-matched controls non-cancer patients mitochondrial oxygen consumption was assessed. Both mitochondrial activity (using high-resolution respirometry) as gene expression were assessed (RNAseq).
Results and Conclusions: Our findings reveal stage-specific mitochondrial dysfunction in CC, with early complex I impairment and a transient transcriptional adaptation in primary CC. These alterations precede clinical cachexia, suggesting mitochondrial dysfunction as a potential early biomarker for cancer-induced muscle loss and a target for early intervention.
Aim of the presentation at the 2025 cachexia conference: 1) To discuss with you the relevante of comparing different stages of the cancer cachexia trajectory. 2) To engage you in a discussion about mechanisms behind a reduction in muscle mitochondrial activity in an early stage of the muscle loss trajectory.

References:

Li X; et al; Primary-Stage Colon Cancer Impairs Muscle Energy Metabolism by Suppressing Mitochondrial Complex I Activity; JCSM; https://doi.org/10.1002/jcsm.70117
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Mitochondrial dynamics in cancer-induced cachexia. Biochim Biophys Acta Rev Cancer. 2018;1870(2):137-50; doi: 10.1016/j.bbcan.2018.07.008.

J1 *(15 minutes)*

EORTC QLQ 30 and its physical functioning domain and EORTC-QLQ-C15-PAL

Markus Anker, Germany

J2 *(15 minutes)*

EORTC QLQ-CAX24

Richard Skipworth
Clinical Surgery, University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, UK

The EORTC QLQ-CAX 24 is a novel endpoint designed specifically for cancer patients with cachexia. It was developed with combined input from both patients and health care practitioners. In this talk, we will describe and discuss the development of this questionnaire tool, and the emerging evidence for its use within clinical studies and interventional trials.

J3 *(15 minutes)*

Stair Climb Power Test and 6 Minute Walk Test

Andrew Coats, Australia

J4 *(15 minutes)*

Morbidity & mortality outcomes

Tim Friede, Germany

K1 *(15 minutes)*

Do hypertrophying muscles reprogram their metabolism like cancer cells?

Henning Wackerhage
Technical University of Munich, TUM School of Medicine and Health, Munich, Germany

One hundred years ago, Otto Warburg posed the question: *"How does the metabolism of growing tissue differ from that of resting?"* Using cancers and embryos as models, Warburg discovered that growing tissues take up glucose at a high rate and release a fraction as lactate. The reason for such metabolic reprogramming remained unclear for decades. Today, it is understood that many cancers shift their metabolism towards glycolysis because glycolysis not only supports ATP production but also provides intermediates for anabolic pathways such as the pentose phosphate pathway and non-essential amino acid synthesis (DeBerardinis and Chandel 2016). Several lines of evidence suggest that a similar, cancer-like metabolic reprogramming occurs in hypertrophying skeletal muscle. First, glycolytic type 2 fibres hypertrophy more than oxidative type 1 fibres. Second, key regulators of cancer metabolism, including Myc and the PI3K–Akt–mTOR pathway, are activated during muscle hypertrophy. Third, enzymes associated with cancer metabolism such as PHGDH and PKM2, are expressed in hypertrophying muscle and can limit growth (Wackerhage, Vechetti et al. 2022). Importantly, muscle hypertrophy influences not only intramuscular but also systemic metabolism. Pharmacological activation of muscle growth through mTORC1, β_2-adrenergic, myostatin, or testosterone signalling generally exerts anti-obesity and anti-diabetic effects, whereas muscle atrophy promotes metabolic dysfunction. In agricultural science, the shift of metabolites toward muscle growth and away from adipose tissue is known as *repartitioning*. We hypothesize that such repartitioning may offer an alternative or complementary strategy to semaglutide-induced weight loss in humans. Finally, to further research this, we have in March 2025 started the DFG-funded Research Unit **HyperMet (FOR 5795)** to elucidate the metabolic mechanisms that underlie skeletal muscle hypertrophy and atrophy.

References:
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Wackerhage, H., I. J. Vechetti, P. Baumert, S. Gehlert, L. Becker, R. T. Jaspers and M. H. de Angelis (2022). "Does a Hypertrophying Muscle Fibre Reprogramme its Metabolism Similar to a Cancer Cell?" Sports Med.

K2 *(15 minutes)*

Tumor-borne ADAMTSL4 drives cancer cachexia via activation of the TGFβ signalling pathway

Juliano Machado[1,2,3], Vignesh Karthikaisamy[1,2,3], Doris Kaltenecker[1,2,3], Pauline Morigny[1,2,3], Pia Benedikt-Kuehnast[1,2,3], Amit Mhamane[1,2,3], Julia Geppert[1,2,3], Amy Rose Fumo[1,2,3], Hermine Mohr[1,2,3], Estefania Simoes Fernandes[1,2,3,4], Anastasia Georgiadi[1,2,3], Joanna Darck Correia Lima[4], Marilia Seelaender[4], Jose Pinhata Otoch[5], Marc E. Martignoni[7], Olga Prokopchuk[6,7], Maria Rohm[1,2,3], Stephan Herzig[1,2,3,8], & Mauricio Berriel Diaz[1,2,3]

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Cancer cachexia (CCx) is a multifactorial wasting syndrome characterized by involuntary body weight loss and associated with reduced quality of life and survival in patients with cancer. [1]
Here, we show that elevated circulating levels of the tumor-derived glycoprotein ADAMTSL4 are associated with the development of cachexia in various preclinical models of CCx, as well as in cachectic patients from independent cohorts of colorectal, pancreatic, and lung cancer.
Using xenograft mouse models implanted with non-cachexia-inducing tumors engineered to stably overexpress *Adamtsl4*, as well as cachexia-inducing tumors with stable *Adamtsl4* knockdown, we demonstrate that increased tumor-derived ADAMTSL4 is both necessary and sufficient to drive cachexia, as well as the wasting of white adipocytes and myotubes *in vitro*. Mechanistically, using ligand-receptor capture technology followed by LC-MS/MS analysis and co-immunoprecipitation assays, we identified the latency-associated peptide (LAP1) of TGF-β1 as an ADAMTSL4-interacting protein on the surface of muscle cells, leading to local activation of TGF-β1.
Genetic and pharmacological inhibition of TGF-β1 or TGF-β receptor signaling attenuated not only wasting but also the activation of a fibrosis-related transcriptional program in both murine and human adipocytes and muscle cells exposed to recombinant ADAMTSL4. In addition, suppression of tumor-derived ADAMTSL4 *in vivo* reduced skeletal muscle fibrosis and downregulated fibrosis-related gene expression in adipose tissue and heart. Notably, in cachectic cancer patients, elevated circulating ADAMTSL4 levels correlated with increased expression of TGF-β-related fibrosis- and atrophy-associated genes in skeletal muscle.
Collectively, our data highlight the central role of ADAMTSL4 in promoting TGF-β1-mediated tissue wasting and fibrosis and suggest the therapeutic potential of targeting ADAMTSL4 to treat cancer cachexia.

References:

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K3 *(15 minutes)*

Integration of single nucleus multi-omics with spatial transcriptomics identifies the molecular signature of muscle wasting in cancer cachexia

Marco Sandri
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One third of cancer death is due to cachexia, a metabolic syndrome for which effective therapeutics have yet to be developed. We have shown that diminished Bone Morphogenic Protein (BMP) signaling is observed with the onset of skeletal muscle wasting associated with cancer cachexia in mouse models and in human cancer patients and promoted myofiber denervation[1,2]. Here, by combining single nucleus (sn) multiomic approach, spatial transcriptomic and human derived neuromuscular organoids (NMOs) we have characterized the cellular and gene networks underpinning cancer-induced cachexia and developed a multi target RNA based therapy to counteract this syndrome. Our findings revealed that FoxOs drove the catabolic signature in different cell types during cachexia. The simultaneous inhibition of FoxO1, 3 restored a normal BMP signaling and resulted in anabolic, anti-catabolic and pro-neurotrophic action in tumor bearing mice and human NMOs. These findings pave the way for an innovative therapy that will match with the concept of precision medicine and could be broadly applied to many other muscle wasting diseases.

References:
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K4 *(15 minutes)*

The role of skeletal muscle fibrosis in cancer cachexia

Andy Judge
University of Florida, USA

Previous work from our lab has identified clinically significant skeletal muscle fibrosis in cachectic pancreatic ductal adenocarcinoma (PDAC) patients that correlated with increased body weight loss and decreased survival (Judge et al. JNCI Cancer Spectr). We subsequently found an increased abundance of collagen type IV in PCAD muscle compared to non-cancer patients, and increased remodeling/damage of collagen type I (D'Lugos et al. JCI). The replacement of muscle with fibrotic tissue is a well-established consequence of myofiber stress, or damage, immune cell infiltration that is non-resolute, and proliferation of fibroadipogenic progenitor cells - each of which are demonstrated to occur in pre-clinical models of PDAC cachexia (Neyroud et al. J Cachexia Sarcopenia Muscle) and cachectic PDAC patients (Judge et al. JNCI Cancer Spectr). Recently published (D'Lugos et al. JCI) and ongoing work in our lab ties these pathologies to activation of the complement system, and our findings in this regard will be presented.

References:
Skeletal Muscle Fibrosis in Pancreatic Cancer Patients with Respect to Survival. Judge SM, Nosacka RL, Delitto D, Gerber MH, Cameron ME, Trevino JG, Judge AR. JNCI Cancer Spectr. 2018 Jul;2(3)

Complement pathway activation mediates pancreatic cancer-induced muscle wasting and pathological remodeling. D'Lugos AC, Ducharme JB, Callaway CS, Trevino JG, Atkinson C, Judge SM, Judge AR. J Clin Invest. 2025 Apr 8;135(12)

Local Inflammation Precedes Diaphragm Wasting and Fibrotic Remodelling in a Mouse Model of Pancreatic Cancer. Neyroud D, D'Lugos AC, Trevino EJ, Callaway CS, Lamm J, Laitano O, Poole B, Deyhle MR, Brantley J, Le L, Judge AR, Judge SM. J Cachexia Sarcopenia Muscle. 2025 Feb;16(1)

L1 *(12 minutes)*

COPD cachexia

Annemie Schols, The Netherlands

L2 *(12 minutes)*

CKD cachexia

Angela Wang, Singapore

L3 *(12 minutes)*

Heart failure with cachexia

Wolfram Doehner, Germany

L4 *(12 minutes)*

Recent advances in Cancer Cachexia. Research in chronic illness – update 2025

Egidio Del Fabbro
Medical College of Georgia, Augusta University, Augusta, GA, USA

Multi-center phase III clinical trials with promising agents are planned or underway.

1. Anti-GDF-15 agents

Ponsegromab, a monoclonal antibody to GDF-15, improved weight, appetite, skeletal muscle and spontaneous physical activity in patients with lung, pancreatic and colorectal cancer (CRC)[1]. benefit occurred even in patients with the least metabolic reserve (grade 4 cachexia), previously considered 'refractory' to therapy. The most effective dose will be compared to monthly placebo SC injections in a multi-center trial of patients with pancreatic cancer. Another monoclonal antibody, Visugromab, begins a phase II/phase III multicenter placebo-controlled trial (VINCIT) next year in patients with lung, gastrointestinal cancer. Weight and appetite are primary measures at 12 weeks with function, physical activity and safety as secondary outcomes. Although these agents appear to increase appetite via the hindbrain, they may also decrease tumor resistance to immunotherapy[2].

2. Anabolic / anti-catabolic

Espindolol demonstrates pro-anabolic, anti-catabolic, and appetite-stimulating effects through β and central 5-HT1α receptors. Late phase trials are planned following a multicenter phase II study [3] showing improved weight and hand grip strength.

Testosterone levels are low in most men being treated for cancer. Replacement therapy may mitigate muscle wasting and improve libido. Fatigue is the primary outcome of an active multi-center Phase III study comparing testosterone gel to placebo in older men with cancer.

Anamorelin, a ghrelin agonist approved only in Japan for cancer cachexia, has demonstrated good tolerability. Other agents in this class are being investigated.

3. Nutrition Intake (NIS)

Nutrition Impact Symptoms compromise patients' desire or ability to eat. Aggregate symptoms correlate with adverse outcomes. Olanzapine, recommended by ASCO cachexia guidelines, has broader applications for symptoms contributing to decreased oral intake, such as nausea and depression.

Multimodal therapy

If these single agents prove to be effective in phase III trials, perhaps combination therapies (pharmacologic and non-pharmacologic) with additive or synergistic effects, should be evaluated in future.

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L5 *(12 minutes)*

Cachexia in neurological diseases

Fabrizio Stocchi, Italy

M1 *(15 minutes)*

Emerging signaling mediators in cancer cachexia

Benjamin R. Pryce[1], Abasi-ama Udeme[1], Carlos Alfaro-Quinde[1], Emma Funk[1], Spencer Miller[1], Jenna Schwesig[1], Anna Crawford[2,3], Brian Neelon[2,3], Michael C. Ostrowski[2,4], Teresa A. Zimmers[5], David J. Wang[1], and Denis C. Guttridge[1,2]

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Although systemic inflammation is considered a hallmark feature of cancer cachexia, it is only recently that the field has been able to appreciate that this feature goes beyond the elevation of circulating cytokines by also encompassing a more local inflammatory environment in peripheral tissues that likely contributes to overall weight loss. This local inflammation, now described in murine adipose, brain, muscle, liver, and bone, is dominated by a myeloid phenotype, consisting mainly of monocyte/macrophages and neutrophils. $CD11b^+$ cells accumulate in tissues during cancer cachexia in association with elevated levels of inflammatory cytokines and chemokines. Recently, we showed that muscle inflammation during cancer cachexia is regulated by NF-κB, whose signaling pathway is activated in multiple cell types within the muscle microenvironment. While NF-κB activity in skeletal muscle stem cells was previous shown to impair muscle regeneration and promote muscle wasting, this signaling pathway in progenitor cells also regulates chemokines to attract infiltrating monocytes into cachectic muscle. NF-κB plays a similar role in myofibers and fibro-adipogenic precursor cells to mediate local muscle inflammation. Our recent efforts focus on understanding differences in subtypes of macrophages and their activities in regulating muscle wasting in cancer and how these cells diverge from macrophage subtypes in the tumor microenvironment under potential similar control by NF-κB. We also seek to understand how NF-κB regulated expression of GDF15 mediates its suppressive activity on immune cells, relevant in pancreatic tumor growth and cachexia.

M2 *(15 minutes)*

The NLRP3 inflammasome signaling pathway in CKD cachexia

Robert H Mak, Hoffman HM
University of California San Diego, USA

Inflammasomes are intracellular multi-protein complexes that form and become activated in response to pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPS). The most well studied inflammasome is the NLRP3 (cryopyrin) inflammasome, which is nucleated by NLRP3. When triggered, NLRP3 oligomerizes with the adaptor protein ASC and the effector protein, caspase-1, resulting in cleavage and activation of caspase-1. Active caspase-1, in turn, cleaves the inactive cytokines, pro-IL-1β and IL-18, to their active forms, IL-1β and IL-18, which can then be released from the cell and exert many inflammatory effects in numerous tissues. The NLRP3 inflammasome is activated by a number of DAMPs including crystals, various toxins, nucleic acids, and reactive oxygen species, positioning this complex as a key sensor of cellular stress. Much of this work has been performed using *Nlrp3* knockout mice. NLRP3 has therefore been implicated in numerous common inflammatory and non-inflammatory diseases including gout, neurodegenerative disease, atherosclerosis, heart failure, fatty liver disease, and acute and chronic kidney disease.

We initially discovered *NLRP3* when we identified heterozygous gain-of-function mutations in patients with a spectrum of inherited autoinflammatory diseases known as the cryopyrin associated periodic syndromes (CAPS). This is supported by the finding that immune cells from CAPS patients have a hyperactive inflammasome and release more IL-1β than cells from controls. We have generated and reported on 3 novel conditional mutant *Nlrp3* knockin mice with a similar, but more severe phenotype to that observed in CAPS patients including systemic inflammation affecting skin, joints, and the CNS. As very few of these mice reach adulthood when the mutation is expressed constitutively, we have also generated inducible mice which develop a similar systemic disease phenotype as an adult allowing for more comprehensive analysis. Our mice have also been treated effectively with a novel NLRP3 specific inhibitor known as MCC950.

Cachexia is prevalent in patients with chronic kidney disease(CKD) and is characterized by anorexia, elevated metabolic rate and weight loss. It is a complex disorder associated with inflammation and metabolic imbalances, resulting in muscle and adipose tissue wasting as well as incapacitating muscle weakness. We demonstrated in a mouse model of CKD cachexia that the NLRP3 inflammasome pathway plays an important role. Wild type C57Bl6 mice with CKD (induced by 5/6 nephrectomy) demonstrated the cachexia syndrome, with anorexia, hypermetabolism and muscle and adipose tissue wasting. Muscle and adipose tissue in wild type CKD mice showed increased expression of the components of this inflammasome pathway: NLRP3, ASC and Capase 1. Mice with a gain-of-function mutation of NLRP3 demonstrated a cachexia phenotype similar to CKD mice. *NLRP3, ASC* and *Capase* 1 null mice did not demonstrate the cachexia phenotype despite the induction of CKD. CRID3 (a NLRP3 inhibitor) administration prevented cachexia in wild type CKD mice. The metabolic pertubations associated with muscle wasting and adipose tissue browning in CKD cachexia are either corrected or ameliorated in mice with null mutation of the inflammasome components as well as in the wild-type CKD mice treated with CRID3. We conclude that the NLRP3 inflammasome pathway has a major role in the pathophysiology of CKD cachexia and the blockade of this pathway represents a novel therapeutic strategy for this devastating co-morbidity of CKD associated with very poor prognosis and for which there is no effective treatment.

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M3 *(15 minutes)*

Markers and mediators of cachexia in pancreatic cancer

Teresa Zimmers, USA

M4 *(15 minutes)*

Novel insights in molecular and cellular mechanisms of pulmonary cachexia

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Cachexia associated with respiratory disease and lung cancer is referred to as pulmonary cachexia. Chronic obstructive pulmonary disease (COPD) is characterized by a high prevalence of cachexia, which has a major impact on patients' quality of life, comorbidities and even survival [1]. While its prevalence and consequence on outcome in COPD is continuously confirmed in additional studies [2], treatment options for cachexia remain very limited.
In this presentation novel insights in tissue wasting dynamics in COPD will be highlighted [3]. The latest evidence supporting or opposing a role for previously implicated [4] triggers of muscle wasting in COPD such as hypoxia [5] and inflammation [6] will be discussed, as well as newly identified mechanisms [7] involved in muscle mass loss in pulmonary cachexia.

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N1 *(15 minutes)*

Changes to muscle mass during weight cycling

Paul Titchenell, USA

N2 *(15 minutes)*

Muscle function during pharmacological and physiological weight loss in humans

Philip J Atherton
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Obesity and type II diabetes present increased risk of morbidity that increases with age. As a countermeasure, weight loss may be achieved through voluntary calorie restriction or novel therapies involving incretin hormone receptor agonism. The acute effects of GLP-1 (glucagon-like peptide 1) on older humans' skeletal muscle metabolism include an increase in muscle blood flow and reciprocal increases in glucose-disposal **(1)**, perhaps owing to GLP-1 receptors present on vascular cells. Notably, in older humans, GLP-1 infusions also enhance muscle protein anabolism **(2)** suggesting direct effects on muscle cells (albeit GLP-1r expression has been queried on myocytes), since prior studies infusing the vasodilator methacholine failed to enhance muscle protein anabolism. In sum, acute GLP-1 actions exert positive impacts on skeletal muscle glucose and protein metabolism.

In a chronic setting GLP-1r modifying like therapies induce weight loss primarily through reducing satiety. Similarly, VLCD (very-low calorie diets) induce marked weight loss, depending upon the degree of calorie restriction. Both approaches induce weight loss and improvements in glycaemic control, although a concern of energy restriction is loss of lean tissue, especially in older humans. In respect to this latter aspect, we investigated **(3)** lean tissue loss with long-term VLCD and/or semaglutide. While all approaches induced loss of lean tissue this was relatively modest and did not result in significantly impaired muscle function.

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N3 *(15 minutes)*

The effect of GLP-1RA on muscle loss during immobilization

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Incretin-based therapies like GLP-1 receptor agonists (RA) have revolutionized the treatment of cardiometabolic diseases. Despite their remarkable success, clinical trials have reported that the loss of lean mass accounts for an alarmingly high portion (~40%) of overall weight loss [1,2], exceeding the commonly expected ~25% ("quarter fat-free mass rule") [3]. This has raised concerns that GLP-1-based drugs may accelerate muscle wasting and sarcopenia. However, lean mass does not necessarily reflect skeletal muscle, and direct evidence for detrimental effects of incretin mimetics on muscle mass and function remains limited. To address this knowledge gap, we compared the effect of a mono-agonist (GLP-1RA, semaglutide) and a dual agonist (GLP-1RA + glucagon [GCG] RA, survodutide) with pair-feeding (i.e., calorie restriction) in mice [4]. We assessed changes in muscle mass and the muscle proteome under conditions of exacerbated wasting induced by unilateral hindlimb immobilization. Additionally, we examined the effects of these distinct modes of weight loss on liver mass and substrate content. Despite comparable reductions in food intake, body weight, and muscle mass across groups, the muscle proteome exhibited robust and distinct alterations. Furthermore, despite similar body weight changes, significant group differences were observed in liver mass as well as hepatic glycogen and triglyceride content. In conclusion, GLP-1RA and GLP-1RA + GCGRA treatments produced similar effects on body weight and muscle mass compared to calorie restriction but led to pronounced alterations in the muscle proteome, liver weight, and hepatic substrate content in mice under subchronic treatment and immobilization-induced wasting. This suggests that GLP-1RA and GLP-1RA + GCGRA have distinct, indirect, and weight loss-independent effects on skeletal muscle and the liver.

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N4 *(15 minutes)*

Pharmacological improvements in weight regain

David Glass, USA

O1 *(15 minutes)*

Neuromuscular disorders in the ICU in 2025

Joerg Schefold, Switzerland

O2 *(15 minutes)*

ICU-acquired weakness: are we creating survivors or victims?

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Intensive care unit acquired weakness (ICUAW) is a clinically diagnosable form of neuromuscular organ failure caused by critical illness, immobility, and systemic inflammation. Affecting up to 50% of mechanically ventilated patients, ICUAW is characterised by severe skeletal muscle wasting, polyneuropathy, and myopathy, which lead to long-term physical, functional, and psychosocial impairments. Despite advances in intensive care, many survivors experience ongoing disability and reduced quality of life – raising the question of whether survival alone can still be considered success.

ICUAW is a key contributor to Post-Intensive Care Syndrome (PICS), which includes physical, cognitive, and mental health domains. Risk factors for the physical aspect involve disease severity, immobility, sedation, corticosteroids, and sepsis.

The prevention of ICUAW and PICS requires an integrated approach, such as the ABCDEF bundle. ABCDEF stands for Assess, Prevent, and Manage Pain; Both Spontaneous Awakening and Breathing Trials; Choice of Analgesia and Sedation; Delirium Assessment, Prevention, and Management; Early Mobility and Exercise; and Family Engagement and Empowerment. Recently, it was proposed to extend the ABDEF bundle with the healing environment to the A2I bundle, with G = “gaining insight into patients’ needs,” H = “holistic and personalised care,” and I = “ICU design redefinition.”

Besides the A2I bundle, prehabilitation concepts can also be applied in the ICU for elective surgical patients. Furthermore, structured post-ICU follow-up programmes or PICS outpatient clinics are promising strategies for restoring function and reintegrating patients into daily life.

Two multicentre initiatives address important topics. **ERUPT** (www.erupt-study.eu) aims to characterise current rehabilitation practices, quantify mobilisation “dose–response” effects, and identify predictors of recovery. The **PICS-DACH** registry (www.pics-dach.eu) aims to investigate PICS and long-term outcomes, including molecular mechanisms of muscle dysfunction. These efforts underline a paradigm shift from survival to survivorship, emphasising recovery, resilience, and rehabilitation as essential outcomes of modern critical care.

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O3 *(15 minutes)*

Muscle and brain dysfunction associated with long-term mechanical ventilation

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The acquired quadriplegia with complete or partial myosin loss in limb muscles (Critical Illness Myopathy, CIM), the prolonged weaning caused by the ventilator induced diaphragm dysfunction (VIDD) and the cognitive dysfunction (ventilator associated brain injury, VABI) associated with long-term mechanical ventilation and immobilization are common negative consequences in modern critical care. CIM, VIDD and VABI have staggering negative consequences on health care costs, morbidity/mortality and patient quality of life, but underlying mechanisms remain elusive, and treatments are typically symptomatic. It is hypothesized that the lung injury caused by positive pressure mechanical ventilation plays an important role in CIM/VIDD/VABI pathophysiology together with additive negative effects of the “mechanical silencing” on limb muscles. To test this hypothesis, treatments with mechanical/electrical stimulation and extracellular vesicles (EVs) derived from bone marrow derived mesenchymal stromal cells targeting the lung injury have been investigated in 5-day mechanically ventilated rats were compared with untreated mechanically ventilated rats. Our hypothesis was supported by the restoring effects of the EV treatment on VIDD/VABI/CIM and mechanical/electrical stimulation on CIM. The current results support a link between lung injury and CIM/VIDD/VABI and EV treatment and muscle loading are forwarded as interventions to alleviate the negative effects

O4 *(15 minutes)*

Sarcopenia of uncertain pathogenesis: the case of systemic sclerosis (SSc)

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Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by progressive fibrosis, widespread vasculopathy, and immune dysregulation [1]. Endothelial cell activation and damage are early pathogenic events, leading to capillary rarefaction, defective angiogenesis, and chronic tissue hypoxia. While skin and internal organ involvement have long been recognized, skeletal muscle (SM) wasting and functional decline, defining sarcopenia, are increasingly identified as major systemic manifestations of SSc, associated with disability, frailty, and higher mortality [2]. The prevalence of sarcopenia in SSc ranges widely (10–50%), but its mechanisms remain poorly understood.

Emerging evidence suggests that sarcopenia in SSc cannot be solely attributed to malnutrition or reduced physical activity. Instead, microcirculatory failure appears to play a central role. Impaired angiogenesis, capillary loss, and altered perfusion may limit oxygen and nutrient delivery to myofibers, inducing metabolic stress, mitochondrial dysfunction, and anabolic resistance. These processes create a self-perpetuating loop in which microvascular injury drives SM loss, while reduced muscularity further compromises vascular homeostasis. Nailfold capillaroscopy and skeletal muscle perfusion studies have revealed that capillary loss correlates with reduced muscle mass and the occurrence of digital ulcers in SSc, supporting a shared microvascular origin for both manifestations [3].

Beyond structural and metabolic mechanisms, microRNAs (miRNAs), potent post-transcriptional regulators involved in fibrosis, angiogenesis, inflammation, and SM homeostasis, may also contribute to SSc-related SM atrophy, as suggested by our recent finding of differential miRNA expression associated with muscularity in SSc patients [4]. Our central hypothesis is that sarcopenia in SSc may arise, at least in part, from impaired microcirculation and dysregulated molecular signaling, rather than solely from nutritional or disuse mechanisms.

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P1 *(15 minutes)*

GLP1-based therapy and cardiac wasting

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GLP1RA therapy is frequently used in obese patients with many comorbidities. The prersentation will discuss what is known about changes in body composition with a focus on changes in cardiac muscle mass in pre-clinical models and clinical trials. Avoiding cardiac muscle loss in the context of a non-hypertrophied cardiac phenotype at baseline may be preferable. Possible adverse consequences of loss of left ventricular mass will be discussed.

P2 *(15 minutes)*

Healthy weight throughout life (impact of exercise on muscle wasting in obesity therapy)

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Background:
Obesity is a chronic, relapsing condition associated with increased risk of cardiometabolic disease, infertility, and premature mortality. Achieving and maintaining a healthy weight throughout life is therefore crucial, yet long-term success is challenged by biological adaptations that favor weight regain and loss of muscle mass during weight reduction. Preservation of lean tissue is essential for sustaining metabolic health, physical function, and long-term weight control.
Methods:
Our Clinical Translational Metabolism Group investigates mechanisms and interventions that support lifelong healthy weight while preserving muscle mass. Through large-scale randomized clinical trials, we evaluate the individual and combined effects of exercise, dietary modification, and GLP-1 receptor agonist treatment on weight loss, muscle health, and metabolic outcomes. Complementary cohort and prevention studies target early-life and intergenerational risk factors.
Results:
Findings from our clinical trials demonstrate that combining GLP-1 receptor agonist therapy with structured exercise not only enhances weight loss and cardiometabolic benefits but also effectively preserves muscle and bone mass, counteracting treatment-induced sarcopenia. Exercise remains the primary determinant of long-term weight maintenance and metabolic resilience after pharmacological or dietary intervention. Early lifestyle interventions may further reduce obesity risk across generations.
Conclusion:
Sustaining a healthy weight across the lifespan requires interventions that integrate biological, behavioral, and environmental dimensions. Our translational research provides evidence for safe, effective, and personalized strategies that promote fat loss while preserving muscle mass, thereby supporting lifelong metabolic health and sustainable obesity treatment outcomes.

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P3 *(15 minutes)*

The Veru experience

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Enobosarm, an oral, novel SARM, has demonstrated in previous 6 clinical studies (1800 subjects) changes in body composition with increases in lean mass and decreases in fat mass, improvements in muscle strength and physical function, no masculinizing effects in women, and neutral prostate effects in men. A positive Phase 2b, placebo-controlled, randomized, dose-finding QUALITY clinical trial was conducted to evaluate enobosarm 3mg, enobosarm 6mg, or placebo as a treatment to augment fat loss and to prevent muscle loss in 168 older patients with obesity receiving semaglutide (Wegovy®) for weight reduction. In this study, older patients who have obesity receiving GLP-1 RA were at higher risk for accelerated loss of lean mass with physical function decline. Enobosarm treatment preserved lean mass which translated into a reduction in the proportion of patients that had a stair climb physical function decline versus subjects receiving semaglutide alone. The study also confirmed that preserving lean mass with enobosarm plus semaglutide led to greater fat loss during the active weight loss period, and after semaglutide was discontinued, enobosarm monotherapy significantly prevented the regain of both weight and fat mass during the maintenance period such that by end of study there was greater loss of fat mass while preserving lean mass for a higher quality weight reduction compared to the placebo. Next, we plan to initiate in early 2026 a Phase 2b PLATEAU clinical study which will evaluate enobosarm 3mg on total body weight, physical function and safety in 200 patients who have obesity and are initiating GLP-1 RA treatment for weight reduction. The primary efficacy endpoint will be total body weight at 72 weeks. An interim analysis will be conducted at 36 weeks to assess lean body mass and fat mass, as measured by DXA. The key secondary endpoints will be total fat mass, total lean mass, physical function (stair climb test), bone mineral density, and patient reported outcome questionnaires for physical function. The Phase 2b PLATEAU clinical study is designed to assess the ability of enobosarm treatment to break through the weight loss plateau observed in patients with obesity receiving GLP-1 RA treatment to achieve clinically meaningful incremental weight reduction by preserving lean mass and physical function at 72 weeks.

P4 *(15 minutes)*

Weight loss drugs and cardiovascular health:
The Actimed experience

Andrew Coats
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Obesity is a chronic complex disease defined by excessive deposits of fat and associated with an increased risk of developing type 2 diabetes and heart diseases and others chronic diseases.
Obesity itself can lead to loss of muscle mass and function, and obese individuals have a high prevalence of underlying chronic diseases that can negatively impact muscle metabolism[1].

GLP1-RAs are widely used for weight management including weight loss and weight maintenance in obese patients. In clinical studies of GLP-1Ras, weight reduction is primarily attributed to the loss of fat mass, however, studies have reported that losses of lean body mass can account for approximately 40% of the total weight reduction observed[2,3].
Whilst loss of body fat in an obese population is desirable, in view of the importance of lean body mass for the maintenance of overall health, the loss of lean body mass is an unwanted effect and a potentially serious concern, particularly for older or frail patients or patients with co-morbidities. Moreover, cessation of GLP-1RA therapy can result in a rebound in body weight in favor of fat mass and at the expense of lean body mass, resulting in a less favorable muscle to fat ratio[4].

ACTIMED THERAPEUTICS is focused on bringing innovation to the treatment of muscle wasting disorders, including cancer-related cachexia and sarcopenic obesity and muscle loss associated with weight loss treatment including glucagon-like peptide 1 receptor agonists (GLP-1RA).
S-pindolol benzoate is a new salt of S-pindolol in clinical development for cancer-related cachexia and muscle wasting associated with GLP-1RA therapy.
In view of its multi-modal action, our lead product (S-pindolol) has been referred to as an Anabolic, Catabolic Transforming Agent (ACTA)
This new class of agents may have multiple effects on the fundamental biology of muscle wasting to reduce catabolism (weight loss), increase and maintain anabolism (weight gain, particularly muscle mass gain), decrease fatigue, and improve appetite.

Actimed has implemented a development programme to investigate the potential benefit of S-pindolol when used during and after GLP-1RA therapy in obese patients. This programme involving nonclinical and clinical studies will evaluate the potential for S-pindolol to improve the fat to lean mass ratio in situations of rapid and significant weight loss.

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Q1 *(15 minutes)*

Muscle-brain axis, exercise and nutrition

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Sarcopenia, physical frailty, and cognitive decline are increasingly recognized as interrelated geriatric conditions that share common biological mechanisms and are functionally connected through the so-called muscle–brain axis.[1] Growing evidence indicates that the deterioration of musculoskeletal health is not only a peripheral phenomenon but also closely linked to neurocognitive impairment in later life. Within the geroscience paradigm, these conditions are conceptualized as consequences of converging age-related molecular pathways, including mitochondrial dysfunction, chronic low-grade inflammation, metabolic dysregulation, impaired regenerative capacity, and altered intracellular signaling.[2] Such mechanisms contribute simultaneously to skeletal muscle wasting and neuronal vulnerability, thereby supporting a bidirectional relationship between muscle and brain aging.

A central element of this interaction is the neuromuscular junction (NMJ), a specialized synapse that mediates communication between motor neurons and muscle fibers. NMJs undergo structural and functional destabilization with advancing age, a process associated with muscle atrophy, motor unit loss, and impaired neural transmission. Parallel to NMJ degeneration, circulating metabolic and neurotrophic mediators, particularly myokines such as brain-derived neurotrophic factor (BDNF), play a regulatory role in muscle–brain crosstalk. Disruptions in these signaling pathways have been associated with increased risk of frailty, sarcopenia, and cognitive decline, suggesting that skeletal muscle tissue may function as both a target and a source of neuroprotective factors.[3]

Current evidence highlights lifestyle-based interventions as the most effective strategies for simultaneously preserving muscle integrity and cognitive function.[1] Resistance and power training counteract muscle wasting, promote NMJ remodeling, and enhance motor performance, while aerobic exercise supports mitochondrial biogenesis, reduces oxidative stress, and stimulates the release of neurotrophins involved in synaptic plasticity. Nutritional interventions, especially protein supplementation and adherence to Mediterranean-style dietary patterns rich in antioxidants, polyphenols, and anti-inflammatory nutrients, further contribute to maintaining muscle mass, metabolic homeostasis, and cognitive resilience.

A more comprehensive understanding of the shared mechanistic pathways linking sarcopenia and cognitive decline may enable the development of multimodal therapeutic approaches, integrating physical exercise, targeted nutrition, and potentially pharmacological agents. Such strategies would not only address age-related muscle loss and neurodegeneration in parallel but also strengthen preventive care models aimed at extending healthy lifespan in aging populations.

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Q2 *(15 minutes)*

GDF15 regulation of energy expenditure and nutrient preference: implications for cancer cachexia

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Abstract:
Growth differentiation factor 15 (GDF15) is a stress-responsive cytokine that signals through its brainstem receptor GFRAL to regulate systemic energy balance and metabolism (Wang *et al.*, *Nat Rev Endocrinol* 2021). Our recent studies show that GDF15 not only suppresses appetite but also enhances whole-body energy expenditure by activating a GFRAL–β-adrenergic axis that increases fatty acid oxidation and calcium cycling in skeletal muscle, maintaining thermogenesis during caloric restriction (Wang *et al.*, *Nature* 2023). In parallel, GDF15 alters food choice, reducing intake of energy-dense foods and promoting fatty acid utilization (Wang *et al.*, *Diabetes* 2023). Together, these findings define GDF15 as a key signal linking nutrient stress to adaptive changes in fuel selection and energy expenditure. Understanding this pathway may help explain the metabolic basis of cancer cachexia and identify strategies to mitigate wasting while preserving metabolic function.

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Q3 *(15 minutes)*

Cancer cachexia: miRNAs, inflammation and beyond

Federica Tambaro
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Cancer cachexia is a complex metabolic syndrome characterized by severe skeletal muscle wasting, adipose tissue depletion, and systemic inflammation, profoundly impacting both survival and therapeutic response. Although inflammation has long been recognized as a central driver, cachexia is increasingly understood as a multidimensional disorder in which metabolic, neuroendocrine, and molecular alterations intertwine in a self-sustaining vicious cycle [1].
Within this loop, chronic inflammation activates catabolic and stress-response pathways, exacerbating mitochondrial dysfunction, while tissue wasting further amplifies systemic inflammation through the release of cytokines, reactive oxygen species, and damage-associated molecular patterns (DAMPs) [2].
Recent evidence highlights microRNAs (miRNAs) as pivotal regulatory elements within this network, capable of fine-tuning transcriptional programs that govern proteolysis, lipid mobilization, and immune modulation. However, whether miRNA dysregulation represents a causal mechanism or an adaptive response to the cachectic state remains unresolved. Distinct miRNA expression signatures identified in cachectic patients indicate that their modulation may not depend solely on inflammatory stimuli but also reflect broader metabolic stress and tissue-specific remodeling processes [3]. Moreover, tumor- and host-derived miRNAs, circulating within extracellular vesicles, contribute to inter-organ communication, reinforcing the wasting-inflammation axis.
Elucidating the intricate feedback among inflammation, miRNA signaling, and metabolic derangement is crucial to move beyond descriptive models of cachexia and toward integrative frameworks that can disentangle causality and uncover actionable molecular targets for intervention.

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Q4 *(15 minutes)*

Immuno-metabolic crosstalk in cancer cachexia

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Cachexia is a wasting disorder causing high morbidity and mortality in patients with cancer. We have recently described cachexia as a multi-level metabolic disease, wherein tumour-derived mediators trigger bioamplification and tissue crosstalk mechanisms which exaggerate and independently contribute to wasting (Berriel Diaz & Rohm et al. *Nat Metab* 2024).

Inflammation is a prime example for a process that amplifies wasting signals: Tumours release proinflammatory factors, causing a systemic inflammatory state, and the resulting activation of the immune system contributes to wasting as immune activation consumes energy and activates muscle and adipose tissue wasting, exemplified by the prominent role of interleukin 6 in promoting cachexia in tumour bearing mice (Bindels et al. *Oncotarget* 2018).

Here, I provide evidence for an additional bioamplification process involving metabolic reprogramming across tissues. Applying integrated RNA sequencing, metabolomics and ^{13}C-glucose tracing in multiple tissues of C26 tumour-bearing mice at different disease stages, we identified one-carbon metabolism as a tissue-overarching pathway characteristic for cachexia. Its over-activation is linked to inflammation, myotube atrophy, and unexpected glucose hypermetabolism in muscle (Morginy et al. *unpublished a*).

We have previously identified elevated levels of circulating ceramides as defining feature of murine and human cachexia (Morigny & Zuber et al. *JCSM* 2020). Here, I discuss the importance of liver-derived ceramides as mediators of tissue crosstalk, causing mitochondrial dysfunction in muscle. Targeting (liver) ceramide synthesis proved effective in counteracting muscle weakening by improving mitochondrial function (Morigny et al. *unpublished b*).

Overall, we provide a molecular framework to understand metabolic reprogramming involved in bioamplification and tissue crosstalk mechanisms, with the aim to identify targetable disease mechanisms driving cachexia.

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R1 *(10 minutes)*

AI in imaging

Faisal Beg, Canada

R2 *(10 minutes)*

Design of multifunctional antibodies with generative AI and high-throughput data iteration

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Our generative protein design platform integrates structure-informed modeling with high-throughput digital biotechnology to enable scalable functional antibody discovery. In an obesity and muscle wasting therapeutic program, dual-binding antibodies generated by this system achieved sub-picomolar potency—over 50-fold higher than current candidates and surpassing clinical benchmarks across early functional metrics. From design to characterization, the complete cycle was accomplished within nine weeks, demonstrating a data-driven, efficient approach to next-generation therapeutic development with minimal experimental overhead.

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R3 *(15 minutes)*

Unifying the sarcopenia terminology – primary / secondary / tertiary sarcopenia

Stephan von Haehling, Germany

T1 *(15 minutes)*

A 3D-tissue-engineering toolbox to model skeletal muscle pathology

Pim Pijnappel, The Netherlands

T2 *(15 minutes)*

Incorporation of macrophages into engineered skeletal muscle models

Nenad Bursac, USA

T3 *(15 minutes)*

Human neuromuscular organoids mimic cancer-induced muscle cachexia

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Cancer cachexia, a devastating metabolic wasting syndrome, affects up to 80% of solid cancer patients and remains incurable despite significant advances in our understanding of tumor biology[1-3]. No existing multicellular and tridimensional in vitro models derived from human cells are available to simultaneously recapitulate the phenotypes observed in a cachectic muscle, which include muscle contraction impairment, and cellular and molecular alterations. Moreover, currently available in vivo and in vitro models not always allow the study of cachexia in a context more relevant to patients[3]. Here we introduce an advanced in vitro platform to investigate cancer-driven muscle cachexia using neuromuscular organoids (NMOs)[4-5] derived from human induced pluripotent stem cells (hiPSCs). Our research demonstrates that NMOs effectively respond to atrophic stimuli and successfully replicate key features of cancer cachexia when exposed to conditioned media derived from cachexia-inducing cancer cells. The cachectic NMOs exhibited several hallmark characteristics of the syndrome, including significant muscle mass loss, impairment of muscle contraction, alteration of intracellular calcium homeostasis, mitochondrial dysfunction, metabolic shift, and enhanced autophagy. These findings strongly support the potential of hiPSC-derived NMOs as an innovative and potentially patient-specific in vitro tool for investigating human muscle cachexia, for dissecting the pathogenetic mechanisms, providing a platform for screening and testing therapeutic approaches. We suggest that such tool can contribute accelerating the development of effective treatments for this debilitating condition, ultimately improving the quality of life for cancer patients worldwide. Future research will focus on further validating this model and exploring its applications in personalized medicine and drug discovery.

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T4 *(15 minutes)*

Synergistic Effects of Substrate Composition and Mechanical Cues on Muscle Cell Differentiation and Maturation: Clinical and Experimental Perspectives

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The differentiation and maturation of muscle cells are profoundly influenced by the biochemical and mechanical properties of their microenvironment. Recent in vitro studies demonstrate that specific substrate compositions—particularly those incorporating extracellular matrix proteins such as laminin, fibronectin, and collagen—enhance myogenic marker expression and myotube formation compared to uncoated or single-component surfaces. Moreover, substrates with specific tissue-like stiffness optimize striation, multinucleation, and gene expression.
Mechanical cues, including aligned topographies, microgrooves, cyclic strain, and electrical stimulation, independently promote cell alignment, fusion, and sarcomere organization. When combined with optimized substrate compositions, these mechanical interventions produce clear synergistic effects, leading to enhanced cell fusion, improved striation, and greater overall myotube density.
Building on this foundation, our research focuses on the relative contribution of microenvironmental characteristics induced by mechanical ventilation and the specific vulnerability of the diaphragm compared to limb muscles such as the quadriceps. This clinical question, central to understanding ventilator-induced diaphragmatic dysfunction, motivated the development of a novel in vitro model: a stretchable and biofunctionalized PDMS scaffold micropatterned via UV photolithography and covalently grafted with ECM-derived RGD peptides. This platform reproduces mechanical constraints similar to those imposed by mechanical ventilation and enables parallel testing of diaphragmatic and quadriceps muscle cells from the same patient, offering a framework to disentangle the relative influence of muscle-specific properties and microenvironmental characteristics.
This approach bridges fundamental muscle biology with clinically relevant questions, offering perspectives for both mechanistic research and therapeutic strategies.

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U1 *(15 minutes)*

Myostatin and activin inhibitors as a treatment for sarcopenia in obese patients

Ken Attie
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Myostatin and activin inhibitors are being investigated as treatments for low muscle mass, or sarcopenia, in obese patients. Sarcopenia is typically defined as age-associated loss of muscle mass and function. Low muscle mass occurs not only with aging, but also with diabetes, disuse atrophy, and reduced protein intake, including appetite suppression for obesity. Low muscle mass and altered muscle quality are associated with reductions in both physical and metabolic function.

Sarcopenic obesity has proved more difficult to define.1 While guidelines exist to classify obesity and overweight, sarcopenia requires evidence of reduced lean mass (e.g., imaging). Muscle mass reduction alone does not always correlate with functional decline. For patients with obesity and a demonstrated impact on physical capacity, we suggest the term Mobility-Limited Obesity (MLO).
Myostatin and activin A are natural inhibitors of muscle growth. Blocking these can be achieved with ligand antibodies or traps, receptor antibodies, and newer technologies. Myostatin-specific antagonists result in significant muscle growth in rodents, whereas blocking activin A is important in primates, especially with aging. Depending on modality and population, muscle growth of 2-6% is typically observed.

Interventions with broader activin pathway inhibition can have effects on both muscle and fat mass. These could lead to benefits in inflammation and insulin sensitivity. Activin type II receptor Abs can inhibit myostatin and activin A in muscle as well as potentially activin pathways in adipose tissue. A study in healthy volunteers with activin receptor antibody bimagrumab prevented muscle loss due to low protein intake.2 In obesity with T2D, bimagrumab treatment led to increased muscle mass, and decreases in fat mass, visceral fat, hepatic fat, and HbA1c.3

The BELIEVE study (N=507) of bimagrumab and semaglutide, alone and in combination, showed additive fat mass reduction and preservation of lean mass when combined.4 Bimagrumab was associated with decreased visceral fat and hsCRP, and increased adiponectin. Adverse events such as muscle cramps and diarrhea were observed with bimagrumab. Future studies of activin pathway inhibitors are being explored to complement obesity treatments and address sarcopenic obesity by preventing further muscle loss.

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U2 *(15 minutes)*

GHSR1a antagonism for sarcopenic obesity

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Sarcopenia, characterized by the progressive loss of muscle mass and strength, poses a significant public health challenge, particularly among the elderly. Affecting over 50 million individuals globally, its prevalence is expected to quadruple in the next 40 years. Despite its clinical impact, there are currently no approved pharmacologic treatments. Our research investigates the therapeutic potential of GHSR1a antagonism in addressing sarcopenic obesity, a condition marked by concurrent muscle degeneration and increased adiposity. Using aged C57BL/6J mice, we observed that GHSR1a inverse agonism mitigates age-related declines in muscle function by enhancing mitochondrial biogenesis, mitophagy, and myogenesis. These effects were accompanied by reductions in food intake, body weight, and fat mass, and improvements in treadmill performance. Notably, sex-specific differences were identified, with male mice exhibiting pronounced declines in muscle contractility and mitochondrial function, while female mice showed attenuated sarcopenic progression. Our findings underscore the importance of targeting mitochondrial pathways and highlight GHSR1a as a promising candidate for therapeutic intervention. This research contributes to a deeper understanding of the molecular mechanisms underlying sarcopenia and offers a foundation for future clinical applications.

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U3 *(15 minutes)*

Enobosarm

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Enobosarm, an oral, novel SARM, has demonstrated in previous 6 clinical studies in 1800 subjects improvements in body composition with tissue selective increases in lean mass and decreases in fat mass, improvements in both muscle strength and physical function, no masculinizing effects in women, and neutral prostate effects in men. A Phase 2b, multicenter, double-blind, placebo-controlled, randomized, dose-finding QUALITY clinical trial was conducted to evaluate the safety and efficacy of enobosarm 3mg, enobosarm 6mg, or placebo as a treatment to augment fat loss and to prevent muscle loss in 168 patients with obesity (≥60 years of age) receiving semaglutide (Wegovy®) for weight reduction. The completed positive Phase 2b QUALITY study is the first human study to report the effects of a muscle preservation drug candidate on body composition in older patients who have obesity and receiving a GLP-1 receptor agonist. Further, the Phase 2b QUALITY clinical trial is the first human study to demonstrate that older patients who have obesity receiving GLP-1 RA are at higher risk for accelerated loss of lean mass with physical function decline. Enobosarm treatment preserved lean mass which translated into a reduction in the proportion of patients that had a clinically significant stair climb physical function decline versus subjects receiving semaglutide alone. The Phase 2b QUALITY and Maintenance Extension clinical trial confirmed that preserving lean mass with enobosarm plus semaglutide led to greater fat loss during the active weight loss period, and after semaglutide was discontinued, enobosarm monotherapy significantly prevented the regain of both weight and fat mass during the maintenance period such that by end of study there was greater loss of fat mass while preserving lean mass for a higher quality weight reduction compared to the placebo group. It is expected that the strategy to preserve lean mass and physical function will increase energy expenditure coupled with the direct effects of enobosarm for additional selective reduction in fat mass will result in incremental weight reduction in a longer clinical study in patients who have obesity.

U4 *(15 minutes)*

Impact of the ACTA s-pindolol on muscle mass during and after GLP1-RA therapy

Andrew Coats, Australia

V1 *(15 minutes)*

Contribution of the endothelium to adipose tissue loss in cancer cachexia

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Cancer cachexia is driven by tumor and host-derived factors, which circulate through the bloodstream. In muscle and adipose tissue, endothelial cells form a tight barrier that prevents free diffusion of proteins from blood to parenchymal cells. Therefore, it remains to be determined how these factors reach myocytes and adipocytes and how the endothelium is involved. We know that solid tumors can alter endothelial gene transcription not only in blood vessels within the cancer mass but also at distant sites. This plays a role in metastasis but might also affect tissue wasting. We are using mouse models of cancer-induces pre-cachexia to study endothelial changes in white adipose tissue, skeletal and cardiac muscle. We observed striking changes in endothelial gene expression patterns upon tumor growth affecting mostly gene programs associated with inflammation and metabolic control. In adipose tissue, cancer-induced hyperactivation of Notch1 signaling promotes expression of leukocyte adhesion facts and chemokines leading to higher infiltration of myeloid cells. In addition, endothelial cells express higher levels of genes involved in vitamin A conversion into retinoic acid. Retinoic acid production was further enhanced by endothelial secretion of IL-33 acting on myeloid cells and adipocytes. Such supraphysiological retinoic acid levels impaired adipocyte regeneration and promoted fibrosis. Using inhibitors of retinoic acid prevented wasting of adipose tissue in a pancreatic cancer model.

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V2 *(15 minutes)*

The tumor-bone-muscle axis in cancer cachexia

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Sex differences in cancer cachexia are well recognized, with males typically showing more severe manifestations, but the underlying mechanisms remain unclear (1). Because cancer cachexia is increasingly linked to bone deterioration (2,3,4) and osteocytes play a central role in bone remodeling and bone–muscle crosstalk, we investigated whether sex influences musculoskeletal decline and osteocyte reprogramming during tumor burden using the Lewis Lung Carcinoma (LLC) model. Male and female C57BL/6 mice received LLC cells and were analyzed after three weeks for muscle mass, bone microarchitecture, mechanical strength, and osteocyte transcriptomics; co-culture systems further examined tumor–bone–muscle interactions. LLC induced a markedly more severe phenotype in males, with greater muscle loss, bone deterioration, and reduced femoral strength. RNA-seq revealed strong downregulation of bone formation and matrix mineralization pathways in both sexes, but the suppression was more pronounced in males, whose osteocytes showed broad inhibition of osteogenic, mechanotransduction, lipid metabolic, and innate immune pathways, along with increased expression of osteoclast-activating genes. In contrast, female osteocytes activated innate immune and metabolic defense programs despite suppressing adaptive immunity. In vitro, LLC cells elicited a stronger inflammatory response in male osteocytes, and only conditioned media from tumor-exposed male osteocytes induced C2C12 myotube atrophy. These findings indicate that osteocytes adopt sex-specific adaptive strategies during CaC, with females displaying greater resilience and males exhibiting broader anabolic and immune dysfunction. Tumor-derived factors appear to reprogram male osteocytes toward a more pro-inflammatory, catabolic phenotype that likely contributes to the more severe musculoskeletal deterioration observed in males, positioning osteocytes as sex-dependent regulators of bone–muscle homeostasis and as potential therapeutic targets in cancer cachexia.

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V3 *(15 minutes)*

The RNA-binding protein HuR impairs adipose tissue anabolism in pancreatic cancer cachexia

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Cachexia is a frequent complication of pancreatic ductal adenocarcinoma (PDAC), and adipose tissue loss negatively impacts patient outcomes [1]. This work contributes to a growing body of data showing that impaired anabolism contributes to adipose wasting in PDAC-bearing mice [2]. Adult C57BL/6J mice received orthotopic PDAC cell (*Kras^{G12D}; p53$^{R172H/+}$; Pdx1-cre*) (PDAC) or PBS (sham) injections. Mice exhibiting moderate cachexia were fasted for 24h, or fasted 24h and refed 24h before euthanasia. We analyzed body mass, gross fat pad mass, and adipose tissue mRNA expression. We quantified lipolytic rate as the normalized quantity of glycerol released from 3T3-L1 adipocytes *in vitro*, and gonadal fat pads (gWAT) *ex vivo*. 3T3-L1 adipocytes treated with PDAC cell conditioned media (CM) liberated less triglyceride into the culture media than control-treated adipocytes and had lower expression of lipolysis and lipogenesis genes than control cells. PDAC gWAT cultured *ex vivo* displayed decreased lipolysis compared to sham gWAT. PDAC and sham mice lost equivalent fat mass after a 24h fast, however, PDAC mice could not restore inguinal fat pads (iWAT) or gWAT mass after refeeding. RNAseq revealed 572 differentially expressed genes in gWAT from PDAC compared to sham mice. Downregulated genes were associated with adipogenesis, and expression of adipogenesis master regulators *Pparg* and *Cebpa* was reduced in gWAT from PDAC mice. Immunohistochemistry revealed increased Human Antigen R (HuR) staining in gWAT and iWAT from PDAC mice. HuR is an RNA-binding protein recently shown to suppress adipogenesis [3]. A separate cohort of PDAC mice was treated with an established HuR inhibitor (KH-3, 100 mg/kg) and subjected to the fast/refeed paradigm. Inhibiting HuR binding resulted in increased iWAT mass. Our work highlights deficient adipose anabolism as a driver of lipid-droplet loss in 3T3-L1 adipocytes treated with PDAC conditioned media and PDAC mice.

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V4 *(15 minutes)*

The critical role of the ovary in colorectal cancer and treatment-induced cachexia

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Successful cancer treatment includes improved survival and quality of life, which are negatively impacted by skeletal muscle loss and metabolic dysfunction. While the mechanistic basis of cancer-induced muscle wasting, metabolic dysfunction, and reduced physical function has been widely investigated in preclinical models, until relatively recently, the translational path forward for these findings has been impacted by the limited understanding of how sex and cancer treatment interact with the mechanisms identified as drivers of cachexia. Historically, the examination of cancer-induced cachexia has focused on tumor-related factors and has not accounted for the effect of chemotherapy treatment, which has strong potential to alter the outcomes in cancer patients. Our mechanistic understanding of chemotherapy's consequences on skeletal muscle metabolism and function has been mainly limited to acute toxicities, often independent of the cancer. Although 5-fluorouracil (5-FU) based chemotherapy treatments, such as Folfox (5-FU, leucovorin, oxaliplatin), can impact skeletal muscle and are widely prescribed for colorectal cancer treatment, the mechanistic cellular underpinnings of colorectal cancer and 5-FU chemotherapy interactions are poorly understood. Furthermore, males and females have been shown to have a differential response to cancer-induced muscle wasting in several preclinical models. We have a limited understanding of how sex impacts the regulation of muscle wasting with cancer and treatment. Our lab and others have previously shown in established preclinical models of colorectal cancer cachexia and treatment that females are resistant to cachexia compared with male mice and exhibit altered sensitivity to circulating IL-6, which is related to gonadal function. Importantly, as with many cancer patients, male and female mice become hypogonadal during cachexia in several preclinical models, which may be associated with increased muscle IL-6 sensitivity. We are now exploring the interactive effects of cancer and FOLFOX chemotherapy on decreased gonadal function in male and female mice. The overall premise of this talk is that the ovary plays a critical role in skeletal muscle regulation of mass and metabolism in the female, a role that can be disrupted by cancer and treatment.

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W1 *(8 minutes)*

Phase 1 trial in healthy participants of KER-065, modified activin receptor ligand trap, supports development in sarcopenia and neuromuscular disorders (8-03)

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Sarcopenia is a progressive and debilitating condition characterized by the pervasive loss of skeletal muscle mass, strength, and function. KER-065 is a modified investigational activin receptor ligand trap designed to inhibit muscle catabolism by blocking activins and myostatin. In preclinical models, KER-065 demonstrated significant anabolic effects on skeletal muscle and bone. Here, we report initial results from a first-in-human trial evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics (PD) of KER-065 in healthy male participants

This double-blind, placebo-controlled trial was conducted in two parts: Part 1, where participants received a single dose (1, 3, or 5mg/kg), and Part 2, where three Q4W doses (1.25 or 2mg/kg) were administered. Beyond safety and PK, exploratory assessments specifically evaluated KER-065's impact on body composition through serum biomarkers, dual-energy X-ray absorptiometry (DXA), and magnetic resonance imaging (MRI).

A majority of the observed treatment-emergent adverse events were mild to moderate in severity, with no dose-limiting toxicities or serious adverse events. The PD analyses revealed anabolic and metabolic effects:

- **Increased Lean Body Mass:** KER-065 significantly increased total lean body mass as measured by DXA.
- **Increased Muscle Volume:** MRI analyses confirmed a direct increase in thigh muscle volume.
- **Improved Body Composition:** KER-065 reduced whole-body and visceral fat mass (via DXA), supported by favorable changes in adipokines (adiponectin and leptin).
- **Bone Anabolic Activity:** KER-065 increased bone mineral density and serum markers of bone formation, supporting overall musculoskeletal health.
- **Changes in structural remodeling proteins** were observed by serum-wide proteomic analysis using SomaScans.

KER-065 was generally well tolerated. The PD analyses provide compelling evidence of robust target engagement, resulting in a direct anabolic effect on skeletal muscle—increasing mass and volume while favorably altering overall body composition. These findings support the continued development of KER-065 as a potential therapy to counteract the core pathophysiology of sarcopenia.

W2 *(8 minutes)*

Efficacy and safety of ponsegromab in patients with cancer-associated cachexia: results from the open-label extension of a randomized, placebo-controlled, phase 2 study (8-07)

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Introduction: Ponsegromab, a growth differentiation factor 15 (GDF-15)–targeted antibody, improved body weight, symptoms, physical activity, and muscle mass in patients with cancer cachexia in a 12-week, double blind phase 2 trial (Part A; NCT05546476). We report findings from the 1-year, open-label extension (Part B).
Methods: Participants with cancer cachexia and serum GDF-15 ≥1500 pg/mL received subcutaneous (SC) ponsegromab (100, 200, 400 mg) or matching placebo Q4W during Part A. At 12 weeks, participants could pursue open-label treatment with ponsegromab 400 mg Q4W SC through Week 64 (Part B). Change in body weight and safety were assessed through Weeks 64 and 72, respectively.
Results: Of 137 participants completing Part A, 117 (85.4%) participants (44.4% non-small cell lung, 29.1% colorectal, and 26.5% pancreatic cancer; 70.9% stage 4) entered Part B. Median (IQR) age and weight at baseline were 68 (61–74) years and 54.7 (46.0–63.8) kg, respectively. Overall, progressive weight gains were observed with mean (SD) increases of 2.74 (4.89), 4.43 (5.95), and 5.18 (5.93) kg at Weeks 24, 52, and 64, respectively. Weight gains were lowest in Part A placebo participants (mean [SD] increases of 2.28 [3.41] kg versus 5.57 [4.48], 4.01 [6.78], and 7.61 [6.72] kg for the ponsegromab 100, 200, and 400 mg groups, respectively, at Week 64). All-cause and treatment-related adverse events were reported in 84.2% and 4.4% of participants from Weeks 12-72, respectively. None of the 23 deaths during Part B were related to treatment.
Conclusions: Improvements in body weight during 12-week Part A were maintained with ponsegromab through 64 weeks in Part B. Part A placebo participants showed weight stabilization during Part B, but weight gain was less than for Part A ponsegromab participants. Ponsegromab continued to be safe and well-tolerated through 72 weeks.

W3 *(8 minutes)*

Efficacy and safety of ponsegromab in patients with pancreatic cancer, cachexia, and elevated growth differentiation factor: insights from the Phase 2 PROACC-1 trial (8-05)

Eric J. Roeland[1], John D. Groarke[2], Susie M. Collins[3], Shannon Lubaczewski[4], Jeffrey Crawford[5], Tateaki Naito[6], Andrew E. Hendifar[7], Marie Fallon[8], Koichi Takayama[9], Timothy Asmis[10], Richard F. Dunne[11], Michelle Rossulek[12], Ruolun Qiu[13], Aditi R. Saxena[2]
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Background: Ponsegromab is a monoclonal antibody targeting growth differentiation factor 15 (GDF-15), a circulating cytokine implicated in cachexia. We report body weight and safety findings from participants with pancreatic cancer (PDAC) in a phase 2, randomized, double-blind trial of ponsegromab vs placebo in patients with cancer cachexia (PROACC-1; NCT05546476).
Methods: Patients with cancer, cachexia, and elevated serum GDF-15 (≥1500 pg/mL) were randomized 1:1:1:1 to receive subcutaneous ponsegromab (100, 200, 400 mg) or matching placebo every 4 weeks for 12 weeks. The primary endpoint was change from baseline (CFB) in body weight at 12 weeks. Safety and tolerability were key secondary endpoints.
Results: Overall, 59 (31.6%) of 187 participants randomized in this phase 2 study had PDAC (aged 64.4±9.9 years; 57.6% male). Baseline mean body weight was 57.1±11.9 kg; 47.5% and 50.8% had a body mass index <20 kg/m^2 and weight loss over the prior 6 months of ≥10%, respectively. There was an imbalance in the frequency of stage IV disease across treatment groups: placebo, 71.4%; 100 mg, 50.0%; 200 mg, 66.7%; and 400 mg, 92.9%. The observed mean (SD) CFB in body weight at Week 12 was −0.36 (1.94) kg for placebo compared to +0.65 (3.16), +1.72 (2.93), and +3.37 (5.54) kg for participants receiving ponsegromab 100, 200, and 400 mg, respectively. Placebo-adjusted LS mean weight gain with ponsegromab 400 mg was 3.29 kg (90% CI: 0.58, 6.00), *P*=0.02. All-causality and treatment-related adverse events occurred in 80.0% and 8.9% of ponsegromab-treated patients and 92.9% and 14.3% of placebo-treated patients, respectively. Nausea and diarrhea were reported less frequently among ponsegromab-treated than placebo participants: 8.9% vs 28.6% and 13.3% vs 21.4%, respectively.
Conclusion: Among patients with PDAC, cachexia, and elevated GDF-15 levels, GDF-15 inhibition with ponsegromab through 12 weeks was associated with body weight gain and was generally well tolerated.

W4 *(8 minutes)*

Biophytis: BIO101 (20E) as a drug candidate targeting the reduction of GLP1-RA-induced muscle mass or function loss in patients with obesity (8-09)

Waly Dioh[1], Mathilde Latil[1], Rob Van Maanen[1], Claudia Ferreira[1], Serge Camelo[1], Sandrine Rabut[1], Robin Deloux[1], Pierre J. Dilda[1], Jean Mariani[1,2] and Marc-Andre Cornier[3].
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Introduction: GLP-1 receptor agonists (GLP-1RAs) effectively reduce body weight. However, up to 40% of the total lost weight is lean body mass, including skeletal muscle mass. BIO101 (20-hydroxyecdysone; 20E), an oral MAS receptor activator, could be a promising treatment to prevent muscle mass or strength loss in patients with obesity or overweight treated with GLP-1RAs.
Methods: Preclinical studies of 20E-treated myoblasts and Diet-Induced Obese (DIO) mice (four weeks treatment of BIO101 in combination with a GLP-1RA) were completed to characterize muscular properties of 20E. In addition, a 12-week double-blind placebo-controlled study (6-week hypocaloric intervention phase + 6-week weight loss maintenance phase) with 37.5mg 20E was conducted in 58 participants with overweight or obesity (BMI ≥ 27 kg/m² and ≤ 38 kg/m²) aged 20-65 years.
Results: 20E has pro-differentiating effects *in vitro* in murine and human myoblasts, increasing myotube diameter. *In vivo*, BIO101, in combination with GLP-1RA, significantly improved animal mobility (endurance) and grip strength when compared to untreated group. Notably, the combination of drugs compensates for muscle contractility alterations induced by GLP-1RA.
In patients with overweight or obesity, 37.5mg 20E significantly decreased android fat mass (p=0.039). Biopsy analyses showed a statistically significant reduction in adipocyte diameter. Compared to placebo, a trend for improvement in handgrip strength occurred in the subpopulation with > 5% body weight loss *versus* baseline. Biophytis designed an interventional, randomized, double-blind, placebo-controlled clinical phase 2 trial targeting obese (BMI≥30) and overweight (BMI≥27) adults treated with semaglutide. Planned primary endpoint is muscle strength. Secondary endpoints include physical performance, body composition parameters and questionnaires.
Conclusions: Supported by these data, a phase 2 trial combining BIO101 plus GLP-1 RA was approved by competent authorities in USA and Belgium and will be initiated shortly. Interactions are ongoing with ethics committees. Biophytis will expand the trial to Brazil.
Disclosures: RvM, CF, ML, RD, SC, SR, PJD, JM WD are employees of Biophytis S.A.

W5 *(8 minutes)*

S-pindolol protects lean body mass and skeletal muscle during incretin-induced weight loss and regain in obese mice

Henning Langer, Germany

W6 *(8 minutes)*

Insights from the BELIEVE phase 2b trial of bimagrumab and semaglutide

Ken Attie, USA

X1 *(15 minutes)*

Optimising nutrition during systemic anti-cancer therapy (SACT)

Alessandro Laviano, Italy

X2 *(15 minutes)*

Holistic impact of cachexia on patients and informal caregivers

Joanne Reid
Chair of Cancer and Palliative Care, Queen's University Belfast

Internationally, cachexia is a severe but under-recognised issue in chronic illness. Cachexia is associated with increased morbidity and mortality, contributing to lower quality of life, elevated levels of depression and higher rates of hospitalisation. The holistic impact of cachexia spans bio-psycho-social domains affecting both people who have the syndrome and their informal caregivers. Empirical work has demonstrated that this profound impact is prevalent across chronic illnesses such as cancer (1), cardiac disease (2) and renal disease (3). Such work highlights the multidimensional ramifications and complex interplay between physical decline, social withdrawal and psychological impact for patients and informal caregivers. To address the burden of cachexia, optimal management should recognise and respond to the holistic impact of this syndrome (4). There is a clear need to raise awareness of the holistic impact of cachexia through education for healthcare professionals, patients, and informal caregivers. Reflective of its multifactorial pathogenesis, a multimodal therapeutic response should address the holistic impact of cachexia. To advance our efforts in person-centred care, the holistic effects of this syndrome on the whole person and the informal caregiver must be fully recognised and addressed.

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X3 *(15 minutes)*

Corticosteroids in cachexia care: who, where, when?

Dominik Modest, Germany

X4 *(15 minutes)*

Nutritional impact symptoms: elephants in the room

David Blum
Center for Palliative Care, University Hospital Zurich, Switzerland

Cachexia and malnutrition are frequent complications in patients with advanced disease and are associated with impaired therapeutic response, reduced quality of life, and decreased survival. Given the multifactorial pathophysiology of cachexia, a multimodal therapeutic approach is essential. Among the key determinants are nutritional impact symptoms (NIS), which are highly prevalent and encompass a broad spectrum of manifestations — from eating-related symptoms such as anorexia or xerostomia, to gastrointestinal disturbances such as nausea and constipation, and to general symptoms including pain, fatigue, or depression. These symptoms range from highly specific to nonspecific and may arise as a consequence of both the underlying disease and its treatment. As a result, responsibility for their recognition and management is often diffuse within the multidisciplinary care team.

A major challenge lies in the frequent coexistence of multiple NIS, which can cumulatively lead to a profound reduction in nutritional intake. Although no specific guidelines for the management of NIS exist, many of these symptoms are readily identifiable and amenable to targeted intervention. A systematic approach encompassing screening, comprehensive assessment, and individualized treatment is therefore recommended. In certain malignancies, such as head and neck or pancreatic cancer, NIS occur particularly frequently, and disease-specific management guidelines are available.

This presentation aims to underscore the prevalence and clinical significance of NIS, to discuss current diagnostic and therapeutic strategies, and to emphasize the need for greater awareness and systematic management of these common yet frequently overlooked and undertreated symptom.

References:

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Y1 *(15 minutes)*

Integrated evaluation of body composition in the oncology setting: paradigm change

David da Silva Dias
Universidade Católica Portuguesa, Faculty of Health Sciences and Nursing, Centre for Interdisciplinary Research in Health (CIIS), Lisbon, Portugal

Background:
Weight loss and muscle wasting are frequent in cancer patients, with sarcopenia impacting outcomes, chemotherapy toxicity, and postoperative complications. Computed tomography (CT) provides an accurate method for assessing sarcopenia.
Methods:
A retrospective multicentric cohort study included 202 patients with locally advanced gastric adenocarcinoma treated between January 2020 and December 2022. Sarcopenia was evaluated using CT scans at the L3 vertebral level with DAFS software. The study assessed its association with relapse-free survival (RFS), overall survival (OS), dose-limiting toxicity (DLT), and postoperative complications.
Results:
The mean age was 69 years; 65% of patients had ECOG 0, and 53% received perioperative FLOT chemotherapy. Mean skeletal muscle index (SMI) was 49.6 cm^2/m^2 in males and 40.9 cm^2/m^2 in females. SMI correlated positively, though moderately, with BMI - body mass index ($p < 0.01$; $r = 0.424$). Patients with below-average SMI showed no significant difference in RFS or OS but had higher risk of FLOT-related DLTs ($p = 0.021$; OR 2.56, 95% CI 1.15–5.73) and postoperative complications ($p = 0.024$; OR 2.16, 95% CI 1.11–4.21).
Conclusions:
Sarcopenia significantly increases the risk of chemotherapy toxicity and postoperative complications in locally advanced gastric cancer. However, its effect on overall survival appears to be less pronounced than in metastatic setting, possibly due to surgical intervention altering disease trajectory. Early detection of sarcopenia through CT imaging may serve as a valuable and precise tool to recognize patients requiring closer monitoring, chemotherapy dose optimization, and early referral for multimodal interventions, including pharmacologic therapy, exercise, and personalized nutritional support.

Y2 *(15 minutes)*

Nutrition, microbiome and cancer response to treatments

Paula Ravasco
Faculty of Medicine and and Centre for Interdisciplinary Research in Health, Universidade Católica Portuguesa; Centre for Interdisciplinary Research Egas Moniz (CiiEM), Instituto Universitário Egas Moniz (IUEM), Portugal

The relation between nutrition and the gut microbiome has emerged as a key determinant of cancer treatment outcomes. The composition and diversity of intestinal microorganisms shape host immunity, drug metabolism, and the efficacy of therapies such as chemotherapy, immunotherapy, and radiotherapy. The presence of bacterial genera like *Akkermansia muciniphila*, *Ruminococcaceae*, and *Lachnospiraceae* has been associated with improved responses to immune checkpoint inhibitors.

Nutrition acts as a primary modulator of the microbiome. Diets rich in fiber, plant-based foods, and Mediterranean-style patterns foster microbial communities that produce short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, which enhance intestinal barrier integrity, reduce systemic inflammation, and support cytotoxic immune cell activity. Conversely, Western dietary patterns (low in fiber but high in saturated fats and ultra-processed foods) promote dysbiosis, chronic inflammation, and poorer therapeutic responses.

Nutritional status, including muscle mass, protein intake, micronutrient sufficiency, and inflammation, further influence the microbiome and treatment efficacy. Patients with higher muscle mass and more favorable microbiota profiles show improved prognosis and better immunotherapy response. The microbiome also modulates drug metabolism: microbial enzymes can activate or inactivate chemotherapeutic agents, alter antigen presentation, and modify the tumor microenvironment, thereby contributing to therapeutic resistance or toxicity.

High-fiber diets promote the growth of beneficial bacteria such as *Faecalibacterium prausnitzii*, *Ruminococcus*, and *Akkermansia muciniphila*. These microbes produce short-chain fatty acids (SCFAs) that strengthen the intestinal barrier, reduce systemic inflammation, and enhance immune cell activation. In melanoma patients, higher fiber intake (>20 g/day) has been correlated with improved responses to PD-1 inhibitors. Specific probiotic strains (*Lactobacillus rhamnosus GG*, *Bifidobacterium longum*, *Akkermansia muciniphila*) can restore microbial balance, limit pathogenic overgrowth, and improve immune modulation. Clinical studies suggest probiotics may reduce chemotherapy-induced mucositis and diarrhea while supporting immunotherapy efficacy. However, strain selection and clinical context are critical, as non-targeted probiotics may have neutral or adverse effects. A Mediterranean diet has been associated with increased microbial diversity and anti-inflammatory metabolites. Prebiotics (inulin, FOS, GOS) selectively stimulate beneficial bacterial growth, while synbiotics combine prebiotics with probiotics. Both approaches enhance SCFA production, protect the gut mucosa, and may mitigate gastrointestinal side effects of chemotherapy and radiotherapy. Limiting processed meats, sugary beverages, and high-fat snacks can prevent dysbiosis and metabolic inflammation caused by lipopolysaccharide (LPS)-producing bacteria. Polyphenols and omega-3 fatty acids exert prebiotic-like effects, supporting microbial diversity and reducing inflammation. Vitamin D status also correlates with microbiome balance and improved immune function during cancer therapy.

The nutrition–microbiome–cancer treatment axis represents a rapidly evolving and promising frontier. Appropriate nutrition shapes a beneficial microbiome, which optimizes immunity and drug metabolism, ultimately improving treatment efficacy. A combined, personalized approach may profoundly influence precision oncology and clinical outcomes.

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Y3 *(15 minutes)*

Immunonutrition: Body of Evidence, Feasibility, and Limits

Marco Cintoni
Clinical Nutrition Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Research and Training Center in Human Nutrition, Catholic University of the Sacred Heart, Rome, Italy

Malnutrition and systemic inflammation are prevalent in cancer patients. These conditions create a vicious cycle leading to cachexia, immunosuppression, and poor treatment tolerance. Immunonutrition (IN) can be defined as nutritional formulas enriched with specific immunomodulating substrates, such as arginine, glutamine, omega-3 fatty acids, and nucleotides, as a therapeutic strategy to break this cycle.

The rationale for IN extends beyond standard nutritional goals.
It is well established that IN plays a pivotal role in surgical oncology, as endorsed by the latest ERAS and ESPEN guidelines. For patients undergoing major tumor surgery, IN is specifically recommended pre- or perioperatively to reduce complications.
Moreover, it actively targets the host's defense response to mitigate cytotoxicity, resolve chronic inflammation caused by tumor burden and therapy, and maintain mucosal barrier integrity. By modulating the immune microenvironment, IN aims to improve tolerance to antineoplastic treatments.

The evidence-based review focuses on three key areas within Medical Oncology and Radiotherapy:

- Mitigation of RCT-Induced Toxicity: Evidence indicates that IN significantly reduces the severity of toxicities, including oral mucositis, esophagitis, and diarrhea, in patients undergoing pelvic or head & neck radiation.
- Cancer Cachexia and Body Composition: In patients receiving chemotherapy, IN has been demonstrated to stabilize weight and preserve lean body mass.
- Modulation of Systemic Inflammation: Clinical data suggest IN can lower circulating levels of inflammatory markers during cytotoxic therapy.

Despite solid clinical evidence, widespread adoption is limited by feasibility challenges, including patient compliance issues related to palatability and mucositis-related pain. Future investigation must focus on identifying predictive biomarkers to personalize IN support for oncological patients.

Y4 *(15 minutes)*

NutrimiRomics: how close we are?

Maurizio Muscaritoli
Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

The beneficial effects of diet are partly mediated through the modulation of endogenous microRNA (miRNA) expression by bioactive dietary components. This well-established interaction between nutrition and miRNAs forms the foundation of NutrimiRomics, an emerging discipline that integrates omics sciences into nutritional research to investigate how diet influences gene regulation [1].
A central extension of this concept is the dietary xenomiR hypothesis, which proposes that food-derived miRNAs may cross biological barriers and modulate host gene expression, with potential implications for health and disease. The notion of cross-kingdom communication through dietary miRNAs has opened a provocative chapter in molecular nutrition [2]. Early reports detecting xenomiRs in animal and human samples suggested that exogenous RNAs might survive digestion, enter circulation, and regulate host genes. However, more than a decade of research has yielded conflicting evidence, hindered by methodological variability, contamination, and the extremely low abundance of foreign sequences [3].
Recent advances in high-throughput sequencing, extracellular vesicle characterization, and bioinformatic stringency have improved detection accuracy, yet the functional relevance of xenomiRs in humans remains uncertain. A more plausible scenario is that a small fraction of xenomiRs escaping gastrointestinal degradation may exert local rather than systemic effects, primarily through interactions with the gut microbiota. In this view, the microbiota may act as a biological interface, modulating the uptake, transformation, or indirect signaling of dietary miRNAs through host–microbe crosstalk. This shift of focus, from systemic gene silencing to local, microbiome-mediated effects, offers a more biologically grounded and experimentally accessible hypothesis [4].
If validated, this paradigm could open new perspectives for epigenetic modulation through diet, paving the way for precision nutrition and personalized therapeutic strategies.

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POSTER SESSIONS

Poster Session 1.1 **Muscle Wasting & Sarcopenia** (posters 4-25 to 4-36)
Chairs: Monty Montano, Stephan von Haehling

4-25
ANGPTL3 as a Modulator of Catabolic Signalling in Insulin-Resistant Skeletal Muscle
***Federica Tambaro*[1], *Valeria Pecce*[1], *Marcello Arca*[1] & *Maurizio Muscaritoli*[1]**
Department of Translational and Precision Medicine, Sapienza University of Rome, Italy

4-26
Structural and Metabolic Muscle Changes with Age: An MRI and MRS Perspective on Mobility
***Yves Fromes*, Jean-Marc Boisserie, Sophie Jouan, Mathias Duventru, B. Matot, Benjamin Marty, Harmen Reyngoudt**
Institute of Myology, Paris, France

4-27
Single-cell transcriptomics reveals cellular drivers of human skeletal muscle regeneration: implications for sarcopenia
***Thomas Nicholson*, Samuel Kemble, Charlotte G Smith, Jason Turner, Adam P Croft, Paul Hindle, Simon W Jones**
University of Birmingham, Birmingham. United Kingdom

4-28
Therapeutic potential of human Wharton's jelly-derived mesenchymal stem cells in an aged mouse model of sarcopenia
***Hyeongseop Kim*, Jang Bin Jeong, Hong Bae Jeon, Jong Wook Chang**
ENCell Co. Ltd., Seoul, Republic of Korea

4-29
Wharton's jelly-derived mesenchymal stem cells attenuate muscle atrophy in-vitro via secreted factor-mediated mechanisms
***HyunJu Kim*[1,2], *Hyeongseop Kim*[1,2], *Jong Wook Chang*[2,3]**
ENCell, Seoul, Republic of Korea

4-30
Automatic Muscle Segmentation for Faster and Easier Assessment of Muscle Trophicity in Sarcopenia and Neuromuscular Diseases Using MRI
***Carlier Pierre*[1,2], *Snezhko Eduard*[2,3], *Bardakov Sergei*[4], *Demonceau Georges*[2]**
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4-31
The adiponectin paradox and muscle mass in older adults: the influence of body fat distribution
***Fawzi Kadi*[1], *Andreas Nilsson*[1], *Laura Smeldy Jurado-Medina*[2], *Agnes A.M. Berendsen*[3], *Lisette C.P.G.M. de Groot*[3], *Joanna Kaluza*[4], *Ewa Sicińska*[4], *Nathalie Meunier*[5], *Corinne Malpuech-Brugere*[6], *Alberto Bazzocchi*[2], *Giuseppe Battista*[2], *Claudio Franceschi*[2], *Aurelia Santoro*[2]**
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4-32
Water distribution explains associations between phase angle and physical outcomes in older adults
Arnar Hafsteinsson, Alfons Ramel
Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland

4-33
Sarcopenic patient-derived myotubes exhibit fusion dysfunction using an automated image analysis pipeline
***Ling Liu*[1], *Hui San Chin*[1], *Jing Han Hong*[2], *Bin Tean Teh*[3], *Frederick Hong Xiang Koh*[4]**
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4-34
Association between intrinsic capacity and risk of dementia in older Mexican adults: analysis of the 2012 and 2015 waves of the Mexican Health and Aging Study
Miriam Teresa López Teros*, *Sara Gabriela Yeverino Castro*[2], *Fabiola Yocupicio Medrano*[1], *Sara Gloria Aguilar Navarro*[3]**
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4-35
Towards a Body Composition–Oriented Definition of Maximal Healthy Weight Loss in Patients with Obesity
Anja Bosy-Westphal*, *Manfred J Müller
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4-36
Risk of sarcopenia in people with long-term conditions and multimorbidity: a prospective UK Biobank study
***Marion Guerrero-Wyss*[1,2], *Carla M Prado*[3], *Bhautesh D Jani*[4], *Stuart Johnston*[5], *Stuart R Gray*[1,6], *Frederick K Ho*[4], *Carlos A Celis-Morales*[1]**
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Poster Session 1.2 **Cachexia – animal models** (posters 2-01 to 2-12)
Chairs: Xiling Shen, Jochen Springer

2-01
Skeletal muscle AMPKα2 as a regulator of muscle strength and fat mass in chemotherapy-induced cachexia
Haiming L. Kerr*, *Nornubari Myree*, *Elizabeth Dacek*, *Kora Krumm*, *Anthony Christiani*, *Jessica Li*, *Suah Kim*, *Jose M. Garcia
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2-02
CHOP chemotherapy induces sex-specific transcriptional changes in skeletal muscle of juvenile mice
***Michael P Wiggs*[1], *Jainil Daredia*[1], *Marc A Magaña*[1], *Carla MC Nascimento*[1], *Jaden M Wells*[1], *Nicholas T Thomas*[2,3], *Yuan Wen*[3,4], *Cory M Dungan*[1]**
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2-03
The role of interleukin-6 signaling in the pathogenesis of cancer-associated cachexia
***Sophia Chrysostomou*[1], *Isabella Pototschnig*[1], *Sandra Eder*[1], *Anna Bidovec*[1], *Martina Schweiger*[1]**
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2-04
Induced ablation of Prmt7 in endothelial cells aggravates cardiac cachexia induced by myocardial infarction
***Shibo Wei*[1], *Yan Zhang*[1], *Wonyoung Park*[1], *Yunju Jo*[1,2], *Jung Ho Han*[3], *June Kim*[4], *Jong-Sun Kang*[4], *Dongryeol Ryu*[1]**
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2-05
LDHA upregulation contributes to CKD-associated cachexia and muscle dysfunction
***Wonyoung Park*[1], *Shibo Wei*[1], *Yan Zhang*[1], *Yunju Jo*[1,2], *Jung Ho Han*[3], *Ki-Tae Ha*[4*], *Dongryeol Ryu*[1*]**
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2-06
Using a proximity labeling approach to investigate lung-secreted proteins in an inflammatory weight loss model
***Jack D Sanford*[1,2], *Philip Moon*[1,2], *Marcus D Goncalves*[1,2,3]**
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2-07
Concurrent chemo- and radiotherapy in an orthotopic lung cancer mouse model: a preclinical platform for studying treatment-induced cachexia
Peiyu Qiu*[1], *Justine M Webster*[1], *Behzad Rezaeifar*[2], *Frank Verhaegen*[2,3], *Annemie MWJ Schols*[1], *Wouter RPH van de Worp*[1]*, *Ramon CJ Langen*[1]
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2-08
Automated µCBCT-based body composition assessment in mice using a 3D nnU-Net model
***Behzad Rezaeifar*[1], *Justine M Webster*[2], *Lars HBA Daenen*[1], *Peiyu Qiu*[2], *Joël de Bruijn*[3], *Giulia Pötgens*[1], *Ramon CJ Langen*[2], *Wouter RPH van de Worp*[2*], *Frank Verhaegen*[1,3*]**
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2-09
Adipose tissue macrophages and IL-4 receptor signaling under hypercatabolic conditions
***Michaela Lang*[1], *Thomas Rauchenwald*[1], *Sandra Eder*[1], *Sebastian Forstreiter*[1], *Martina Schweiger*[1,2]**
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2-10
Ablation of FKBP5 counteracts cancer-induced musculoskeletal wasting
Felipe Polo[1], Paola Gonzalez[1], Joshua R. Huot[1,2,3,4]
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2-11
MEK inhibition rescues muscle wasting in C-26 tumor mice independent of muscle regeneration
Mikayla Kolpin, Jacqueline Ott, Ana Kronemberger, Erin E. Talbert
Department of Health, Sport, and Human Physiology, University of Iowa, Iowa City, IA, USA

2-12
Characterization of novel cancer cachexia preclinical models implementing chemotherapy and surgery
Emma Elisabeth Cappellato[1], Claudia Fornelli[1], Natalia Erica Cortez[1], Valentina Schiavo[1], Paola Costelli[1], Fabio Penna[1]
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Poster Session 1.3 **Cancer Cachexia** (posters 3-13 to 3-21)
Chairs: Mauricio Berriel Diaz, Paola Costelli

3-13
Body mass index but not percentage weight loss was associated with the race/ethnicity of patients with advanced lung cancer: A retrospective study.
Patricia S. Bramati[1*], Sonal Admane[1*], James Troyer[1], Yi Huang [2], Eduardo Bruera[1], Rony Dev[1]
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3-14
The influence of obesity on wasting during neoadjuvant chemotherapy in curative oesophagogastric cancer
Cathleen M. Grossart[1], Hesham Zalghana[1], Leo R. Brown[1], Richard J.E. Skipworth[1]
[1]Department of UGI Surgery, Royal Infirmary of Edinburgh

3-15
Body image distress associated with emotional distress but not cachexia in patients with advanced cancer
Rony Dev, Patricia Bramati, Marvin Omar Delgado Guay, Daniel Gilbey, Jegy Tennison, Josue Becerra, Eduardo Bruera
Department of Palliative Care, Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

3-16
Volumetric muscle phenotyping and cytokine dynamics (IL-6, GDF-15) in advanced biliary tract cancer: secondary analysis of a randomized trial
Laura Amira Kassem[1], Casper Simonsen[1], Simon Nørskov Thomsen[1], Julia Sidenius Johansen[2], Troels Dreier Christensen[2], Louise Lang Lehrskov[1,2]
[1]Centre for Physical Activity Research, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [2]Department of Oncology, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark

3-17
Testosterone replacement tHerapy in hypOgonadal male advanced canceR patients: preliminary results of THOR trial
***Alessandro Misotti*[1], *Silvia Colatruglio*[1], *Sabrina Corvasce*[1], *Giorgia Preziati*[1] , *Luca Zambelli*[2], *Ernesto Zecca*[2], *Valentina Ferri*[1], *Serena Della Valle*[1]**
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3-18
Proposal of a tool for screening the risk of cachexia in cancer patients
Thais Manfrinato Miola, Liane Brescovici Nunes de Matos, Susana da Rocha Dias
Department of Nutrition, ACCamargo Cancer Center, São Paulo, Brazil

3-19
HFA-PEFF and H_2FPEF scores in advanced cancer patients
***Iulia Baluta*[1,2,3], *Sara Hadzibegovic*[1,2,4], *Jan Porthun*[1,3,5], *Jonathan L. Hella*[1,2,4], *Danara Krug*[1,2,3], *Markus S. Anker*[1,2,4,6]**
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3-20
Determination of a novel prognostic variable based on body composition radiodensity in gastric cancer
***Daniela Padilha*[1,2], *Mariana Caleffi*[1], *Vinicius Bassete*[1], *Gianni Liveraro*[1], *Maria Emilia Seren Takahashi*[1], *Leo Victor Kim*[1], *Maria Carolina Santos Mendes*[1], *Jun Takahashi*[1], *José Barreto Campello Carvalheira*[1]**
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3-21
Elevated Lipocalin-2 Levels are Associated with Weight Loss and Anorexia in Patients with Gastrointestinal Cancer
***Giovanni Imbimbo*[1], *Federica Tambaro*[1], *Simona Orlando*[1], *Carmen Gallicchio*[1], *Maurizio Muscaritoli*[1] & *Alessio Molfino*[1]**
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Poster Session 1.4 **Muscle Wasting & Sarcopenia** (posters 4-37 to 4-48)
Chairs: Guilherme Fonseca, Joerg Schefold

4-37
Handgrip Strength <10 kg as a Saudi-Specific Cut-off for Sarcopenia in Women
***Nouf Aljawini*[1,2*], *Syed Shahid Habib*[2]**
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4-38
Handgrip strength and sit-to-stand performance as complementary markers of muscle function in patients with OSA and OHS
***Tatjana Kosten*[1], *Andraž Jug*[1], *Kristina Ziherl*[1,2], *Irena Šarc*[1,2]**
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4-39

Sex-specific associations between hand-grip strength and inflammatory markers in the general population

Sebastian Graeger*[1,2], *Sabine Ameling*[2,3], *Joany Mariño Coronado*[1,2], *Jens Fielitz*[1,2], *Christian Templin*[1,2], *Uwe Völker*[2,3], *Nele Friedrich*[2,4], *Marcello Ricardo Paulista Markus*[1,2], *Till Ittermann*[2,5]*, *Martin Bahls*[1,2]

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4-40

Predictive value of handgrip strength in muscle and malnutrition assessment

***Hanna Taleisnik Halimi*[1,2], *Neriya Levran*[1,3], *Nirit Agay*[4], *Dana Weiner*[1]**

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4-41

Low Masseter Muscle Volume and Risk of Cognitive Decline in Older Adults: A Longitudinal Analysis from the Bunkyo Health Study

***Saori Kakehi*[1,2], *Abudurezake Abulaiti*[2], *Hideyoshi Kaga*[3], *Hiroki Tabata*[2], *Ryuzo Kawamori*[1 2 3], *Hirotaka Watada*[2 3], *Yoshifumi Tamura*[1,2,3,5,6]**

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4-42

Sarcopenia in older individuals with hip fracture: study on the prevalence, correlation with obesity and ultrasonography of the rectus femoris

***Maurício Miyasaki*[1], *Rodrigo Andraus*[2], *Juliano Casonatto*[3], *Carolina Miyasaki*[4], *Bruno Baruki*[5], *Yano Sá*[5]**

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4-43

Effect of resistance exercise combined with β-hydroxy-β-methylbutyrate supplementation in older individuals with and without sarcopenia treated for hip fracture.

***Mauricio Rodrigues Miyasaki*[1], *Juliano Casonatto*[2], *Carolina Morgado de Mello Miyasaki*[3], *Yano Alto-Mar de Sá*[4], *Rodrigo Antonio Carvalho Andraus*[2]**

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4-44

Role of Growth Hormone Resistance In IGF-I Deficient Sarcopenic Patients

Michael Drey*, *Olivia Tausendfreund, Michaela Rippl, Sabine Schlüssel, Linda Deißler, Ralf Schmidmaier, Sebastian Martini, Katharina Schilbach, Martin Bidlingmaier

Department of Medicine IV, Geriatrics, University Hospital of LMU Munich, Germany

4-45
Low skeletal muscle mass and radiodensity are predictive of acute radiation-induced gastrointestinal toxicity in head and neck cancer patients
Mariana Vieira Barbosa[1], Hadria Karoline Furtado[1], Nilian Carla Silva Souza[2], Renata Brum Martucci[1]
[1]Universidade do Estado do Rio de Janeiro, [2]Instituto Nacional de Câncer

4-46
A Comprehensive Assessment of Sarcopenia and Sarcopenic Obesity in Prostate Cancer *Patients on Androgen Deprivation Therapy Using a Range of Validated Diagnostic Criteria*
Haya Khalaf[1], Ursula McGovern[2,3], Adrian Slee[1]*
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4-47
Serum irisin in women with obesity and sarcopenic obesity: insights into a distinct metabolic phenotype
Nouf Aljawini[1,2*], Syed Shahid Habib[2], Khalid Al-Regaiey[2]
[1]Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia; [2]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

4-48
Role of osteosarcopenia in predicting overall mortality among older adults with cancer undergoing colorectal cancer resection
Efthymios Papadopoulos[1], Brian A. Irving[1], Heather Allaway[1], Guillaume Spielmann[1], MingDe Lin[2,3], Kelly R. Finan[4]
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Poster Session 1.5 **Nutrition & Appetite** (posters 5-01 to 5-10)
Chairs: Alessandro Laviano, Paula Ravasco

5-01
The anti-inflammatory effects and safety of omega-3 fatty acids regarding dose, active ingredients, ratio and source in patients receiving haemodialysis: a systematic review and meta-analysis
Carolyn Blair[1]*, Adrian Slee[2], Clare McKeaveney[1], Peter Maxwell[3], Faizan Awan[4], Malcolm Brown[5], Andrew Davenport[6], Damian Fogarty[7], Denis Fouque[8], William Johnston[9], Kamyar Kalantar-Zadeh[10], Dr Robert Mullan[11], Helen Noble[1], Sam Porter[12], David S. Seres[13], Joanne Shields[7], Ian Swaine[14], Miles Witham[15], Joanne Reid[1]
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5-02
glp-1 receptor agonists and skeletal muscle mass preservation: insights from bis monitoring during initial 12-week weight loss course
Maureen McBeth, Richelle Gaw, Katie Newsome
ImpediMed, Ellicott City, United States

5-03
Real-World Impact of Nutritional Support on Hospital Readmissions and Costs in Elderly Patients: Evidence from Brazil's Private Healthcare Sector
Daniela F. A. Gomez, Bruna O. Maia, Christine M. Oliveira, Jesiel M. L. Assis, Jader S. Andrade, Anna C.A.P. Silva
Fundação Zerrenner, São Paulo, Brasil

5-04
Taste and smell changes and quality of life among ambulatory cancer patients receiving systemic treatment
Doireann Ní Chonaill[1], Erin Stella Sullivan[1, 2], Derek G. Power [3, 4], Aoife M. Ryan[1, 3]
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5-05
Leptin as a biomarker for nutritional status in patients with onco-hematological diseases undergoing chemotherapy
Juliana Maria Faccioli Sicchieri[1], Jéssica Micheletti[2], Lorena Lobo Figueiredo Pontes[2], Anderson Marliere Navarro[2]
[1]Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo; [2]Ribeirão Preto Medical School, University of São Paulo

5-06
The burden of malnutrition in patients with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF): a systematic literature review
Reshma Merchant[1], Hidenori Arai[2], Oluwaseyi Dina[3], Daniela Fliegner[4], Michelle Rossulek[5], Xunming Sun[3], Karen Smoyer[6], Bruno Vellas[7]
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5-07
Territorial differences in vitamin d status and gait performance among chilean older people: a multi-regional analysis across 30 degrees of latitude
Bárbara Angel[1], Viviana Sánchez[2], Bárbara Leyton[2], Ana Unda[1], Mariane Lutz[3], Sigrid Sanzana[4], Paola Aravena[5].
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5-08
Optimising amino acid availability in older adults: contrasting the effects of essential amino acid supplementation and a standard protein-content breakfast in a randomised crossover trial
Luke Aldrich[1], Antonis Stavropoulos-Kalinoglou[1], Oliver Wilson[1], Theocharis Ispoglou[1]
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5-09

Optimising Patient Treatment with Immuno-Nutrition: A Study Protocol Evaluating the Impact of an Omega-3-Enriched Nutritional Supplement in Cancer Patients at Risk of Malnutrition

***Fiona A. MacLeod*[1], *Seamus Coyle*[2], *Kerry Waterfield*[3], *Olav Dajani*[4], *Paul H. Lee*[5], *Elizabeth Dixon*[5], *Katy Courtnell*[5], *Andrew Cook*[6], *Richard J.E. Skipworth*[7], *Barry J.A. Laird*[8]**

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5-10

Effects of nutrition combined with exercise on inflammation and muscle damage in older adults: systematic review and meta-analysis

***Rubab Zahra*[1], *Robert G. Memelink*[1,2,3], *Reyhanh Nejati Bervanlou*[2,4], *Peter J.M. Weijs*[2,3,5], *Ivan Bautmans*[1,6,7,8]**

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Poster Session 2.1 **Therapeutic Development (pre-clinical)** (posters 7-01 to 7-12)
Chairs: James Carson, Mitja Lainscak

7-01
Low-magnitude high-frequency vibration combined with β-hydroxy-β-methylbutyrate treatment prevents neuromuscular junction degeneration in age-related sarcopenia
Qianjin Wang, Can Cui, Ning Zhang, Wujian Lin, Senlin Chai, Maihemuti Abudureheman, Xiaoxu Xu, Ronald Man Yeung Wong, Wing-Hoi Cheung
Musculoskeletal Research Laboratory, Department of Orthopaedics and Traumatology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China

7-02
AGE breaker mitigates hyperglycemia, muscle dysfunction and bone loss in aged mice
Wayne Yuk-wai Lee[1, 4, 5, 6], Wei Ting Hsiao[1,4], Chien-Wie Lee[2, 3]
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7-03
Is vitamin D good for muscle? A preclinical study elucidating the vital role of cyp27b1 in muscle mitochondrial function
Wayne Yuk-wai Lee[1,2,6,7], Jessica Hiu-tung Lo[1,2], Tszlam Yiu[1,2], Daniel Kam-Wah Mok[3, 4, 5], Man-Sau Wong[3, 4, 5]
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7-04
Deciphering the role of vasculature in cancer cachexia
Emilia Oksaranta[1], Kialiina Tonttila[2], Arja Pasternack[1], Olli Ritvos[1], Riikka Kivelä[1,2]
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7-05
Myostatin/activin A neutralization improves muscle quality and function during GLP-1 receptor agonism-induced weight loss in obese mice.
Bruno Moukette[1], Danielle Archambault[1], Shreya Kumar[1], Natalie Daurio[1], Ryan Reese[1], Akash K. Kaushik[1], Annette Sievers[2], Rocío Saavedra Peña[1], John Griffin[1], Jeffrey Morin[3], Kendra K. Bence[1], Danna M. Breen[1]
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7-06

Nicotinamide Riboside Mitigates Adipose Tissue Wasting and Systemic Metabolic Dysregulation in Ritonavir-Induced Lipodystrophy

***Yan Zhang*[1], *Shibo Wei*[1], *Yunju Jo*[1,2], *Wonyoung Park*[1], *Jung Ho Han*[3], *Karim Gariani*[4,*], *Dongryeol Ryu*[1,*]**

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7-07

Platelet Releasate partially rescues C2C12 myoblasts from chemotherapeutic drug-induced impairments

***Aisha Nazam Ikhlaq*[1], *Laura Sadofsky*[1], *Antonios Matsakas*[2]**

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7-08

UCN2 treatment enhanced fat mass loss while increasing muscle mass and function in preclinical models

***Pablo Vidal*[*1], *Patricia A.M. Baumgarten*[2], *Natalie R. Janzen*[1], *Elizabeth R.M. Zunica*[2], *Dylan C. Seiler*[1], *Yevgenia Khodor*[1], *Andrew P. Ryan*[1], *Mark R. Wade*[1], *Steve M. Bauer*[1], *Valentina Pirro*[1], *Paul M. Titchenell*[1], *John P. Kirwan*[2], *Christopher L. Axelrod*[2], *and Joseph T. Brozinick*[1].**

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7-09

Peripheral administration of long-acting Y5R agonist PEP-300 induces hyperphagia and shifts energy homeostasis in mice

***Camilla Lund*[1], *Jenna E Hunt*[1,2], *Elizabeth Lansbury*[2], *Oksana Dmytriyeva*[2], *Bandy Chen*[3], *David Meseguer*[3], *Marc Schneeberger*[3,4], *Karin Mörl*[5], *Christoffer Clemmensen*[2], *Annette G Beck-Sickinger*[5], *Søren L Pedersen*[1], *Keld Fosgerau*[1]**

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7-10

AntimiR therapy improves muscle mass and function in in vivo models of muscle wasting

***Andrea García-Rey*[1], *Beatriz Román-Payan*[2,3], *Darío Castro-Izurieta*[2,3], *Virginia Alzás-Gómez*[2,3], *Francisco Hernández-Torres*[3,4], *Amelia E. Aránega*[2,3], *Francisco Javier López-Soriano* [5], *Silvia Busquets*[5], *Beatriz Llamusí*[1], *Estefanía Cerro-Herreros*[1]**

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7-11

Characterization of the Systemic Impact of Glucocorticoid-Treated Exacerbation of COPD in a Novel mouse model

***Justine M. Webster*[1], *Sandra J. van Krimpen*[1], *Peiyu Qiu*[1], *Behzad Rezaeifar*[2], *Sami O. Simons*[1], *Annemie M.W.J. Schols*[1], *Harry R. Gosker*[1], *Ramon C.J. Langen*[1]**

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7-12

Activin Type II Receptor Blockade Impacts Muscle Wasting in Glucocorticoid-Treated Exacerbations of COPD

Sandra J. van Krimpen[1], Justine M. Webster[1], Peiyu Qiu[1], Pauline Henrot[2], Behzad Rezaeifar[3], Sami O. Simons[1], Annemie M.W.J. Schols[1], Ramon C.J. Langen[1], Harry R. Gosker[1]

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Poster Session 2.2 **Muscle Wasting & Sarcopenia** (posters 4-80 to 4-90)
Chairs: Gustavo Duque, Andreas Fischer

4-80

Impact of Nutritional and Radiomic Index of Sarcopenia in Retroperitoneal Sarcoma

Michael Wong[1], Anant Desai[2], Andrew Beggs[3]

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4-81

Novel sex-specific cut-offs for subcutaneous adipose tissue radiointensity in patients with cirrhosis: a post-hoc analysis

Simone Di Cola[1], Gennaro D'Amico[2], Giulia Cusi[1] and Manuela Merli[1]

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4-82

Sarcopenic Obesity in Men with Castration Sensitive Prostate Cancer treated with Androgen Deprivation Therapy

Nagi B. Kumar[1, 2], Nathan Parker[3], Jingsong Zhang[2], Julio Pow-Sang[2], Jong Park[1-2], Yoganand Balagurunathan[4], Jung Choi[5], Michael J Schell[6]

Cancer Epidemiology Program[1], Genitourinary Oncology[2], Health Outcomes and Behavior[3], Machine Learning[4], Radiology[5], Biostatistics & Bioinformatics[6] Moffitt Cancer Center and Research Institute, Tampa, FL USA

4-83

Association between sarcopenia, body composition, functionality, and blood biomarkers in elderly individuals with obesity: cross-sectional findings from a prospective cohort in São Paulo

Georgia M. C. Dalle Lucca[1], Luciana Paganini Piazzolla[1], Luiz Eugenio Garcez Leme[1] , Marcus V. L. Dos Santos Queresma[2], Raphael Einsfeld Simões Ferreira[1], Mara Graziele Maciel Silvera[1], Rafaella Fagundes Xavier[3], Luciana Correia da Silva Vieira[3], Vitoria Ybrahim Ruiz[1]

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4-84

***Vaccinum macrocarpon* extract abolishes the aging-like effect of Western diet consumption by hindering the advanced glycation end-products (AGEs)/RAGE axis.**

Laura Salvadori[1,2], Martina Paiella[2,3], Tommaso Raiteri[2,3], Giulia Gentili[2,3], Sara Chiappalupi[2,3], Tommaso Manenti[4], Guglielmo Sorci[2,3], Flavia Prodam[5], Nicoletta Filigheddu[1,2], Francesca Riuzzi[2,3]

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4-85

Preoperative screening for sarcopenic obesity in bariatric surgery: diagnostic challenges

***Renata Brum Martucci*[1], *Larissa Davel Miana Gomes*[1], *Giulia Negromonte Nunes Rodrigues*[1], *Giovanna Brandão Biscaia*[1], *Fernando Lamarca*[1]**

[1]University of the State of Rio de Janeiro

4-86

Distinct microRNA and ANGPTL Signatures in Sarcopenic Obesity Associate with Muscle Loss and Metabolic Dysfunction

***Federica Tambaro*[1], *Ilenia Minicocci*[1], *Eleonora Poggiogalle*[2], *Marcello Arca*[1], *Maurizio Muscaritoli*[1]**

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4-87

Unravelling metabolic dysregulation in heart failure with frailty: insights from plasma metabolomics

Konstantinos Prokopidis

Department of Musculoskeletal Ageing and Science, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

4-88

Circulating microRNA-22-3p as a potential diagnostic tool in patients with primary sarcopenia

***Mirela Vatic*[1,2], *Anselm A. Derda*[3,4,5], *Tania Garfias-Veitl*[1,2,6], *Ryosuke Sato*[1,2], *Goran Lončar*[1,7,8], *Guglielmo Fibbi*[1,2,9], *Felix Wiedmann*[1,2], *Wolfram Doehner*[10,11,12], *Christian Bär*[4,13], *Francesco Landi*[14,15], *Riccardo Calvani*[14,15], *Matteo Tosato*[15], *Roberto Bernabei*[14], *Emanuele Marzetti*[14,15], *Robert Kob*[16], *Cornel Sieber*[16], *Stefan D. Anker*[10,111,17,18], *Thomas Thum*[4,13], *Constanze Schmidt*[1,2], *Stephan von Haehling*[1,2]**

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4-89

Sarcopenia and Hypotension in Heart Failure

***Tania Garfias-Veitl*[1,2], *Guglielmo Fibbi*[1], *Ryosuke Sato*[1,2], *Mirela Vatic*[1,2], *Wolfram Doehner*[3,4,5], *Stefan D. Anker*[3,5,6], *Stephan von Haehling*[1,2]**

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4-90
Quorum Sensing Peptides in Sarcopenia: Insights from iAM373
***Liesbeth Crombez*[1,2*], *Sumaira Jabeen*[3*], *Petar Naumovski*[1,3], *Nele Van Den Noortgate*[1,2], *Bart De Spiegeleer*[1,3] , *Evelien Wynendaele*[1,3] *and Anton De Spiegeleer*[1,2]**
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Poster Session 2.3 **Physical Activity & Training** (posters 6-01 to 6-13)
Chairs: Volker Adams, Andrew Judge

6-01
Gait speed and associations with muscular imbalance in community dwelling older adults
Arnar Hafsteinsson, Alfons Ramel
Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland

6-02
Selfperception of health and short physical performance battery in Icelandic older adults.
Arnar Hafsteinsson, Alfons Ramel
Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland

6-03
Aerobic exercise effect of belt electrode skeletal muscle electrical stimulation assessed by lower-limb muscle oxygenation
***Takumi Hirabayashi*[1,2], *Nobuto Nakanishi*[3], *Yoshitada Sakai*[1,4]**
[1]Division of Rehabilitation Medicine, Kobe University Hospital, Kobe, Japan; [2]Department of Medical Device Engineering, Kobe University Graduate School of Medicine, Kobe, Japan; [3]Department of Disaster and Emergency Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [4]Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

6-04
Progressive Resistance Exercises in Older Adults with Sarcopenia
***Allan Cerqueira da Silva*[1], *Ana Brotero Farah*[1], *Ana Julia Teles de Souza*[1], *Andrey Gibin Fialcoski*[1], *Antônio Pedro Bertarini Vieira*[1], *Bruna Yamada Hosomomi*[1], *Luciana Paganini Piazzolla*[2], *Luciane Correia da Silva Vieira*[1], *Rafaella Fagundes Xavier*[1], *Renata Cléia Claudino Barbosa*[1]**
[1]Physiotherapy Program, Centro Universitário São Camilo; [2]Physical Therapy Program, Centro Universitário São Camilo

6-05
Resistance exercise intervention restores functional capacity and reverses frailty biomarkers in centenarians
***Michelle Bonvini*[1], *Diego Marcos-Perez*[1], *Adrián Hernandez-Vicente*[2], *Nuria Garatachea*[2], *Ander Matheu*[1]**
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6-06
Association between cardiovascular health metrics and self-reported walking difficulty in community-dwelling middle-aged and older adults: results from the Longevity Check-up 8+
***Stefano Cacciatore*[1,2], *Emanuele Marzetti*[1,2], *Riccardo Calvani*[1,2], *Matteo Tosato*[2], *Francesco Landi*[1,2]**
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6-07

Body composition abnormalities and their association with physical function in patients with idiopathic pulmonary fibrosis

***Felipe V. C. Machado*[1,2], *Anouk W. Vaes*[3], *Paula van Melick*[3], *Miriam T. J. Groenen,*[3] *Roy Meys*[3], *Frits F.M. Franssen*[3,4], *Chris Burtin*[1,2], *Carla M. Prado*[5], *Martijn A. Spruit*[3,4]**

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6-08

Resistance training and protein supplementation during first-line chemotherapy in patients with incurable gastroesophageal cancer: a randomized feasibility trial

***Rikke Krabek*[1], *Kasper Birch Kristensen*[1], *Simon Nørskov Thomsen*[1], *Anne Hauge Sørensen*[1], *Pernille Lykke Christensen*[1], *Kit Crusell Pedersen*[1], *Ane Rytter*[2], *Christina Dieli-Conwright*[3], *Charlotte Suetta*[4,5], *Lykke Sylow*[6], *Bente Klarlund Pedersen*[1], *Morten Mau-Sørensen*[7], *Casper Simonsen*[1]**

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6-09

Associations of long-term physical activity levels with sarcopenia in older adults: the HUNT study

***Karina Hammer Tømmerdal*[1,2], *Javaid Nauman*[1,3], *Ulrik Wisløff*[1,4], *Arnt Erik Tjønna*[1], *Jonathan Berg*[1]**

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6-10

Low-density lipoprotein cholesterol levels and exercise capacity in patients with chronic heart failure: Findings from the BIOSTAT-CHF study

***Ryosuke Sato*[1], *Tania Garfias-Veitl*[1,2], *Mirela Vatic*[1,2], *Guglielmo Fibbi*[1,2], *Adriaan A. Voors*[3], *Stephan von Haehling*[1,2]**

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6-11

Effects of 4 weeks of multimodal prehabilitation on physical performance in head and neck cancer patients: preliminary results from a multicenter prospective trial

***Lisa Vigo*[1], *Sara Demurtas*[1,2], *Antonio Ciarfella*[1,2], *Valentina Tibollo*[3], *Gaia Riboni*[3], *Chiara M. Palo*[3], *Marco Benazzo*[4,5], *Laura D. Locati*[2,1] *and Simone Porcelli*[6,7]**

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6-12
Enhancing adherence and affective response to resistance training in females: a scoping review of strategies and protocols with implications for sarcopenia prevention
Akanksha Arora[1], Matthew Barlow[1], Meghan Brown[1], Luke Aldrich[1], Nick Harris[1 2], Ernest Schilders[1 3], James McKenna[1], Theocharis Ispoglou[1]
[1]Carnegie School of Sports, Leeds Beckett University, Leeds, United Kingdom;[2]Spire Leeds Hospital, Leeds, United Kingdom;[3]Department of Orthopaedic Surgery, Fortius Clinic, London, United Kingdom

6-13
Iron Deficiency and Impaired Skeletal Muscle Functional Capacity in Patients with ME/CFS
Nadja Jauert[1,2,3,4], Katrin Schilling-Ziese, Claudia Kedor, Carmen Scheibenbogen, Wolfram Doehner
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Poster Session 2.4 **Muscle Wasting & Sarcopenia** (posters 4-01 to 4-12)
Chairs: Philip Atherton, Henning Langer

4-01
Myostatin antisense administration prevents sepsis-induced muscle atrophy and weakness in male mice
Nobuto Nakanishi[1], Kazuhiro Maeta[2], Yuko Ono[1], Takumi Hirabayashi[3], Kensuke Nakamura[1], Masafumi Matsuo[4], Joji Kotani[1]
[1]Department of Disaster and Emergency Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan; [2]KNC Laboratories Co., Ltd. Quality Assurance Section, Pharmaceutical Quality Assurance Dept., Shimane, Japan; [3]Division of Rehabilitation medicine, Kobe University Hospital, Kobe, Japan; [4]Faculty of Health Sciences, Kobe Tokiwa University, Kobe, Japan

4-02
Bimagrumab preserves lean mass and sustains fat loss during semaglutide-induced weight reduction in diet-induced obese mice
Malte H. Nielsen, Nina Sonne[1], Nicolas Eskesen[1], Anitta Kinga Sárvári[1], Simone Bossi[1], Jacob Nersting[1], Michael Feigh[1], and Marco Tozzi[1]
[1]Gubra, Hørsholm, Denmark

4-03
Semaglutide inhibits proteolysis in skeletal muscle of obese mice
Matheus Leonardo Moro[1], João Batista Camargo Neto[2], Leticia Ruiz[1], Gabriel Skiba[1], Andressa Pereira[2], Natália Lautherbach[2], Iana Mizumukai De Araujo[3], Neusa Zanon[2], Isis do Carmo Kettelhut[2], Luiz Carlos Navegantes[1]
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4-04
Liraglutide preserves soleus muscle mass in obese mice and modulates calcium handling in isolated single fibres
Gabriel Hunzicker Skiba[1,2], Aldo Meisozo-Huesca[2], Matheus Leonardo Moro[1], João Batista Camargo Neto[1], Bradley S. Launikonis[2], Isis do Carmo Kettlehut[1], Luiz Carlos Carvalho Navegantes[1]
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4-05

Fracture risk in heart failure

Guglielmo Fibbi[1,2], Tania Garfias-Veitl[1,2], Mirela Vatić[1,2], Ryosuke Sato[1,2], Wolfram Doehner[3,4,5], Stefan D. Anker[3,5,6], Constanze Schmidt[1,2], Stephan von Haehling[1,2]

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4-06

ExermiR-129-3p enhances muscle function by improving mitochondrial activity through PARP1 inhibition

Yeo Jin Shin[1], Jae Won Yang[1], Kwang-Pyo Lee[1]

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4-07

Exercise-induced CLCF1 reverses age-related skeletal muscle and bone decline

Jae Sook Kang[1,2*], Min Ju Kim[1,2*], Kwang-Pyo Lee[1,2], Ki-Sun Kwon[3], Yong Ryoul Yang[1,2*]

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4-08

Establishment of a mouse model of disuse-induced muscle wasting and evaluation of the therapeutic efficacy of human Wharton's jelly-derived mesenchymal stromal cells

Jang Bin Jeong[1], Hyeongseop Kim[1], Su yeon Jeon, Sang Eon Park[1], Hunnyun Kim[2], Hong Bae Jeon[1], Jong Wook Chang[1]

[1]ENCell, Seoul, Republic of Korea, [2]Samsung Medical Center

4-09

Heterogeneity in mitochondrial adaptations to pulmonary inflammation and hypoxia across oxidative and glycolytic muscles

Angelos Gavrielatos[1], Cindy Tellier[1], Amel Achouri[1], Hervé Dubouchaud[1], Clovis Chabert[1]

[1]University Grenoble Alpes, Inserm U1055, Laboratory of Fundamental and Applied Bioenergetics (LBFA), Grenoble, France

4-10

JUV-161 preserves muscle mass and function in a mouse model of cast immobilization atrophy

Vengadeshprabhu Karuppagounder, Ritwik Datta, Hee Ju Kim, Ashil Koranne, Annie Yang, Ted Yu, Danielle Yi, Kimberly Crutcher, Zhihua Li, Thach Mai, Banmeet Anand, Colin Hislop, Priya Handa, Hanadie Yousef, Jeremy D. O'Connell

Juvena Therapeutics, Redwood City, CA, USA

4-11

JUV-161 is effective in reversing skeletal muscle myopathy in mouse models of DM1 and Sarcopenia

Hee Ju Kim, Ashil Koranne, Han Song, Vengadeshprabhu Karuppagounder, Ritwik Datta, Zhihua Li, Thach Mai, Banmeet Anand, Colin Hislop, Priya Handa, Jeremy D. O'Connell, Hanadie Yousef

Juvena Therapeutics, Redwood City, CA, USA

4-12

JUV-161 Accelerates Muscle Recovery and Attenuates Fibrosis in a Sarcopenic Mouse Model of Cardiotoxin-Induced Injury

Hee Ju Kim, Ashil Koranne, Han Song, Vengadeshprabhu Karuppagounder, Ritwik Datta, Zhihua Li, Thach Mai, Banmeet Anand, Colin Hislop, Priya Handa, Jeremy D. O'Connell, Hanadie Yousef

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Poster Session 3.1 **Muscle Wasting & Sarcopenia** (posters 4-49 to 4-60)
Chairs: Guglielmo Sorci, Florian Strasser

4-49
Ultrasound assessment of quadriceps muscle architecture as a diagnostic and prognostic tool in hospitalized older adults with sarcopenia
***Zahira Zohari*[1], *Muhammad Nizamuddin Othman*[2], *Mohammad Nazri Md Shah*[1], *Terence Ong*[3]**
[1]Geriatric Unit, Medical Department, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia; [2]Radiology Department, University Malaya Medical Centre; [3]Geriatric Unit, Medical Department, University Malaya Medical Centre

4-50
A novel melanoma variant associated with myosteatosis
***Nico Boelter*[1], *Cynthia Stretch*[1], *Victoria Armstrong*[1], *Donna L. Senger*[2], *Oliver F. Bathe*[3]**
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4-51
Assessment of Sarcopenia Status in Post Metabolic Surgery Patients with Suboptimal Weight Loss Outcomes and the Effect of Subsequent Liraglutide 3.0mg
Chloe Stanley*[1,2†], *Adrian Slee*[1†], *Jessica Mok*[1], *Janine Makronidis*[1,2,3] *on behalf of Barioptimise trial team
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4-52
Effects of synbiotic supplementation on strength and physical performance in community-dwelling older Australians.
***David Barry*[1,2], *Andrew Betik*[3], *Jackson Fyfe*[3], *Lilia Convit*[4], *Joshua Farragher*[5], *Sara Caballero-Calero*[6], *Varuni Nagulesapillai*[6], *Marie-Laure Oula*[6], *Sylvie Binda*[6], *Matthew Cooke*[7]**
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4-53
Change in Skeletal Muscle Mass among Patients with Cancer undergoing Chemotherapy or Immunotherapy: A Systematic Review and Meta-analysis
***Lukas Svendsen*[1, 2], *Stine Hansen*[3], *Sandra Jensen*[3], *Victor Sørensen*[4], *Susanne Dalton*[1, 2, 5], *Christoffer Johansen*[3, 5], *Charlotte Suetta*[5,6], *Helle Pappot*[5, 7], *Casper Simonsen*[8], *Lars Tang*[8], *Gunn Ammitzbøll*[1, 2*], *Bolette Rafn*[3, 5*]**
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4-54

Case Report - Muscle Mass Assessment in Obese Hemodialysis Patient

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4-55

Muscle Quality Index in patients on Peritoneal Dialysis: Associations with clinical, nutritional parameters, and outcomes

Maryanne Z C Silva[1], Barbara P Vogt[2], Carla Maria Avesani[3], Fabiana L Costa[1], Pasqual Barretti[1], Jacqueline C T Caramori[1]

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4-56

Low Relative Muscle Power in Patients on Haemodialysis: Poor Health Outcomes of the SARC-HD Cohort

Maryanne Z C Silva[1], Marvery P Duarte[2], Dario R Mondini[3], Henrique S Disessa[4], Angélica N Adamoli[5], Daiana C Bündchen[6], Rodrigo R Krug[7], Maristela Bohlke[8], Maycon M Reboredo[9], Heitor S Ribeiro[2,10] on behalf of the SARC-HD Study Group

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4-57

Utility of Calf Circumference–Adjusted Body Mass Index for Assessing Muscle Wasting in Hemodialysis: Results from the SARC-HD Cohort

Maryanne Zilli Canedo Silva[1], Marvery Duarte[2], Dário Mondini[3], Henrique Disessa[4], Daiana Bundchen[5], Angélica Adamoli[6], Maycon Reboredo[7], Heitor Ribeiro[2,8], Jacqueline Costa Teixeira Caramori[1], Carla Maria Avesani[9]

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4-58

Intramuscular sex hormone concentrations in healthy males and females across the lifespan

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4-59
Maximum bite force as a simple screening tool for malnutrition and sarcopenia risk in older adults undergoing dental surgery
***Federica Tambaro*[1], *Eleonora Assanto*[1], *Ottavia Poli*[2], *Giorgia Fusco*[1], *Maurizio Muscaritoli*[1]**
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Italy; [2]Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Italy

4-60
Exploratory study of factors associated with respiratory sarcopenia in patients with non-small cell lung cancer
***Zhuzhu Wang*[1], *Ruifeng Tang*[2], *Jingfang Hong*[1,2], *Jinyu He*[2]**
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Poster Session 3.2 **Therapeutic Development (clinical)** (posters 8-01 to 8-10)
Chairs: Mitja Lainscak, Emanuele Marzetti

8-01
Motor Unit Potential and Nerve Conduction Velocity as Novel Electrophysiological Correlates of Muscle Health in Sarcopenia
Can Cui*[1], *Shichen Qi*[2], *Yeeling Au*[1], *Ronald Man Yeung Wong*[1], *Ning Zhang*[1], *Yong Hu*[2], *Wing-hoi Cheung*[1]
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8-02
Bioimpedance analysis for the detection of intensive care unit acquired weakness: a prospective observational study
***Annika Bald*[1], *Julius J. Grunow MD*[1], *Nils Daum MD*[1,2], *Emely Beck*[1], *Linus Warner*[1], *Tina Ramishvili MD*[3], *Vera Karner*[4], *Bernhard Ulm*[5,6], *Manfred Blobner MD*[5], *Stefan J Schaller MD*[1,4]**
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8-03
Phase 1 Trial in Healthy Participants of KER-065, Modified Activin Receptor Ligand Trap, Supports Development in Sarcopenia and Neuromuscular Disorders
***Harveen Natarajan*[1], *Suresh Bobba*[1], *F. Martin Fisher*[1], *Mohammed Taimi*[1], *Stephen Hall*[2], *Sasha Bogdanovich*[1], *and Jasbir Seehra*[1]**
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8-04
Efficacy and safety of kyung-ok-ko for cancer-related fatigue in patients with lung cancer: a randomized, double-blind, placebo-controlled, parallel-group trial
Sung-Woo Kang, Beom-Joon Lee
Department of Clinical Korean Medicine, College of Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea

8-05

Efficacy and safety of ponsegromab in patients with pancreatic cancer, cachexia, and elevated growth differentiation factor: insights from the Phase 2 PROACC-1 trial

Eric J. Roeland[1], John D. Groarke[2], Susie M. Collins[3], Shannon Lubaczewski[4], Jeffrey Crawford[5], Tateaki Naito[6], Andrew E. Hendifar[7], Marie Fallon[8], Koichi Takayama[9], Timothy Asmis[10], Richard F. Dunne[11], Michelle Rossulek[12], Ruolun Qiu[13], Aditi R. Saxena[2]

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8-06

RIVER-mPDAC: a phase 2b/3 study of ponsegromab for the treatment of cachexia in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving first-line (1L) chemotherapy

Eric J. Roeland,[1] Imran Ali,[2] Timothy R. Asmis,[3] Jeffrey Crawford,[4] Richard F. Dunne,[5] Marie T. Fallon,[6] Alexandra Palmer,[7] Glenn Pixton,[7] Jan Kiszko,[7] Keith Wilner,[7] Andrew E. Hendifar[8]

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8-07

Efficacy and safety of ponsegromab in patients with cancer-associated cachexia: results from the open-label extension of a randomized, placebo-controlled, phase 2 study

John D. Groarke[1], Jeffrey Crawford[2], Susie M. Collins[3], Shannon Lubaczewski[4], Eric J. Roeland[5], Tateaki Naito[6], Andrew E. Hendifar[7], Marie Fallon[8], Koichi Takayama[9], Timothy Asmis[10], Richard F. Dunne[11], Michelle Rossulek[12], Ruolun Qiu[13], Aditi R. Saxena[1]

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8-08

Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-07258669, a small-molecule MC4R antagonist: Results from first-in-human Phase 1 studies

Adam G. Ogden, Nicole Sherry, Frances Hackman, Susie M. Collins, Santosh Wagh, Jennifer Winton, Kari Fonseca, Michelle Rossulek, Aditi R. Saxena, John D. Groarke

Pfizer Inc, New York, NY, USA

8-09
Biophytis: BIO101 (20E) as a drug candidate targeting the reduction of GLP1-RA-induced muscle mass or function loss in patients with obesity.
***Waly Dioh*[1], Mathilde Latil[1], Rob Van Maanen[1], Claudia Ferreira[1], Serge Camelo[1], Sandrine Rabut[1], Robin Deloux[1], Pierre J. Dilda[1], Jean Mariani[1,2] and Marc-Andre Cornier[3].**
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8-10
Trial-in-progress: A phase 1b dose escalation study of AV-380 (anti-GDF15 monoclonal antibody) in combination with standard-of-care therapy in cancer patients with cachexia
***Eric J. Roeland*[1], Mohamedtaki A. Tejani[2], Eric Cheung[3], Toros Dincman[4], Vipin R. Lohiya[5], Rajiv Agarwal[6], Saleha Sajid[7], Afshin Eli Gabayan[8], Jaykumar Thumar[9], Bo Jin[10], Claudia Lebedinsky[10], *Edgar Braendle*[10], Richard Zuniga[11]**
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Poster Session 3.3 **Muscle Wasting & Sarcopenia** (posters 4-70 to 4-79)
Chairs: Christopher Perry, Erin Talbert

4-70
Mitochondrial protein modulation as a therapeutic approach to counteract muscle wasting in cancer cachexia, steroid use, and disuse conditions
***Ibotombi Singh Sinam*[1], Min-Ji Kim[2], Jae-Han Jeon[2,3], In-Kyu Lee[3,4]**
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4-71
DNA methylation as a driver of long-term muscle transcriptome alterations in critical illness survivors
***Ceren Uzun Ayar*[1], Fabian Güiza[1,2], Inge Derese[1], Greet Van den Berghe[1,2], Ilse Vanhorebeek[1]**
[1]Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium; [2]Clinical Division of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

4-72
Role of inflammatory macrophages in skeletal muscle impairment in COPD
***Pauline Henrot*[1,2], Jalal Mosayebi Amroabadi[1], Luna Louwe[1], Sandra van Krimpen[1], Sven Manse[1], Jenna Spence[1], David Baião Barata[1,3], Harry Gosker[1], Ramon Langen[1]**
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4-73

Decreases in RyR1 content extend beyond recessive RYR1-related myopathies and trigger ER and metabolic stress.

Jeremy Vidal[1], Martin Wohlwend[2], Pirkka-Pekka Laurila[3], Julien Ochala[4], Alexander J. Lobrinus[5,6], Bengt Kayser[1], Isabel C. Lopez-Mejia[7], Nicolas Place[1], Nadège Zanou[1]

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4-74

Molecular mechanisms mediating exercise-induced maladaptations *in vitro*

Giuseppe Sirago[1,2], Clément Lanfranchi[1,2], Justin Carrard[3], Vincent Gremeaux[1,4], Nadège Zanou[1,2], Nicolas Place[1,2]

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4-76

Body Composition Shapes MicroRNA Signatures in Newly Diagnosed Breast Cancer Patients

Simona Orlando[1], Federica Tambaro[1], Maria Ida Amabile[2], Giovanni Imbimbo[1], Carmen Gallicchio[1], Maurizio Muscaritoli[1], Alessio Molfino[1]

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4-77

AI-driven ultrasound radiomics for predicting sarcopenia, muscle strength and nutritional risk in hospitalized geriatric patients

Ricardo Teresa Ribeiro[1], Théo Coutaudier[1], Jennifer Wegrzyk[1], Robina Alfred[1], Elisabeth Stamm[2], Patrizia D'Amelio[2]

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4-78

C-Peptide promotes myogenic differentiation *in vitro* and its low serum levels associate with sarcopenia in adults and the elderly

Samantha Maurotti[1], Yvelise Ferro[2], Carmelo Pujia[3], Luana Mirabello[1], Elisa Mazza[1], Alberto Castagna[2], Arturo Pujia[2,4] and Tiziana Montalcini[1,4]

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4-79

Sex-specific reference ranges for CT body composition analysis in healthy adults: comparison with published cut points

Alanood Aljanahi[1], Raneem AlAskar[1,2], Erin Stella Sullivan[1]

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Poster Session 3.4 **Cancer Cachexia** (posters 3-22 to 3-31)
Chairs: Paige Arneson-Wissink, Egidio Del Fabbro

3-22
Longitudinal Changes of Body Composition Parameters are Associated with Clinical Outcomes in HER2-Positive Metastatic Breast Cancer Receiving Trastuzumab Deruxtecan
***Giovanni Imbimbo*[1], *Simona Pisegna*[2], *Simone Scagnoli*[2], *Claudia Alabiso*[1], *Massimiliano Ardovino*[1], *Carmen Gallicchio*[1], *Veronica Rizzo*[2], *Andrea Botticelli*[2], *Maurizio Muscaritoli*[1] *and Alessio Molfino*[1]**
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3-23
Histomorphological and Inflammatory Differences Between Subcutaneous and Visceral Adipose Tissue in Cancer Patients
***Giovanni Imbimbo*[1], *Federica Tambaro*[1], *Raffaella Carletti*[1], *Simona Orlando*[1], *Veronica Rizzo*[2], *Elena Belloni*[3], *Giuseppe Nigri*[3], *Maurizio Muscaritoli*[1], *Alessio Molfino*[1]**
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3-24
The GDF-15-neutralizing antibody visugromab induces immune modulation and metabolic reprogramming in cancer-induced cachexia.
***Matthias Kist*[1], *Julia Weigandt*[1], *Kristin Eichler*[1], *Laura Giese*[1], *Sarah Lutzenberger*[1], *Thorsten Ross*[1], *Kathrin Klar*[1], *Felix S. Lichtenegger*[1], *Eugen Leo*[1], *José Medina-Echeverz*[1], *Christine Schuberth-Wagner*[1]**
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3-25
Exploring experiences and impacts of changes in physical function among people with cancer cachexia
***Megan Bowers*[1], *Irene Higginson*[1], *Matthew Maddocks*[1]**
[1]Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, London, United Kingdom

3-26
Meaningful within-patient change (MWPC) of PROMIS-Fatigue and PROMIS-Physical Function (PF) in patients with cancer cachexia in the phase 2 ponsegromab study
***Jarjieh Fang*[*,1], *Joshua A. Roth*[1,2], *Andrew Bushmakin*[3], *Magdalena A. Harrington*[1], *John D. Groarke*[4], *Susie M. Collins*[5], *Jeffrey Crawford*[6], *Eric J. Roeland*[7], *Joseph C. Cappelleri*[3]**
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3-27
Psychometric validation and meaningful within-patient change of the Functional Assessment of Anorexia-Cachexia Therapy 5-Item Anorexia-related Symptoms Scale (FAACT-5IASS) in patients with cancer cachexia
***Jarjieh Fang*[1], *Joshua A. Roth,*[1,2] *Magdalena A. Harrington,*[1] *John Groarke,*[3] *Susie M. Collins,*[4] *Joseph C. Cappelleri,*[5] *Andrew Bushmakin*[5]**
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3-28

An assessment of the healthcare resource use and cost impacts of cachexia among cancer patients in the United States: a Medicare claims study

Xunming Sun[1], Mitchell Henschel[1], Bruce Zhou[1], Stephen Schachterle[1], Oluwaseyi Dina[1], Adina Lemeshow[1], Joshua Roth[1,2]

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3-29

Accelerometer-determined physical activity and sarcopenic obesity risk in older European men and women

Andreas Nilsson[1], Hadil Limem[2], Aurelia Santoro[3], Laura Smeldy Jurado-Medina[3], Agnes A.M. Berendsen[4], Lisette C.P.G.M. de Groot[4], Joanna Kaluza[5], Ewa Sicińska[5], Amy Jennings[6], Susan Fairweather-Tait[7], Alberto Bazzocchi[3], Giuseppe Battista[3], Claudio Franceschi[3], Tarak Driss[2], Fawzi Kadi[1]

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3-30

Diet-derived Advanced glycation end-products (AGEs) worsen cancer cachexia. Identification of *Vaccinium macrocarpon* extract as an antiglycation strategy.

Laura Salvadori[1,2,] Martina Paiella[2,3], Giulia Gentili[2,3], Sara Chiappalupi[2,3], Tommaso Manenti[4], Guglielmo Sorci[2,3], Nicoletta Filigheddu[1,2], Francesca Riuzzi[2,3]

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3-31

The meaning of the EORTC Physical Functioning domain as a potential clinical endpoint in trials of patients with cancer cachexia: the association to direct physical assessments

Jonathan L Hella[1,2,3], Sara Hadzibegovic[1,2,3], Jan Porthun[1,4,5], Stefan D Anker[4,6,7,8], Andrew JS Coats[9], Markus S Anker[1,2,3,10]

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Poster Session 4.1 **Muscle Wasting & Sarcopenia** (posters 4-61 to 4-69)
Chairs: Gustavo Duque, Andreas Fischer

4-61
Functional tests and SARC-F score as predictors of sarcopenia in elderly people
Miguel Augusto Passoni Amianti[1], Agnes Caroline Lima da Silva[1], Luiz Eugênio Garcez Leme[1], Rafaella Fagundes Xavier[2], Mara Graziele Maciel Silveira[1], Mateus Deckers Leme[1], Luciana Paganini Piazzolla[1], Raphael Einsfeld Simões Ferreira[1]
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4-62
Worse Self-Rated Health as a Marker of Sarcopenia in Older Adults: Preliminary Findings from a Prospective Cohort
Maria Fernanda Moreira Alves Fernandes[1], Luciana Paganini Piazzolla[2], Luiz Eugênio Garcez Leme[2], Mateus Deckers Leme[2], Mara Graziele Maciel Silveira[2], Marcus Vinicius Lucio dos Santos Quaresma[3], Luciane Correia da Silva Vieira[4], Raphael Einsfeld Simões[2], Matheus Paroneto Alencar de Souza[1], Rafaela Machado Pires Ribeiro[1]
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4-63
The impact of EWGSOP2-defined sarcopenia on treatment tolerance and survival in patients with lung cancer – preliminary data from a prospective cohort study
Gunn Ammitzbøll[1,2], Lukas Svendsen[1,2], Morten Quist[3,4], Michael E Andersen[5], Malene S Frank[4,5], Uffe Bødtger[6,7], Gitte Alstrup[6], Casper Simonsen[8], Charlotte Suetta[4,9], Susanne O Dalton[1,2,4]
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4-64
Validation of anthropometric sarcopenia scores in brazilian elderly: A preliminary study of Lee equations versus DEXA
Matheus Paroneto Alencar de Sousa[1], Luciana Paganini Piazzolla[2], Luiz Eugênio Garcez Leme[2], Mara Graziele Maciel Silveira[2], Marcus Vinicius Lucio dos Santos Quaresma[3], Raphael Einsfeld Simões[2], Maria Fernanda Moreira Alves Fernandes[1], Rafaela Machado Pires Ribeiro[1]
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4-65
Socioeconomic impacts and sarcopenia: Evidence from a brazilian cohort
Matheus Paroneto Alencar de Sousa[1], Luciana Paganini Piazzolla[2], Luiz Eugênio Garcez Leme[2], Mateus Deckers Leme[2], Mara Graziele Maciel Silveira[2], Marcus Vinicius Lucio dos Santos Quaresma[3], Luciane Correia da Silva Vieira[4], Raphael Einsfeld Simões[2], Aline de Sousa Pereira Silva[5], Beatriz Ettore do Valle Rocca[2]
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4-66
Trajectories of skeletal muscle index in patients with endometrial cancer after surgery: A group-based trajectory modeling analysis
***Kiriko Abe*[1,2], *Aiko Ishikawa*[3,4], *Michiyuki Kawakami*[3], *Ayako Wada*[3], *Takuma Yoshimura*[5], *Kensuke Sakai*[5], *Megumi Yokota*[5], *Wataru Yamagami*[5], *Tetsuya Tsuji*[3]**
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4-67
Correlation Between Sarcopenia and the Risk of Falling, Assessed Using the FES-I Scale, in Older Adults
***Renata Souza Felício*[1], *Mara Graziele Maciel Silveira*[2], *Luciana Paganini Piazzolla*[2], *Luciane Correia da Silva Vieira*[3], *Luiz Eugenio Garcez Leme*[2], *Ari Alves de Oliveira Junior*[4], *Marcus Vinicius Lucio dos Santos Quaresma*[5], *Raphael Einsfeld Simões*[2], *Graziela Bianca Bortolo Ivanov*[2]**
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4-68
Functional decline and risk of falls in elderly people: cross-sectional findings from a prospective cohort in São Paulo
***Ana Carolina Silva Ferreira Santos*[1], *Carolina Honorato Fante*[1], *Gabrielle Santos Mello*[1], *Isabella Lacerda Silva*[1], *Raissa Lucas Ciardi*[1], *Samira Matsuzaki Souza*[1], *Luciana Paganini Piazzolla*[2], *Luciane Correia da Silva Vieira*[1], *Rafaella Fagundes Xavier*[1], *Renata Cléia Claudino Barbosa*[1]**
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4-69
Low sarcopenia prevalence but consistent declines in strength, muscle, and bone across menopausal stages in healthy females
***Akanksha Arora*[1], *Matthew Barlow*[1], *Meghan Brown*[1], *Luke Aldrich*[1], *Nick Harris*[1 2], *Ernest Schilders*[1 3], *Theocharis Ispoglou*[1]**
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Poster Session 4.2 **Cancer Cachexia** (posters 3-01 to 3-12)
Chairs: Mauricio Berriel Diaz, Paola Costelli

3-01
Myo-Tumour: A novel role for skeletal muscle in tumour growth and proliferation
***Laura Cussonneau*[1,2], *Sabrina Zorzato*[1,2], *Alessia Geremia*[1,2], *Luca Maniero*[1,2], *Jorge Ruas*[3,4], *Markus Krueger*[5],*Sebastian Proschinger*[5], *Bert Blaauw*[1,2]**
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3-02
Skeletal muscle cell's anti-proliferative effect on cancer cells
***Anine Aunan*[1], *Charlotte Claeyssen*[1, 2], *Mohamed Abelhalim*[1], *Jérôme Ruzzin*[1]**
[1]Department of Molecular Medicine, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [2]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

3-03
Cancer and heart failure: insights from a zebrafish model of hepatocellular carcinoma
***Alessio Carletti*[1], *Marco Tarasco*[1], *Hans-Martin Maischein*[1], *Didier Y.R. Stainier*[1]**
[1]Max Planck Institute for Heart and Lung Research – Department of Developmental Genetics, Bad Nauheim, Germany

3-04
Adaptation to a high-protein, carbohydrate-free diet prevents skeletal muscle wasting induced by cancer cachexia in mice
***João Batista Camargo Neto*[1], *Matheus Leonardo Moro*[2], *Leticia Cirelli Ruiz*[2], *Andressa Pereira-Silva*[1], *Millena Brandao*[3], *Lucas Eduardo Botelho de Souza*[3], *Luiz Carlos Carvalho Navegantes*[2], *Isis Do Carmo Kettelhut*[1].**
[1]Department of Biochemistry and Immunology, Ribeirao Preto Medical School, University of São Paulo, Brazil; [2]Department of Physiology, Ribeirao Preto Medical School, University of São Paulo, Brazil; [3]Center for Cell-based Therapy, Regional Blood Center of Ribeirão Preto, University of São Paulo, Brazil

3-05
Localized chemotherapy drives tumor regression and halts cancer-associated cachexia
***Franciska Telebar-Žbulj*[1,2], *Vito Telebar-Žbulj*[1,2,3], *Astrid Gorischek*[1], *Waltraud Huber*[5], *Nassim Ghaffari Tabrizi-Wizsy*[5], *Rainer Schindl*[1], *Martina Schweiger*[4], *Julia Kargl*[3], *Linda Waldherr*[1,2]**
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3-06
Muscle-targeted OPA1 overexpression confers sex-specific protection against pancreatic cancer cachexia
***Ruqaiza Muhyudin*[1], *Nicole N. Noga*[1], *Francielly Morena*[2], *Sydney Hilgenbrink*[1], *Tyrone A. Washington*[1], *Nicholas P. Greene*[1]**
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3-07
Time course of changes to the skeletal muscle microenvironment with cancer cachexia
***Alex Brown*[1], *Nicholás Collao*[2,3,4], *Aisha Saleh*[1], *Natasha Strong*[1], *Michael De Lisio*[2,3,4], *Nadine Wiper-Bergeron*[4*]**
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3-08
Disrupted pancreatic enzyme dynamics in cancer cachexia
***Tuna Felix Samanci*[1,2,3], *Pauline Morigny*[1,2,3], *Doris Kaltenecker*[1,2,3], *Marilia Seelaender*[4], *Maria Rohm*[1,2,3]**
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3-09

Walker-256 ascitic fluid induces *in vitro* features of cardiac cachexia: impact on mitochondrial and metabolic function modulated by leucine

***Ninon Melany Flores Barrios*[1], *Maiara Caroline Colombera*[1], *Gabriela Matuoka Chioccetti*[1], *Antonio Thiago Pereira Campos*[1,2], *Bruno Sergio Maia Madeira*[1], *Rogério Williams Santos*[1], *Lais Rosa Viana*[1], *Maria Cristina Cintra Gomes-Marcondes*[1]**

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3-10

MyoRep: a novel reporter system to detect early muscle atrophy *in vitro* and *in vivo*

***Andrea David Re Cecconi*[1,#], *Nicoletta Rizzi*[2,#], *Mara Barone*[1,#], *Federica Palo*[1], *Martina Lunardi*[1], *Mara Forti*[1], *Adriana Maggi*[3], *Paolo Ciana*[3], *Giulia Terribile*[1], *Michela Chiappa*[1], *Lorena Zentilin*[4] , *Rosanna Piccirillo*[1,*]**

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3-11

Impaired cAMP/PKA/CREB1 signaling drives mitochondrial dysfunction in skeletal muscle in cancer cachexia

***Elia Angelino*[1,2], *Lorenza Bodo*[1], *Roberta Sartori*[3], *Simone Reano*[2], *Nicoletta Filigheddu*[2], *Andrea Lauria*[1], *Suvham Barua*[1], *Beatrice D'Anna*[1], *Alessia Meschi*[1], *Carolina Sciavolino*[1], *Paolo Porporato*[1], *Valentina Proserpio*[1], *Marco Sandri*[3], *Vittorio Sartorelli*[4], *Giuseppina Caretti*[5] *Andrea Graziani*[1]**

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3-12

Effects of multicomponent interventions on physical function for people with cancer cachexia

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Poster Session 4.3 **Cachexia** (posters 1-01 to 1-11)
Chairs: Andrea Bonetto, Denis Guttridge

1-01

Glycerol kinase mediated lipid cycling contributes to fat loss in cancer associated cachexia

***Pia Benedikt*[1], *Tina Dahlby*[3], *Sandra Eder*[2], *Erwin F. Wagner*[4], *Christian Wolfrum*[3], *Mauricio Berriel Diaz*[1], *Rudolf Zechner*[2], *Martina Schweiger*[2]**

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1-02

Eye of the beholder: portraiture of patients with cachexia by their loved ones

***Angelike Koniaris*[1], *Teresa Zimmers*[2,3]**

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1-03

Cachexia risk classification using the Asian Working Group for Cachexia criteria in patients with sarcopenic dysphagia

Hideaki Wakabayashi

Department of Rehabilitation Medicine, Tokyo Women's Medical University Hospital

1-04

Multimodal interventions for cachexia management: Cochrane Review

Joanne Reid[1], Carolyn Blair[1*], Martin Dempster[2], Clare McKeaveney[1], Adrian Slee[3], Donna Fitzsimons[1]

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1-05

Multi-Modal Integrated intervention combining Exercise, Anti-inflammatory & Dietary advice (MMIEAD) for kidney cachexia: a mixed-methods feasibility cluster randomised controlled trial and process evaluation

Joanne Reid[1], Carolyn Blair[1]*, Adrian Slee[2], Clare McKeaveney[1], Peter Maxwell[3], Vicki Adell[4], Marion Carson[5], Sinead Comer[5], Faizan Awan[6], Malcolm Brown[7] Andrew Davenport[8], Damian Fogarty[9], Denis Fouque[10], Oonagh Gooding[5], Teresa McKinley[11], Samantha Hagan[4], Carolyn Hutchinson[11], William Johnston[12], Kamyar Kalantar-Zadeh[13], Karen Magee[14], Ryan McCullough[5], Dr Robert Mullan[5], Dr Neal Morgan[11], NICRN Clinical Research Team[15], Helen Noble[1], Sam Porter[16], David S. Seres[17], Joanne Shields[14], Ian Swaine[18], Miles Witham[19], Alastair Woodman[20]

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1-06

Chronic kidney disease associated cachexia and other wasting syndromes: Definitional challenges and interactions with gut microbiome, uremic toxins and inflammation

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1-07

Cachexia in Patients with Fabry Disease: A Cross-Sectional Multicenter Study

***Yuri Battaglia*[1,2], *Giorgia Gugelmo*[3], *Federica Baciga*[1,2], *Sara Sponchiado*[1], *Gianni Carraro*[4], *Giacomo Marchi*[5], *Andrea Gasparetti*[6], *Federica Duregon*[6], *Federica Caccia*[1], *Nicola Vitturi*[3]**

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1-08

Evaluating the Prevalence of Cachexia in Chimeric Antigen Receptor (CAR) T-cell Therapy Patients using Multiple Recommended Diagnostic Criteria

Brittany Cucchiaro*[1,2], *Nathan Davies*[1], *Elizabeth Weekes*[1], *Maeve O'Reilly*[3], *Claire Roddie*[4], *Adrian Slee*[1]

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1-09

DNA Methylation–Based Liquid Biopsy for Cachexia Risk Stratification in Glioma via Transformer-Enabled Muscle Transcriptome Inference

***Aierpati Maimaiti*[1,2], *Yan Sun*[2,3,4]**

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1-10

Integrated myomiRs and stress cytokine profiling reveals the molecular signature of cachexia in patients with chronic hearth failure

***Federica Tambaro*[1], *Giovanni Imbimbo*[1], *Simona Orlando*[1], *Carmen Gallicchio*[1], *Alessio Molfino*[1], *Maurizio Muscaritoli*[1]**

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1-11

Impact of Ruxolitinib on GDF-15, Appetite, and Body Composition in Myelofibrosis Patients

Carmen Gallicchio[1], Federica Tambaro1, Giovanni Imbimbo[1], Ottavio Martellucci[1], Emilia *Scalzulli*[1], *Massimo Breccia*[1], *Alessio Molfino*[1], *Maurizio Muscaritoli*[1]

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Poster Session 4.4 **Muscle Wasting & Sarcopenia** (posters 4-13 to 4-24)
Chairs: Christopher Perry, Erin Talbert

4-13

JUV-161: Identification of a novel clinical candidate for the treatment of myopathy and sarcopenia

Thach Mai, Zhihua Li, Hee Ju Kim, Ashil Koranne, Vengadeshprabhu Karuppagounder, Ritwik Datta, Rohit Jadhav, Han Song, Banmeet Anand, Colin Hislop, Priya Handa, Hanadie Yousef, Jeremy D. O'Connell

Juvena Therapeutics, Redwood City, CA, USA

4-14

Therapeutic Potential of JUV-161 in Enhancing Muscle Health and Insulin Sensitivity in Diabetic Myopathy and Sarcopenia

Vengadeshprabhu Karuppagounder, Ritwik Datta, Hee Ju Kim, Ashil Koranne, Annie Yang, Ted Yu, Danielle Yi, Kimberly Crutcher, Zhihua Li, Thach Mai, Banmeet Anand, Colin Hislop, Priya Handa, Hanadie Yousef, Jeremy D. O'Connell

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4-15

High-throughput 3D imaging and quantification of mouse hindlimb muscles using light sheet fluorescence microscopy

Alex Addinsall[1], M. Hahn[1], K.Andersen[1], A. Hamilton[1], L. L. Larsen[1], A. Højrup Runegaard Thomsen[1] and U. Roostalu[1]

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4-16

A MRI *vs* histology study of C57Bl/6J Rj, a murine model of muscle aging in a context of sedentary lifestyle.

Beatrice Matot[1], Agathe Perney[1], Bruno Cadot[2], Sebastien Bougnaud[1], Maud Beuvin[3], Emmanuelle Lacene[3], Benjamin Marty[1], Harmen Reyngoudt[1], Teresinha Evangelista[3,4], Yves Fromes[1]

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4-17

MicroRNAs altered during ageing affect mitochondria in skeletal muscle

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4-18

Local TGF-β signaling causes impaired contractability and low-response to exercise in human skeletal muscle

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4-19

Myofiber aryl hydrocarbon receptor is essential for maintaining skeletal muscle integrity.

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4-20

Correlation of CT-measured myopenia with two-year overall survival in older adults with non-small cell lung cancer treated with immunotherapy in a third level hospital in Mexico.

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4-21

Insights into the effects of platelet-based applications on skeletal myoblasts proliferation

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4-22

Obesity reprograms adipose extracellular vesicles to induce muscle atrophy via miR-150-5p-mediated transcriptional silencing

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4-23

Tyrosine Nitration/Phosphorylation Crosstalk: A Molecular Switch Modulating HGF/c-Met Signaling and Satellite Cell Dysfunction in Aging

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4-24

Large-Scale Screening Identifies Novel Compounds Promoting Myotube Hypertrophy Through Distinct Mechanistic Clusters

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POSTER ABSTRACTS

1-01

Glycerol kinase mediated lipid cycling contributes to fat loss in cancer associated cachexia

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Introduction: Cancer-associated cachexia (CAC) is a hypermetabolic wasting syndrome marked by muscle and adipose tissue (AT) loss. Survival rates for cancer patients with solely AT wasting are as poor as for patients with combined skeletal muscle and AT wasting, attributing an important role to AT in CAC. The mechanisms of cancer associated AT loss remain incompletely understood. We aimed to identify processes of AT loss in CAC.
Methods: AT was excised and analyzed from wild-type (WT), UCP1 deficient (UCP1ko), adipocyte specific inducible glycerol kinase deficient (GYKΔATko), or double knock out (DkoΔAT) mice. To study CAC, the genetically engineered mouse model K5-SOS+ and the syngeneic allograft model CHX207 was used. For cold exposure, mice were housed at 5°C – 16°C for 7 days. AT was analyzed histologically, for protein and mRNA expression, mitochondrial content, and for metabolic activity. Mechanistic studies were performed in beige differentiated WT and UCP1ko adipocytes with or without shRNA mediated GYK deletion (GYK-KD).
Results: UCP1-deficiency did not protect from AT loss but aggravated catabolic AT remodeling. GYK-dependent substrate cycling accelerates lipolysis, fatty acid re-esterification, and oxidative metabolism, thereby driving AT catabolism in CAC and during cold exposure. Disruption of this futile cycle protected UCP1ko mice from AT wasting, but severely impaired cold tolerance. GYK-deficiency blunted PKA signaling and lipolysis, highlighting its essential role in controlling lipid catabolism and ß3-adrenergic responsiveness. Notably, GYK was elevated in AT from cachectic patients, and GYK-KD reduced lipolysis and oxidative gene expression in human adipocytes.
Conclusion: Our findings establish GYK as a key mediator of non-canonical thermogenesis and a potential target to preserve AT in CAC.

1-02

Eye of the beholder: portraiture of patients with cachexia by their loved ones

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Introduction: This paper examines portraits of people with cachexia of different etiologies created by the friends and family of the subjects.
Methods: Two individual artworks (a painting and a sculpture) and one series of works (drawings and paintings) are analyzed for their form, content, and context.
Results: "Aubrey Beardsley" (1894, tempera on canvas) was painted by Walter Richard Sickert, a friend of the titular subject; Beardsley died from tuberculosis at 25. Details such as his emaciated frame, kyphoscoliosis, and the cane in his right hand are clinical hallmarks of cachexia. His posture, hunched and turned away from the viewer, indicates fatigue and perhaps represents demoralization and the social disconnection of his disorder, underscored by the composition and colors. Ferdinand Hodler obsessively depicted his mistress Valentine Godé-Darel in a series of portraits (1913-1915, mixed media) from their meeting, through her difficult pregnancy, to her diagnosis and treatment for an unspecified (perhaps gynecological) cancer, and finally, to her death. Hodler captures the bed-bound Godé-Darel progressive decline (here seen as physical wasting, fatigue, and anhedonia), using line, color, and medium to differentiate the stages of her health. Finally, "Untitled (Portrait of Ross in L.A.)" by Felix Gonzalez-Torres (1991, mixed media) is a sculptural representation of Ross Laycock, Gonzalez-Torres's lover, manifested as a pile of brightly wrapped candies. Viewers are invited to take a piece; as they do, the pile shrinks from its "ideal weight" of 175 pounds, just as Laycock's body wasted progressively from AIDS-induced cachexia. It poignantly references the anorexia and loss of pleasure in eating experienced by people with cachexia.
Conclusions: The selected artworks depict not only the physical effects of cachexia and wasting disorders, but also the social effects of disease. They reflect the suffering of the caregiver through and by the representation of the cachectic patient.

1-03

Cachexia risk classification using the Asian Working Group for Cachexia criteria in patients with sarcopenic dysphagia

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Introduction: The purpose is to evaluate the clinical relevance of a cachexia risk classification based on the Asian Working Group for Cachexia (AWGC) criteria in patients with sarcopenic dysphagia.
Methods: This retrospective cohort study examined 271 adult patients with sarcopenic dysphagia from the Japanese sarcopenic dysphagia database. Patients without a cachexia-related condition were classified as having "no risk of cachexia." Those with a cachexia-related disease but no additional risk indicators were classified as "low risk of cachexia." Patients with a cachexia-related disease who experienced weight loss of more than 2% within three to six months, have a BMI of less than 21 kg/m², have low grip strength (less than 28 kg for men and less than 18 kg for women), or have a CRP level greater than 0.5 mg/dL were classified as "at risk of cachexia." Participants meeting the AWGC criteria were categorized as "Cachexia". The prevalence of each group, as well as mortality and functional outcomes, were compared across the groups.
Results: The mean age was 83.7 (8.4) years, with 119 men and 152 women participating. One hundred forty (52%) were categorized as the no risk group, one (0.4%) as the low risk group, 33 (12%) as the at risk group, and 97 (36%) met the AWGC criteria for cachexia. Mortality was significantly higher in the cachexia group (no risk: 2%, at risk: 3%, cachexia: 15%, $p < 0.001$). The median follow-up Barthel Index (no risk: 50, at risk: 60, cachexia: 55, p=0.652) and median Food Intake Level Scale (no risk: 8, at risk: 7.5, cachexia: 7, p=0.635) did not differ significantly among the three groups.
Conclusion: Cachexia and at risk of cachexia are common in patients with sarcopenic dysphagia. Classifying cachexia risk using the AWGC criteria may serve as a practical and accessible tool for identifying vulnerable patients.

1-04

Multimodal interventions for cachexia management: Cochrane Review

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Introduction: Cachexia is a debilitating condition linked to chronic illnesses, marked by unintentional weight and muscle loss, fatigue, and reduced quality of life. Multimodal interventions combining nutrition, pharmacology, and exercise aim to address its complex causes. This review evaluated their safety and effectiveness.
Methods: We searched CENTRAL, MEDLINE, Embase, PsycINFO, and two trials registries in July 2024. Studies compared multimodal interventions with treatment as usual, a variation of the intervention, or unimodal approaches. Primary outcomes were physical function, strength, and adverse events. Secondary outcomes included body composition, weight, quality of life, appetite, fatigue, and biochemical markers. Certainty of evidence was rated using GRADE.
Results: The review included nine randomised controlled trials involving 926 adults with cachexia or at risk of it. There were six studies in people with cancer, and one each in people with COPD, chronic kidney disease, and HIV/AIDS.
Compared to treatment as usual, one cancer study (46 participants) found no clear benefit from multimodal intervention in physical function (MD −16.10 m), strength (MD 3.80 kg) or adverse events (RR 1.36). Against variations of the intervention, three cancer studies and one HIV/AIDS study (192 participants) showed no significant differences in physical function (MD 10.0 m), strength (MD 0.7 kg) or adverse events (RR 0.87). In comparison with unimodal interventions six studies across cancer, COPD, CKD and HIV/AIDS (802 participants) found no meaningful improvements in physical function (SMD 0.02), strength (SMD 0.23), or adverse events (RR 0.87). Across all comparisons, there was no clear evidence for an effect of a multimodal intervention on the secondary outcomes. Evidence was consistently downgraded due to risk of bias, imprecision, and heterogeneity.
Conclusion: There is currently insufficient and very low-certainty evidence to determine whether multimodal interventions are effective for managing cachexia. High-quality, large-scale trials are needed to establish their role in clinical care.

1-05

Multi-Modal Integrated intervention combining Exercise, Anti-inflammatory & Dietary advice (MMIEAD) for kidney cachexia: a mixed-methods feasibility cluster randomised controlled trial and process evaluation

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Introduction: Integrating exercise, anti-inflammatory agents and dietary advice is likely to be beneficial in treating cachexia, however, this has never been trialled in kidney cachexia.
Methods:
Objectives:
- Determine patient eligibility and recruitment rates;
- Identify intervention retention and adherence rates;
- Determine statistical and methodological considerations for optimal study design and data collection burden;
- Conduct a qualitative process evaluation to assess intervention acceptability and practicality;
- Assess the feasibility of conducting a definitive economic evaluation.

Design: Phase 1: deliver and evaluate a 12-week multimodal intervention using a feasibility cluster randomised controlled trial (cRCT) design. Phase 2: conduct a process evaluation with healthcare professionals (HCPs) and patients. Phase 3: assess the feasibility of conducting a definitive economic evaluation.
Participants: Patients will be eligible if they are CKD Stage 5 in receipt of haemodialysis for >3 months, have oedema-free weight loss of at least 5% in 12 months or BMI less than 20 kg/m2, aged >18 years. HCPs will be eligible if they have been a member of the multidisciplinary healthcare team for more than three months and have exposure to the study.
Randomisation: Two sites have been randomly assigned to the intervention group and two to the control group.
Sample: Phase 1 and 3: 10 research participants per intervention site; 10 research participants per control site; 40 in total across all sites (n=4). Phase 2: 15 patients for interviews and 15 HCPs for interviews or focus groups across all sites.
Results: Trial registration number (NCT07107087), ethical approval is in place for study commencement (REC reference: 25/NI/0069). Recruitment will commence on 08.09.25.
Conclusion: The results of this study will be used to determine the feasibility and acceptability of the MMIEAD intervention in preparation for a larger definitive UK wide multi-site cRCT.

1-06

Chronic kidney disease-associated cachexia and other wasting syndromes: Definitional challenges and interactions with gut microbiome, uremic toxins and inflammation

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Introduction – In patients with chronic kidney disease (CKD), several syndromes related to muscle wasting can be observed, including malnutrition, protein-energy wasting (PEW), cachexia

and sarcopenia. Although these conditions share overlapping features, they differ in underlying mechanisms, diagnostic criteria and reversibility. In practice, these distinctions are often blurred, leading to inconsistent prevalence and suboptimal management. Among them, cachexia represents a particularly severe form, associated with poor outcomes. Inflammation and uremic toxins are recognized as central drivers of CKD-associated cachexia, but their interplay with the gut microbiome remains poorly understood.
Methods – The DYNAMICA study (NCT06986265) is designed to investigate the links between cachexia, gut microbiome, inflammation and uremic toxins in CKD patients under dialysis. A prospective cohort of 157 patients treated with peritoneal dialysis or hemodialysis (in-center, self-care satellite and home-based) is being established. Each patient undergoes deep phenotyping including evaluation of cachexia and body composition by bioelectrical impedance analysis and CT scan (L3), with one-year follow-up. Incidence of cachexia and other wasting syndromes will be compared using multiple definitions (GLIM for malnutrition, ISRNM for PEW, EWGSOP for sarcopenia, oncology-derived criteria for cachexia). Comparisons will be made between cachectic and non-cachectic patients in terms of gut microbiota, inflammatory markers, uremic toxins, dialysis dose and modality. *In vitro* experiments will assess the effects of uremic toxins on muscle cells, with *in vivo* validation through human muscle biopsies.
Results – Preliminary analyses (> 40 patients) will be presented, focusing on definitional overlaps and discrepancies in identifying wasting syndromes.
Conclusions – This study will provide the first longitudinal evaluation of cachexia, inflammation, uremic toxins and gut microbiota in dialysis patients. By integrating clinical, biological and mechanistic approaches, DYNAMICA aims to clarify definitions and pathophysiology of CKD-associated wasting syndromes and pave the way for rationally designed microbiome-based interventions.

1-07

Cachexia in Patients with Fabry Disease: A Cross-Sectional Multicenter Study

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Introduction: Cachexia is a complex, multifactorial syndrome characterized by muscle wasting, reduced physical performance, and impaired quality of life. While Fabry Disease (FD) is primarily known for its cardiac and renal complications, cachexia-like features have not been systematically investigated. This study aimed to evaluate body composition, muscle strength, and functional capacity in FD patients and to explore their association with phenotype, sex, and treatment.
Methods: Adults with genetically confirmed FD were recruited from four Italian referral centers. Assessments included bioelectrical impedance analysis (BMI, Fat-Free Mass Index [FFMI], Fat Mass Index [FMI], Phase Angle [PA]), cardiopulmonary exercise testing (CPET, VO_2 peak), and functional evaluations (6-minute walk test [6MWT], handgrip [HG], chair-stand, isometric/isokinetic strength). Analyses were stratified by phenotype (classic vs. late-onset/VUS), sex, and treatment status (ERT/chaperone vs. untreated).
Results: Forty-two patients (29 females, 13 males; mean age 46±13.9 yrs) were included. Classic phenotype patients had lower BMI (20.7 vs. 27.6 kg/m², p=0.001), FFMI (males: 16.7 vs. 21.5 kg/m², p=0.003; females: 16.0 vs. 17.4 kg/m², p=0.032), and FMI (females: 4.6 vs. 9.3 kg/m², p=0.003) compared to late-onset/VUS patients. VO_2 peak was reduced (<85% predicted) in 23.8% of the cohort, more frequently in males (53.8% vs. 10.3% in females, p=0.005), in classic phenotype patients (53.8% vs. 10.3%, p=0.005), and in treated individuals (34.6% vs. 6.3%, p=0.036). PA was below reference in males (5.4°) and significantly lower in treated vs. untreated patients (p=0.036), correlating with VO_2 peak (r=0.879, p=0.01). HG strength was <50th percentile in 74.3% of patients, with all classic males affected (p=0.015). Functional tests confirmed widespread muscle weakness and impaired performance.
Conclusions: FD patients, particularly males with the classic phenotype, showed cachexia-like features, including reduced muscle mass, strength, and exercise capacity. Comprehensive body composition and functional assessments should be incorporated into FD care to detect and manage cachexia early.

1-08

Evaluating the Prevalence of Cachexia in Chimeric Antigen Receptor (CAR) T-cell Therapy Patients using Multiple Recommended Diagnostic Criteria

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Introduction: CAR T-cell therapy is a novel cellular immunotherapy, available to patients with relapsed or refractory haematological malignancies. While cachexia prevalence has been described in patients receiving conventional systemic cancer therapies, data in CAR T candidates are lacking, representing an unmet need. The aim of the study is to investigate baseline pre-treatment cachexia prevalence in adults with refractory/relapsed haematological malignancies scheduled to receive CAR T-cell therapy.
Methods: Patients were recruited from a tertiary UK facility (Mar 2024-present), as part of an ongoing observational study. Baseline assessments were conducted at apheresis: body weight (BW), BMI, BW loss (BWL), body composition (fat-free mass (FFM-kg), appendicular skeletal muscle mass (ASM-kg), and corresponding indexed values (kg/m^2)-FFMI and ASMI, handgrip strength (HGS), and validated nutrition screening tools. Blood markers included haemoglobin, C-reactive protein (CRP), and albumin. Assessment scores were classified using criteria by Fearon et al, Evans et al, modified Glasgow Prognostic Score (mGPS) and Global Leadership Initiative for Malnutrition (GLIM).
Results: 38 patients (24 male, 59.5±13.7 years) participated. Pre-treatment assessments (39 [22-149] days pre-CAR T infusion) included: BMI: 25.8±4.4kg/m^2, FFMI: 18.2±2.8kg/m^2, ASMI: 7.3±1.2kg/m^2, HGS: 29.9±11.1kg, haemoglobin: 12.0±1.7g/dL, CRP: 6.6 [0.6-148.7mg/L], albumin: 41.7±5.8g/L. At baseline, 20 patients experienced recent BWL, with 34% (n=13) >5% BWL in the previous six months; 21 patients had low muscle strength by HGS, with 55% and 39.5% experiencing fatigue and anorexia, respectively. Pre-treatment, 44.7% (n=17) patients met Fearon criteria for cancer cachexia, 34.2% (n=13) using Evans et al, 42.1% (n=16) using mGPS, and 57.9% (n=22) indicated malnutrition using GLIM.
Conclusion: The preliminary findings from this study indicate a high pre-treatment prevalence of cachexia in the adult CAR T-cell treatment cohort, with overlap observed regardless of the definition used. These findings require urgent investigation as cachexia is known to significantly impact upon successful cancer treatment and increase the risk of mortality.

1-09

DNA Methylation–Based Liquid Biopsy for Cachexia Risk Stratification in Glioma via Transformer-Enabled Muscle Transcriptome Inference

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Background: DNA methylation profiling informs tumor diagnosis and classification, yet translating it into non-invasive glioma assessment is challenging. Critically, glioma-associated cachexia—a muscle-wasting syndrome—still lacks reliable non-invasive monitoring. We present a blood DNA methylation–based framework that infers skeletal muscle transcriptomes to stratify cachexia risk, while simultaneously providing accurate glioma classification.
Methods: We built a DNA methylation atlas (15,606 samples) and an interpretable Transformer model to predict gene expression from methylation, using 7,525 paired samples to learn from promoter/enhancer CpG sites. For cross-tissue inference, a multi-task encoder–decoder was trained on GTEx blood–muscle pairs (n=710), enabling prediction of muscle expression from blood. We then applied this framework to 4,274 glioma methylomes to infer patient-specific muscle transcriptomes and assessed their similarity to a known cachexia muscle signature using cosine similarity.
Results: Inference of muscle transcriptomes revealed a greater similarity to cachexia signatures in IDH-wildtype than IDH-mutant gliomas, non-invasively linking tumor molecular status to systemic wasting risk. The framework's underlying predictive power was high, with robust methylation-to-transcriptome prediction (R^2 = 0.939). As a core validation of the platform, the model also achieved 99.23% accuracy for glioma subtype classification (AUC > 0.95). Attention visualization highlighted key regulatory genes (HDAC4, CASZ1), and a blood cfDNA marker panel was identified that included the IDH-associated marker cg05549077 (FOXP1).
Conclusion: This interpretable Transformer framework provides a novel liquid biopsy for muscle-related risk assessment by non-invasively inferring cross-tissue transcriptomes. By linking glioma molecular subtype to a systemic cachexia signature, our platform offers a new tool to stratify patients and advance research into wasting disorders while also enabling accurate tumor classification.

1-10

Integrated myomiRs and stress cytokine profiling reveals the molecular signature of cachexia in patients with chronic hearth failure

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Introduction: Cardiac cachexia (CC) is a severe complication of chronic heart failure (CHF), affecting up to 40% of patients and associated with poor prognosis and mortality. Reliable biomarkers for early detection and risk stratification are still lacking. Circulating myomiRs (miRs) and stress-responsive cytokines, such as growth differentiation factor-15 (GDF-15) and fibroblast growth factor-21 (FGF-21), have been implicated in muscle wasting, inflammation, and metabolic stress. We investigated whether combined profiling of miRs, GDF-15, and FGF-21 could reflect the catabolic–anabolic imbalance and structural remodeling associated with this syndrome.
Methods: We studied 25 CHF patients and 10 healthy controls (HC). CC was diagnosed according to Anker's criteria. Circulating miRs were quantified by RT-qPCR, while GDF-15 and FGF-21 by ELISA. CHF were analyzed according to cachexia status (CC vs nCC) and as having reduced (HFrEF) or preserved ejection fraction (HFpEF). Associations with New York Heart Association (NYHA) classes and left ventricular mass index (LVMI) were evaluated.
Results: In CHF, miR-15b and -486 were downregulated in both CC/nCC vs HC ($p<0.05$), along with downregulation of miR-29b between CC vs nCC ($p=0.019$) and vs HC ($p<0.001$). Upregulation of GDF-15 was observed in both CC/nCC vs HC ($p<0.001$), while FGF-21 levels were upregulated in CC vs HC ($p<0.05$) and between CC vs nCC ($p=0.012$). miR-29b was lowest in HFrEF+CC compared with HFpEF+nCC ($p=0.019$). FGF-21 was higher in HFrEF than HFpEF ($p = 0.039$), and in NYHA III versus II ($p=0.05$). GDF-15 correlated positively with miR-29b and miR-486 in CHF, while FGF-21 correlated inversely with LVMI and miR-486 in CC.
Conclusions: CHF is associated with a distinct molecular profile of myomiRs downregulation and stress cytokine elevation. In CC, these alterations intensify, highlighting miR-29b, GDF-15, and FGF-21 as promising biomarkers of disease progression. Further investigations are ongoing to clarify their potential involvement in the mechanisms driving CC.

1-11

Impact of Ruxolitinib on GDF-15, Appetite, and Body Composition in Myelofibrosis Patients

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Introduction: Myelofibrosis (MF) is a BCR/ABL-negative myeloproliferative disorder characterized by abnormal clonal expansion of hematopoietic progenitors, bone marrow fibrosis, and systemic inflammation. Cachexia and reduced food intake are often observed in MF, driven by inflammation and splenomegaly. Aim of the present study was to evaluate the impact of Ruxolitinib, a JAK1/2 inhibitor widely used for MF treatment, on changes in body composition.
Methods: We collected data from MF patients before (T0) (n=18) and after 6 months (T1) (n=22) of Ruxolitinib treatment. Nutritional risk and malnutrition were evaluated with MUST and GLIM respectively. Anorexia was assessed with FAACT and body composition estimated with BIA. Sex-specific cut-off values for Fat Free Mass Index (FFMI, kg/m²) were made according to ESPEN criteria. Circulating GDF-15 was assessed with xMAP Intelliflex.
Results: At baseline T0, 50% of patients (n=9) were classified at risk of malnutrition (MUST), while 52% (N=11) fulfilled the GLIM criteria for malnutrition. At T1, MUST decreased from 50% to 12%, and GLIM decreased from 52% to 8%. A significant reduction in circulating GDF-15 concentrations was documented from T0 to T1 (p=0,010), as well as a significant increase of FAACT score (35(29;40) vs 41(37;44), p=0,01). Interestingly, changes in GDF-15 levels between T0 and T1 were inversely correlated with changes in FAACT (r=–0.531, p=0.023), FFMI (r=–0.488, p=0.047), muscle mass (r=–0.504, p=0.039), and lean body mass (r=–0.490, p=0.046).
Conclusion: Ruxolitinib treatment was associated with improvements in body composition among patients with MF, which cannot be ascribed only to the reduction of splenomegaly or overall disease control, but also likely to the concomitant decreases in GDF-15 levels, suggesting a potential role of Ruxolitinib in the management of MF-induced anorexia and cachexia.

2-01

Skeletal muscle AMPKα2 as a regulator of muscle strength and fat mass in chemotherapy-induced cachexia

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Introduction: Cisplatin is a widely used chemotherapeutic agent, but its clinical benefits are often accompanied by cachexia-related symptoms. Effective interventions to mitigate these adverse effects remain limited. 5'-adenosine monophosphate-activated protein kinase (AMPK), an intracellular energy sensor typically activated by exercise and decreased food intake, plays a central role in mitochondrial function, energy homeostasis, and muscle metabolism. This study aimed to investigate the role of AMPK in chemotherapy-induced muscle wasting and its potential role as a therapeutic target.
Methods: Adult male wild-type (WT) and muscle-specific AMPKα2-inactive transgenic (AMPKα2i TG) FVB mice received daily cisplatin or saline injections for 5 days, followed by a 4-day recovery before terminal analyses. Food intake, body composition, and muscle function (grip strength, treadmill endurance) were assessed throughout the study. Muscle mass was measured at terminal surgery, and tissues were collected for molecular analyses.
Results: At baseline, TG mice showed impaired endurance and greater fatigue, with a reduced proportion of slow-twitch (type IIA) fibers compared to WT. Cisplatin reduced food intake, body weight, fat mass, and lean mass in both genotypes, although fat loss was less pronounced in TG mice. Muscle mass was modestly reduced, and endurance was unaffected by cisplatin in either genotype. Notably, cisplatin impaired grip strength in TG but not WT mice. Basal fatty acid oxidation (pACC/ACC ratio) was lower in TG than WT, but cisplatin elevated pACC/ACC in TG mice to WT levels. TG mice also exhibited consistently higher autophagy markers (LC3II/I) and lower mitochondrial biogenesis marker (PGC-1α) expression than WT, independent of cisplatin.
Conclusions: AMPK is critical for endurance and fatigue resistance through maintenance of mitochondrial biogenesis and slow-twitch fibers. In cisplatin-induced cachexia, loss of AMPKα2 activity selectively impaired muscle strength but attenuated fat loss, indicating its complex, context-dependent role in chemotherapy-induced cachexia.

2-02

CHOP chemotherapy induces sex-specific transcriptional changes in skeletal muscle of juvenile mice

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Introduction: Multi-agent chemotherapy regimens are standard in pediatric oncology, yet their impact on the transcriptional landscape of developing skeletal muscle remains unclear. We used RNA sequencing to investigate CHOP-induced changes in juvenile male and female mouse muscle.
Methods: 28-day old C57Bl/6 mice received two cycles of a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) or PBS. Total RNA was isolated from gastrocnemius muscle and sequenced (20 million PE150 reads/sample). Differential gene expression (DEG) analysis was performed using DESeq2 with FDR-adjusted p-value < 0.05.
Results: CHOP treatment led to 217 DEGs in males and 214 in females, with only 29 shared transcripts. Males showed reduced expression regulators of myogenic processes (Calcr, Myf5, Myod1) and elevated Eif2ak2, a negative regulator of translation. Females exhibited higher expression of ECM remodeling genes (Postn), protein turnover markers (Ube2c, Ube2b), and cell-cycle regulators (Cdkn1a, Cdk1). GO analysis of pooled DEGs highlighted enrichment in cell-cycle processes, cytoskeletal remodeling, and muscle differentiation pathways.
Conclusions: Pediatric CHOP chemotherapy elicits robust, sex-specific transcriptional changes in developing muscle, affecting myogenic regulation, protein turnover, and extracellular remodeling. These findings underscore divergent molecular responses between males and females and identify potential targets for protecting muscle health in pediatric cancer patients.

2-03

The role of interleukin-6 signaling in the pathogenesis of cancer-associated cachexia

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Introduction: Cancer-associated cachexia (CAC) is a devastating syndrome associated with reduced quality of life and poor prognosis of cancer patients. CAC is characterized by unintended loss of body weight due to muscle- and adipose tissue loss. Cachexigenic tumors secrete a plethora of cytokines that are suggested to directly signal catabolism in host tissues. One of these so-called cachexokines is interleukin-6 (IL-6). IL-6 and the activation of its IL-6 receptor alpha (IL-6Rα)-dependent signaling pathway, involving the phosphorylation and activation of STAT3 (pSTAT3) by Janus kinases (JAK), have been shown to play a pivotal role in the pathogenesis of cachexia. In accordance, in murine models of CAC, we and others found increased IL-6 in the circulation and elevated pSTAT3 levels in adipose tissues. Therefore, we aimed to decipher the role of IL-6 signaling in adipose tissue loss during CAC.
Methods: 10-14-week-old wildtype (wt) or whole-body IL-6Rα-ko mice were inoculated with CHX207 cachexigenic cancer cells or phosphate-buffered saline (PBS) as control. STAT3 signaling was blocked by administering the JAK inhibitor Ruxolitinib (25 mg/kg) by intraperitoneal (i.p.) injections twice daily. Tumor growth and cachexia development were monitored. Tissues were excised and weighed. Adipose tissue lysates were analyzed for protein expression by Western Blotting analysis.
Results: Surprisingly, cachexigenic tumor-bearing mice (tumor-mice) globally lacking IL-6Rα did not show reduced pSTAT3 levels and were not protected from CAC. To investigate whether STAT3 signaling is responsible for weight loss in CAC, we prevented STAT3 activation by administering the JAK inhibitor Ruxolitinib. Ruxolitinib treatment prevented STAT3 phosphorylation in adipose tissues of tumor-mice. However, Ruxolitinib did not ameliorate tissue atrophy or body weight loss in tumor-mice, indicating that STAT3 signaling is not the main driver of weight loss in CAC.
Conclusion: These data suggest that IL-6 is unable to directly induce adipose tissue loss or acts via an IL-6Rα-independent pathway.

2-04

Induced ablation of Prmt7 in endothelial cells aggravates cardiac cachexia induced by myocardial infarction

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Introduction: Cardiac cachexia, a debilitating complication of myocardial infarction (MI), is marked by progressive skeletal muscle wasting and portends poor prognosis, yet its molecular determinants remain incompletely defined. Because the vascular endothelium governs perfusion and nutrient flux, endothelial signaling is poised to influence systemic muscle homeostasis. We investigated whether endothelial protein arginine methyltransferase 7 (Prmt7), previously identified as critical for vascular integrity and post-MI recovery, restrains ischemic muscle waste.
Methods: Inducible endothelial-specific Prmt7 knockout mice were subjected to experimental MI and evaluated using integrative physiological, histological, molecular, and transcriptomic analyses. Complementary endothelial stress models with pharmacologic modulation of Prmt7 were employed to validate mechanistic pathways.
Results: Loss of endothelial Prmt7 precipitated overt cachexia after MI, manifesting as impaired limb perfusion, diminished neuromuscular strength, disproportionate lean and adipose loss, myofiber atrophy, and enhanced fibrosis. Mechanistically, deficiency drove hyperactivation of the AMPK–FoxO axis, upregulation of MuRF1/Atrogin-1, and amplification of hypoxia-induced unfolded-protein-response signaling (HIF-1α–eIF2α–ATF4), culminating in CHOP-mediated apoptosis. Mitochondrial protein abundance was markedly reduced, and transcriptomic profiling revealed broad catabolic reprogramming. In vitro, Prmt7 activation attenuated hypoxic injury and preserved mitochondrial homeostasis, confirming a causal, endothelium-centric mechanism.
Conclusions: Endothelial Prmt7 emerges as a central molecular safeguard against MI-associated muscle wasting by constraining maladaptive catabolic signaling and sustaining mitochondrial integrity. Targeting this axis offers a promising therapeutic strategy to attenuate ischemic cachexia.

2-05

LDHA upregulation contributes to CKD-associated cachexia and muscle dysfunction

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Introduction: Chronic kidney disease (CKD) is frequently accompanied by skeletal muscle wasting and impaired contractility, which contribute to morbidity and reduced quality of life. However, the molecular mechanisms underlying CKD-induced muscle dysfunction remain poorly defined. Metabolic reprogramming has emerged as a key driver of muscle atrophy. Lactate dehydrogenase A (LDHA), a glycolytic enzyme catalyzing the conversion of pyruvate to lactate, has been implicated in metabolic alterations that may exacerbate muscle dysfunction.
Methods: A CKD animal model was established by left kidney removal followed one week later by 2/3 right kidney ligation (5/6 nephrectomy). Functional performance was evaluated one week after surgery by measuring forelimb and all-limb grip strength. Tibialis anterior (TA) muscles were collected for histological and biochemical analyses. Cross-sectional area (CSA) was measured, and LDHA expression was determined by Western blotting.
Results: Grip strength was significantly decreased in the 5/6 nephrectomy group compared with controls. Histological analysis revealed reduced CSA in TA muscle, consistent with atrophy and impaired contractile function. Western blotting showed that LDHA expression was markedly upregulated in atrophied TA muscle, suggesting that enhanced LDHA activity contributes to CKD-induced muscle dysfunction through metabolic dysregulation.
Conclusions: Our findings demonstrate that CKD induces skeletal muscle weakness and wasting, partly through LDHA upregulation, identifying LDHA as a potential therapeutic target in CKD-associated cachexia. As a next step, we will perform proteomic analysis to define secretome-derived factors that may further regulate muscle function and reveal additional therapeutic opportunities.

2-06

Using a proximity labeling approach to investigate lung-secreted proteins in an inflammatory weight loss model

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Background: Cachexia involves weight loss, muscle and fat wasting, anorexia, and systemic inflammation, yet the secreted factors driving these systemic responses remain poorly defined.
Methods: To investigate lung-derived mediators, we developed a mouse model enabling lung-specific expression of the promiscuous biotin ligase BirA*. Secreted proteins biotinylated in the lung can be captured from distal tissues using streptavidin pulldown. Following intranasal lipopolysaccharide (LPS), a model of acute inflammation-induced anorexia and weight loss, we profiled the plasma secretome.
Results: We identified 86 proteins significantly increased in plasma after LPS, including 11 secreted directly from the lung. Cross-referencing with cancer cachexia datasets revealed several candidates with putative roles in wasting. Functional testing using genetic knockouts demonstrated divergent effects: SPP1 deletion exacerbated lean mass loss after LPS, but protected against fat mass loss. LRG1 deletion attenuated LPS-induced splenomegaly without altering food intake or weight loss.
Conclusions: These studies reveal lung-secreted proteins as key contributors to systemic responses to LPS and nominate novel factors that may drive cachexia. Ongoing work is extending this approach to KRAS; LKB1 lung cancer and elastase+LPS emphysema models to define shared and disease-specific mediators of cachexia.

2-07

Concurrent chemo- and radiotherapy in an orthotopic lung cancer mouse model: a preclinical platform for studying treatment-induced cachexia

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Background: Lung cancer cachexia is a debilitating syndrome that impairs quality of life, treatment tolerance, and survival. While tumor-induced wasting has been extensively investigated, our understanding of treatment-induced cachexia remains limited due to the lack of clinically relevant preclinical models.
Methods:
Immune-competent 11-week-old male 129S2/Sv mice were randomly assigned to sham-operated or tumor-bearing (TB) groups. Syngeneic lung adenocarcinoma cells (K-ras^{G12D}; p$^{53R172H\Delta G}$) were inoculated into the left lung. Two weeks later (mean tumor volume: 35 mm³), TB mice received vehicle (TB), radiotherapy alone (TB-RT), or concurrent chemoradiotherapy (TB-CCRT). (CC)RT consisted of three weekly radiotherapy (4 Gy) cycles with or without chemotherapy (4:16 mg/kg cisplatin: etoposide). Body weight and food intake were measured daily, and grip strength, tumor growth, and body composition (by µCBCT) were measured weekly. At surrogate survival endpoint, mice were euthanized and tissues collected for morphological and molecular analyses.
Results:
Cachectic TB mice showed progressive, concomitant loss in body weight (-14.3±3.9%), fat mass (subcutaneous adipose tissue (SAT) -30.9±4.6% and visceral adipose tissue (VAT) -34.9±5.1%), muscle mass (-13.8±1.8%) and grip strength (-6.1±5.9%) over time. RT alone did not impact the development and progression of cachexia, while TB-CCRT mice showed more pronounced loss of body weight (-22.3±2.0%), including muscle (-15.3±1.0%) and fat mass (SAT -49.1±6.1% and VAT -60.1±6.0%), over time. Body weight ($p<0.001$) and fat mass ($p<0.01$) loss were significant compared to TB mice, while changes in muscle mass were not. In contrast to TB mice, the development of cachexia in the TB-CCRT mice was accompanied by anorexia. Despite increased cachexia, tumor growth was significantly suppressed in TB-CCRT mice compared with TB mice (–48.02 mm³, $p=0.04$).
Conclusion: This study establishes and characterizes a novel, treatment-induced lung cancer cachexia mouse model, providing a robust and clinically relevant platform to investigate mechanisms and evaluate targeted interventions during chemoradiotherapy.

2-08

Automated µCBCT-based body composition assessment in mice using a 3D nnU-Net model

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Introduction: Loss of skeletal muscle and fat mass is a frequent complication of lung cancer, associated with increased mortality and reduced quality of life. Reliable preclinical models with longitudinal body composition monitoring are essential to study disease progression and evaluate therapies. We developed a fully automated deep learning algorithm to segment seven anatomical structures in micro–cone beam computed tomography (µCBCT) images of mice, enabling fast, reproducible, and scalable body composition analysis.
Methods: µCBCT data from 105 mice (tumor-bearing and sham controls) were acquired using an XRad225Cx scanner (50 kV, 2.6 mA) under approved protocols. Manual segmentations of seven structures were performed on five sham controls for ground truth. A two-phase no-new U-Net (nnU-Net) model training strategy was used: initial training on controls (4:1 split), followed by semi-automatic annotation and expert correction of ten tumor-bearing cases, yielding 15 annotated datasets. Performance was evaluated quantitatively (n=5) and qualitatively (4-point Likert scale; n=85).
Results: The model achieved a mean Dice Similarity Coefficient (DSC) of 93.5 ± 2.7% across all structures (range: 89.6–97.4%), indicating robust segmentation accuracy. Qualitatively, the median score across all structures was 4. Over 75% of bone and spinal cord contours were directly usable, while 60–70% of adipose and muscle contours required minor adjustments. AI-assisted contouring reduced refinement time to 12 ± 5 minutes per case, compared to approximately 9 hours for full manual segmentation. Longitudinal follow-up revealed progressive body composition changes in tumor-bearing mice, clearly separating them from controls and confirming cachexia development.
Conclusion: Our nnU-Net–based pipeline provides accurate, efficient, and reproducible segmentation of key anatomical structures in preclinical µCBCT imaging. This approach markedly reduces manual workload and enables robust longitudinal body composition studies in mouse models of lung cancer.

2-09

Adipose tissue macrophages and IL-4 receptor signaling under hypercatabolic conditions

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Introduction: Adipose tissue macrophages (ATMs) aid to ensure tissue integrity in health and disease. Upon prolonged catabolic stimulation, adipose tissue undergoes catabolic remodeling, characterized by alternative activation of ATMs, as well as by elevated lipolysis and non-shivering thermogenesis of adipocytes. The resulting increase in energy expenditure contributes to heat production upon cold but is detrimental for patients suffering from cancer-associated cachexia (CAC). Previously, we found that Interleukin-4 receptor (IL-4r) signaling and, hence, alternatively activated ATMs, contribute to catabolic remodeling of white adipose tissue (WAT) in tumor-bearing mice. However, the mechanisms by which ATM composition is altered and IL-4r signaling in macrophages is involved in adipose tissue loss during CAC remain unclear.
Methods: CAC was induced by injecting Lewis lung cancer cells (LLC) or PBS as control into 12-19-week-old male and female mice. In the pre-cachectic state (body weight loss ≤ 5%), mice were sacrificed, tissues excised and WAT was analyzed using single-nucleus RNA sequencing. To study the role of alternatively activated macrophages, we employed macrophage-specific IL-4r knock out mice (IL-4r$^{Cx3cr1+}$). A physiological catabolic state was studied in IL-4r$^{Cx3cr1+}$- and WT mice exposed to cold for seven days.
Results: In general, the number of macrophages was decreased in WAT of LLC tumor-bearing male mice, with distinct differences observed in ATM subpopulations. Although IL-4r-deficiency did not prevent body and tissue weight loss in LLC tumor-bearing mice, CAC progression was slightly delayed in female but not male IL-4r$^{Cx3cr1+}$ mice. Similarly, only female IL-4r$^{Cx3cr1+}$ mice significantly gained weight during 7 days of cold exposure.
Conclusions: Our findings demonstrate that ATM composition is altered in pre-cachectic tumor-bearing mice. Moreover, IL-4r-signaling in macrophages likely affects CAC progression and cold adaptation in a sex-specific manner.

2-10

Ablation of FKBP5 counteracts cancer-induced musculoskeletal wasting

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Background: Cancer is frequently accompanied by cachexia, an uncured multi-organ wasting syndrome that impairs musculoskeletal health, physical function, and overall survival. FK506-binding protein-51 (FKBP5) is a co-chaperone and mediator of the stress response, with recent findings suggesting a regulatory role of FKBP5 in metabolic disease. Here, we investigated FKBP5's role in the development of cancer cachexia.
Methods: Expression of skeletal muscle FKBP5 was assessed in tumor-bearing and control mice. Cultured C2C12 myotubes were overexpressed with FKBP5, or FKBP5 was silenced in myotubes exposed to tumor cells. 10-week-old male wildtype (WT) C57BL/6J or FKBP5$^{-/-}$ (KO) mice (n=6-12/group) were intrasplenically injected with MC38 colorectal cancer cells ($1.25x10^5$) to induce liver metastases (LM), while controls received saline (Sham). Animals were assessed for indices of cachexia including muscle mass, torque, and bone quality.
Results: Expression of FKBP5 was significantly increased ($p<0.05$) in skeletal muscle of mice bearing lung (LLC), pancreatic (KPC), and colorectal (C26, HCT116, MC38) cancers. *In vitro* studies demonstrated that FKBP5 overexpression caused myotube atrophy (-26%; $p<0.0001$) and reductions in AKT/mTOR, while genetic blockade of FKBP5 protected against cancer-induced myotube atrophy (+20%; $P<0.0001$). WT-MC38 hosts displayed reductions in muscle mass (quadriceps: -25%; gastrocnemius: -24%; tibialis anterior: -20%; $p<0.0001$) and plantarflexion torque ($p<0.01$) compared to WT-Sham. Meanwhile, muscle mass and torque were unchanged in KO-MC38 compared to KO-Sham. Supporting the phenotype, we observed significant upregulation of murf1 and atrogin1 in the skeletal muscle of WT-MC38, which was counteracted in KO-MC38. Like muscle, cortical bone volume fraction (Ct.BV/TV: -9%) and trabecular bone volume fraction (Tb.BV/TV: -33%) were reduced in WT-MC38 compared to WT-Sham, while differences were not observed between KO-MC38 and KO-Sham.
Conclusion: Our data suggests that targeting FKBP5 protects against cancer cachexia, representing a new strategy to improve musculoskeletal health and quality of life in cancer patients.

2-11

MEK inhibition rescues muscle wasting in C-26 tumor mice independent of muscle regeneration

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Inhibitors targeting mitogen-activated protein kinase kinase (MAP2K, also known as MEK) are common anti-cancer treatments and have been incidentally found to prevent muscle wasting. Animal studies have generally demonstrated that MEK inhibition (MEKi) is sufficient to prevent muscle wasting, but the mechanisms by which MEKi preserves muscle mass remain mostly unknown. Because of the known role of MEK signaling in muscle progenitor cells, we hypothesized that MEKi would improve dysfunctional muscle progenitor cell differentiation in cancer cachexia.
Methods: Mice (n=6-7) bearing subcutaneous colon 26 (C-26) tumors were either treated with the MEKi binimetinib or vehicle. Mice received daily oral gavage of 30 mg/kg binimetinib beginning when tumors were palpable (day 8 post-injection) until euthanasia at day 21. Vehicle mice were treated daily with 1% carboxymethyl cellulose and 0.5% Tween 80. Details of muscle mass preservation have been previously published. Gastrocnemius muscles were used for histology and protein expression, while tibialis anterior muscles were used for gene expression. C2C12 proliferation was measured by CellTiter-Blue after 24 hours of treatment with MEKi compounds cobimetinib, trametinib, selumetinib, or binimetinib.
Results: Consistent with previous work, Pax7 protein was reduced in binimetinib-treated muscle. However, examination of regeneration markers showed that MyoD expression was not altered by binimetinib, and myogenin expression was significantly reduced. Centrally-located nuclei were similar between binimetinib and vehicle-treated mice. No embryonic myosin heavy chain-positive fibers were present in either MEKi- or vehicle-treated muscle. Unexpectedly, binimetinib decreased dystrophin expression at both the RNA and protein levels. Clinically relevant concentrations of all four MEKi did not impair proliferation of C2C12 myoblasts *in vitro*, suggesting that MEKi does not prevent muscle progenitor cell division.
Conclusions: Binimetinib does not appear to prevent muscle atrophy by improving muscle regeneration, potentially due to loss of dystrophin protein following binimetinib treatment.

2-12

Characterization of novel cancer cachexia preclinical models implementing chemotherapy and surgery

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Introduction: Cancer cachexia (CC) is a multifactorial syndrome characterized by profound muscle wasting, adipose tissue depletion, and systemic metabolic dysregulation, severely impacting patients' quality of life. The C26 mouse model is commonly used as a preclinical model to study CC; however, its rapid tumor growth and lack of metastatic progression represent crucial limitations to its clinical relevance, as it fails to recapitulate cancer patient's trajectory. In colorectal cancer, treatment interventions involve chemotherapy and primary tumor resection, often resulting in tumor relapse and/or metastasis. This study aims to refine experimental protocols in C26 mice to investigate tissue-specific metabolic alterations during cancer progression and treatment.
Methods: Two experimental treatment protocols were evaluated in 3-month-old female BALB/c mice subcutaneously inoculated with $5×10^5$ colon carcinoma cells (C26). Both protocols combined FOLFOX neoadjuvant chemotherapy with tumor surgical resection: (1) two pre-resection doses (C26+2F), (2) a single pre-resection dose (C26+F). Tumor excision was performed 4 days following chemotherapy. A group of control mice was included in each experiment. Muscles and tissues were collected for biochemical, histological, and metabolomic analyses.
Results: Tumor-bearing mice displayed signs of cachexia in both experiments, with severity correlating with chemotherapy duration and metastatic progression. Few mice exhibited no evidence of tumor relapse and regained both body weight and muscle mass. Others developed pulmonary metastases, highlighting that curative interventions lead to different trajectories even among syngeneic mice. Metabolomics of the gastrocnemius muscle and liver revealed distinct metabolic profiles between control and tumor-bearing animals, with non-relapsing mice clustering closer to the control group.
Conclusions: Muscle and liver tissues exhibit significant metabolic alterations in response to cancer progression and treatment intervention, with different extent and potential for recovery depending on therapeutic strategy and early intervention. Further investigations are necessary to identify the specific metabolic pathways implicated with either bad prognosis or cancer survivorship and recovery.

3-01

Myo-Tumour: A novel role for skeletal muscle in tumour growth and proliferation

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Introduction: Cancer cachexia is a multi-organ syndrome characterized by severe body weight loss, primarily due to reductions in both muscle and adipose tissue. It affects over 20% of cancer patients and significantly worsens prognosis and response to chemotherapy. While cachexia is clearly of great significance for disease prognosis and overall survival, it is mainly considered as a consequence of tumour presence. However, recent studies suggest that preventing or reversing muscle mass loss can significantly improve survival and well-being. For example, treating cachectic mice with a soluble activin receptor 2B to inhibit myostatin signaling prolongs lifespan, and exercise-induced muscle remodeling also reduces muscle wasting, affects tumour biology, and improves survival, in both mice and humans. However, the direct role of skeletal muscle in overall survival and tumour progression is not fully established, as most studies focus on tumour mass without directly assessing the impact of muscle wasting on tumour growth and proliferation.
Methods and Results: Our previous work showed that overexpression of the anabolic kinase Akt in skeletal muscle *in vivo* reverses cancer cachexia-induced muscle loss. In this study, we found that reversing muscle wasting via Akt activation also alters tumour growth in C26 Colon Carcinoma model. Notably, our data indicate an impairment of tumour vasculature following cachexia reversion, as shown by an abnormal CD31 staining, suggesting changes in vascular permeability in tumours from Akt-overexpressing animals. Moreover, our recent data highlight that Akt-overexpressing animals respond better to chemotherapy efficacy than the Wt-treated animals.
Conclusions: While muscle-wasting factors have been widely studied, our findings highlight a complex interplay in which muscle growth may influence tumour progression. Identifying key mediators in this muscle-tumour communication could reveal new therapeutic targets for improving outcomes in cancer cachexia and enhancing cancer treatment.

3-02

Skeletal muscle cell's anti-proliferative effect on cancer cells

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Introduction: Metastasis is the primary cause of cancer-related mortality. Skeletal muscle is remarkably resistant to tumor cell colonization; among ~4,000 cancer patients with 41 different cancer types only 16 patients were found to have skeletal muscle metastases. Why skeletal muscle provides an inhospitable environment for tumour colonization remains largely unknown.
Methods: We performed cocultures of EO771 or 4T1 (breast cancer cells) with either MLg (lung stroma cells), C2C12 or Sol8 (myotubes). We assessed cancer cell proliferation by IncuCyte Live Cell Imaging system, cellular transcriptomic rewiring by RNA-seq, exposed cells to hypoxic conditions and performed treatment with different lactate and pH conditions.
Results: When cultured together with MLg cells, EO771 and 4T1 breast cancer cells displayed vigorous proliferation, in sharp contrast to the strong growth inhibition observed when these cancer cells were cultured with C2C12 or Sol8 myotubes. After only two days of co-culture, both the tumour and their host cells exhibited clear niche-dependent transcriptional adaptations. Remarkably, EO771 cells co-cultured with C2C12 myotubes developed a hypoxia-related gene expression programme despite being maintained at normoxic oxygen levels (~20% O_2). When oxygen availability was experimentally reduced to 3% O_2, C2C12 myotubes nearly eliminated EO771 proliferation, confirming that oxygen depletion reinforces this suppressive effect. Importantly, neither treatment with exogenous lactate, medium acidification, nor their combination reproduced the inhibitory microenvironment generated by C2C12 myotubes. Under hypoxia, EO771 proliferation was further stimulated in MLg co-cultures, highlighting the permissive character of the lung stromal niche.
Conclusions: Our results reveal an unexpected, muscle-driven pseudo-hypoxic program that actively suppresses tumour cell proliferation. Therapies aimed at inhibiting hypoxia signalling may unintentionally undermine skeletal muscle's innate protection against metastasis.

3-03

Cancer and heart failure: insights from a zebrafish model of hepatocellular carcinoma

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Introduction: *Cancer-induced cardiomyopathy* is a heart failure-like complication of cancer cachexia, whose underlying cellular and molecular mechanisms remain poorly understood. Clinical studies are scarce, and murine models do not always capture early disease events or cell-cell interactions. Two major drivers have been proposed: (1) metabolic stress in cardiomyocytes and (2) systemic or tissue-specific immune activation. Key unanswered questions include whether cardiac wasting is initiated by systemic metabolic dysfunction or by immune activation driven directly by the tumor. Zebrafish provide unique advantages to address these questions, combining genetic tractability, low cost, and suitability for both cancer and cardiovascular research.
Methods: We repurposed a zebrafish hepatocellular carcinoma (HCC) model, previously shown to develop cachexia, to study the associated cardiac phenotype. In this zebrafish transgenic line, liver tumours are induced genetically by doxycycline induction of activated Kras expression, and we assessed the cardiac phenotype at 1-, 2-, and 4-weeks post-induction (wpi).
Results: Tumor growth was confirmed by EGFP fluorescence and macroscopic examination. By 2 wpi, tumor-bearing zebrafish displayed ventricular remodeling, fibrosis, and intracardiac thrombi. Cardiomyocyte and non-cardiomyocyte apoptosis appeared at 1 wpi, peaking at 2 wpi, coinciding with leukocyte recruitment and proliferation. At 4 wpi, cardiomyocytes re-expressed embryonic myosin heavy chain and displayed sarcomere disassembly. Neutrophils were the earliest immune responders, increasing as early as 1 wpi.
Conclusions: Liver cancer in zebrafish induces progressive cardiomyopathy characterized by cardiomyocyte apoptosis, fibrosis, immune cell recruitment, and cardiomyocyte dedifferentiation. Ongoing studies include time-course single-cell transcriptomics to define immune and cardiac subpopulations, as well as comparative plasma proteomics between zebrafish and patients with liver cancer. These approaches should uncover conserved pathways driving cancer-induced cardiomyopathy.

3-04

Adaptation to a high-protein, carbohydrate-free diet prevents skeletal muscle wasting induced by cancer cachexia in mice

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Introduction: High-protein diets have been ineffectively used as a nutritional support to counteract skeletal muscle wasting in cancer cachexia, however its prior adaptation effects on cancer and cachexia progression remain poorly investigated.
Methods: C57BL/6J male mice (~8 weeks old) were fed control (20% protein; 66% carbohydrate; 8% lipids) or high-protein (HP) (86% protein; 0% carbohydrate; 8% lipids) diet for 30 days and subsequently inoculated subcutaneously with B16F10 cells (5×10^4) to induce cancer cachexia (24 days). Body weight, body composition (magnetic resonance), tumor volume (caliper and in vivo imaging system), survival and energy expenditure were monitored. *In vitro* total proteolysis, cross-sectional area of muscle fibers and expression (by western blotting and RT-qPCR) of atrogenes (Atrogin-1, Murf1, LC3b, Gabarap, p62, and cathepsins) were investigated in skeletal muscle. Two-way ANOVA was performed, with $p \leq 0.05$ considered statistically significant. (CEUA 1403/2025).
Results: In tumor-bearing animals, HP diet markedly reduces the tumor growth (↓60%) and increases survival. Notably, HP-adapted animals were protected from the increased energy expenditure and loss of body weight, lean mass, and fat mass induced by the tumor in control-diet animals. Consistently, muscle wasting (EDL, gastrocnemius, and tibialis anterior) observed in tumor-bearing animals on the control diet was not seen in HP-adapted mice. Additionally, the pronounced reduction in muscle fiber area (↓20%) and the increase in EDL total proteolysis (↑30%) induced by tumor cachexia were not observed in HP-adapted animals. Accordingly, skeletal muscles from HP-fed mice were protected from the ~8-fold increase in protein content and gene expression of key atrogenes (Atrogin-1, Murf1, LC3b, Gabarap, p62, and cathepsins) observed in tumor-bearing animals fed a control diet.
Conclusion: Mice adapted to a high protein diet are protected from cancer-induced skeletal muscle loss, an effect likely mediated by the attenuation of tumor growth and cachexia-associated catabolic pathways.

3-05

Localized chemotherapy drives tumor regression and halts cancer-associated cachexia

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Introduction: Cancer-associated cachexia (CAC) often presents a roadblock in patient treatment due to an increase in chemotherapy side effects. We hypothesize that confining chemotherapy treatment to the tumor site could effectively treat the tumor while still mitigating cachexia onset. Here we compare systemic treatment to local injections, as well as continuous local delivery.
Methods: Ten-week-old male mice bearing subcutaneous CHX207 tumors received gemcitabine/ doxorubicin by (a) peritumoral bolus injection, (b) continuous local infusion through an implantable pump, or (c) standard systemic dosing. CAC was assessed by body weight measurements and terminal quantification of quadriceps, inguinal, and gonadal white adipose tissue, liver, and tumor mass. Serum interleukin-6 (IL-6) served as a systemic inflammatory marker. Skeletal muscle and hepatic histology were assessed by hematoxylin–eosin and Masson's trichrome staining. Drug distribution was determined in the tumor, kidney, liver, and heart. Immune populations in spleen, tumor, and tumor-draining lymph nodes were analyzed by flow cytometry.
Results: CHX207 tumors reproducibly induced cachexia approximately 20 days post-implantation. Local chemotherapy significantly reduced tumor burden, often resulting in complete regression. Compared with systemic administration, localized delivery prevented weight loss, muscle atrophy, adipose tissue depletion, and systemic inflammation, as reflected by lower circulating levels of IL-6. Neutrophil and myeloid populations normalized in blood and spleen; peritumoral doxorubicin further augmented adaptive immune activation. Pump implantation elicited minimal foreign-body reaction and did not affect tumor immunobiology or cachexia metrics.
Conclusions: Spatially targeted chemotherapy via peritumoral injection or continuous micro-pump infusion maintained antitumor activity while attenuating hallmark features of CAC. While both treatments show effective tumor regression, the continuous delivery method proved much more potent than the interspersed local injections. These findings support the development of localized chemotherapeutic strategies and the refinement of pump flow rates and dosing parameters to optimize the efficacy-tolerability balance, enabling combination regimens within a single device.

3-06

Muscle-targeted OPA1 overexpression confers sex-specific protection against pancreatic cancer cachexia

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Introduction: Mitochondrial degeneration may precede muscle atrophy during cancer cachexia (CC). OPA1, a key regulator of mitochondrial fusion, is downregulated in cachectic muscle. We investigated whether targeted OPA1 overexpression can preserve muscle mass and contractile function in an orthotopic pancreatic CC model.
Methods: Male and female C57BL/6J mice received bilateral injections of MyoAAV vector encoding OPA1 (2*10^10vg/TA) or PBS (sham control) to tibialis anterior muscle (TA), two weeks before tumor implantation. Orthotopic tumors were induced by injecting 150,000 KPC-FC1245 cells into the pancreas of cancer groups (KPC). In-vivo muscle function assessment and tissue collection were performed at humane endpoint.
Results: In male KPC mice, cachexia was confirmed by significantly lower muscle and fat mass (plantaris ~-15%, $p=0.0003$; fat ~-47% $p<0.0001$) and splenomegaly (+~130%, $p<0.0001$) compared to controls. This systemic effect did not differ between KPC-sham and KPC-OPA1 groups, indicating OPA1 did not alter the overall cachectic state but provided a localized effect to the TA. TA from KPC-sham mice showed atrophy compared with controls (-15%, $p=0.0025$), whereas KPC-OPA1 mice were not significantly different from controls (mean loss 6.3%, ns), indicating partial rescue of TA mass. KPC-sham mice showed significantly lower force production at submaximal frequencies compared to controls (80–125 Hz; -26-48%, $p \leq 0.05$), while KPC-OPA1 mice were not significantly different from controls (mean loss 4.3-26.5%, ns). Torque production at higher frequencies was not different

among groups, indicating specific effect of OPA1 at submaximal frequencies. In females, systemic cachexia was mild, primarily reflected by splenomegaly ($p<0.0001$). Female KPC-OPA1 mice exhibited greater TA mass compared with KPC-sham (+9%, $p=0.03$), with no differences between conditions for contractile function.
Conclusion: Muscle-directed OPA1 overexpression was associated with preservation of TA mass and improved submaximal torque in males. These findings support mitochondrial fusion as a potential target to mitigate muscle dysfunction in CC.

3-07

Time course of changes to the skeletal muscle microenvironment with cancer cachexia

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Background: Cancer cachexia is a complex disorder that causes loss of body mass, skeletal muscle mass, and fat mass with certain types of cancer. Muscle is comprised of several cell types that make up the microenvironment and coordinate for proper function, and while several studies have observed changes to this microenvironment, no work has comprehensively characterized these changes and when they occur (which is the purpose of this study).
Methods: Mice were inoculated with subcutaneous Lewis-lung Carcinoma tumours, grown for 2-weeks, 2.5-weeks, and 3.5-weeks, timepoints determined to encompass pre-cachexia, an intermediary stage, and cachexia. Single-cell RNA-sequencing and flow cytometry were performed on hindlimb muscles.
Results: We observed a 55% decrease in fat mass changes at 2-weeks, 124% body mass and 351% lean mass change decrease at 2.5-weeks, and 15% decrease in muscle cross-sectional area at 3.5-weeks in tumour-bearing mice compared to Sham. There were significant increases in myeloid cell populations at 2-weeks (928% CD11b+, 1,081% Ly6C^{low}, 920% Ly6C^{high}, 299% F4/80+/CD206-, 1,466% F4/80+CD206+ cells) which returned to baseline at 2.5-weeks, with no changes in lymphoid populations. Similar cell proportion changes were observed in immune populations from the single-cell RNA-sequencing. A transient increase in FAPs (53%) were observed at 2-weeks, and a decrease in endothelial cells at 2-weeks (57%) and 3.5-weeks (40%) with no changes in satellite cell populations. Single-cell RNA-sequencing revealed a novel cachectic satellite cell subcluster at 3.5-weeks that are primed for activation (larger and more MYOD+ cells after 24 hours culture on EDL myofibres) and are enriched for TNF, NF-κB, FoxO, TGFβ, Jak-Stat, and MAPK signaling pathways, all shown to cause satellite cell dysfunction with cancer cachexia.
Conclusions: We reveal a timecourse of cell-specific changes to the muscle and observed changes to the muscle microenvironment that precede cachexia and may cause a cachectic phenotype in satellite cells.

3-08

Disrupted pancreatic enzyme dynamics in cancer cachexia

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Introduction: Cancer cachexia is an irreversible metabolic disorder characterized by involuntary loss of muscle and/or adipose tissue, affecting up to 80% of patients in some cancer types, and estimated to contribute to approximately 30% of cancer-related death [1-3]. Cancer cachexia is a multi-organ syndrome that involves persisting systemic inflammation [4] and gut barrier dysfunction [5]. While reduced exocrine function has been linked to tissue wasting in PDAC [6], digestive enzyme homeostasis in cachexia associated with non-pancreatic tumors remains unexplored.
Methods: Cancer cachexia was studied using the C26 mouse model, with NC26 cells (non–cachexia-inducing) as tumor controls and PBS as healthy controls.
Results: Fecal samples from cachectic mice showed increased levels of pancreatic proteases and elevated overall fecal protease activity. In contrast, cancer cachexia was associated with reduced expression, protein levels, and plasma activity of pancreatic enzymes. The data suggest that microbial clearance of proteases is impaired in cachectic animals and that accelerated small intestine, but not large intestine, transit may underlie the discrepancy. Notably, pancreas atrophy was observed in cachectic mice without any evidence of pancreatic tissue damage. Enhancing pancreatic enzyme levels in cancer cachexia by administering pancreatic enzyme replacement therapy (PERT) worsened gut permeability, suggesting elevated pancreas enzyme activity in the gut may contribute to gut dysfunction in cancer cachexia. Additionally, PERT treatment of tumor-bearing mice accelerated lean mass loss compared to untreated controls.
Conclusions: In summary, cancer cachexia may disrupt exocrine pancreas homeostasis by suppressing pancreas protease turnover and/or accelerating protease gut passage, resulting in increased intraluminal protease activity despite reduced pancreatic enzyme expression. The elevated protease activity could influence nutrient utilization and compromise gut barrier integrity, potentially exacerbating systemic inflammation in cancer cachexia.

3-09

Walker-256 ascitic fluid induces *in vitro* features of cardiac cachexia: impact on mitochondrial and metabolic function modulated by leucine

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Introduction: Cardiac cachexia in cancer is a complex syndrome characterised by structural and functional cardiac remodelling, which compromises contractility and is associated with increased mortality and reduced quality of life. Tumour progression promotes systemic inflammation and proteolysis, driving mitochondrial impairment, oxidative stress, and myocardial atrophy.

Materials and Methods: In this study, we investigated the potential protective effects of leucine supplementation on cardiomyoblasts exposed to a cachexia-like environment induced by ascitic fluid (AF) obtained from Walker-256 tumour-bearing rats (CEUA/IB/UNICAMP, protocol 5828-1/2021/2024). Cardiomyoblast H9c2 cells were exposed to 5% AF and treated or not with 250 μM leucine supplementation for 48 hours. Data from the experimental groups (n = 3–5) were analysed by ANOVA followed by Tukey's test ($p < 0.05$).
Results: Mitochondrial function, assessed by Seahorse XF respirometry, revealed a significant reduction in oxygen consumption rates in AF-exposed cells, which was accompanied by decreased expression of electron transport chain complex II subunits, as detected by Western blot. Alterations in lipid metabolism were also evident, with Coherent Anti-Stokes Raman Scattering (CARS) microscopy showing an increased intensity and number of intracellular lipid droplets in AF-exposed cells. To further characterise the metabolic profile, NMR-based metabolomics assay of AF revealed elevated levels of aromatic amino acids, ketone bodies, and nucleotide derivatives, reflecting increased proteolysis and enhanced lipid oxidation. Importantly, Fluorescence Lifetime Imaging Microscopy (FLIM) analysis of NADH and FAD lifetimes in AF-exposed cardiac cells revealed a metabolic shift towards glycolysis, whereas cells treated with leucine maintained a profile closer to controls, suggesting preserved oxidative phosphorylation.
Conclusion: Taken together, our findings suggest that AF drives cardiomyoblasts into a glycolytic and energetically compromised phenotype consistent with cardiac cachexia, while leucine supplementation partially restores mitochondrial bioenergetics, reduces lipid accumulation, and maintains oxidative metabolic function, supporting its potential as a modulatory nutrient in cancer-induced cardiac dysfunction.
Financial Support: FAPESP (2019/14803-4; 2017/02739-4; 2020/13222-5; 2021/08931-0; 2022/13789-0; 2023/00608-0; 2024/07207-4), CNPq (302997/2022-9); CAPES; FAEPEX; SAE-UNICAMP

3-10

MyoRep: a novel reporter system to detect early muscle atrophy *in vitro* and *in vivo*

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Introduction: Even if skeletal mass constitutes 30-40% of our body content, surprisingly, it is the most "undrugged" tissue. Muscle atrophy consists of progressive loss of protein content and occurs during physiological (i.e., fasting, aging) and pathological (i.e., ALS or cancer) conditions anticipating death. Since not all patients will undergo muscle wasting, it is crucial to identify them in advance to intervene early saving lives.
Methods: We have studied the promoters/enhancers of a subset of atrogenes (atrophy-related genes) upregulated in muscles of rodents during various kinds of atrophy. Through comparisons of their upstream uncoding regions, using as backbone MuRF1 promoter (one of the earliest muscle-specific genes induced by wasting), we cloned various promoters upstream of a doubled reporter system (Firefly Luciferase/Tdtomato). Luciferase assays of cells transfected with such reporter plasmids served to identify the best sequence to sense atrophy at times when the cells have not reduced yet their protein content.
Results: Through in vitro and in vivo studies in mice subjected to denervation or cancer injection, we selected a sequence (i.e., MyoRep, previously named GREDEL) able to predict muscle atrophy. In vivo imaging of MyoRep mice emit a bioluminescent signal earlier than muscle loss. Of note, MyoRep was selected also because unable to sense in mice atrophy induced during 48 hours-fasting or physiological stress variations following the circadian rhythms. In fact, in vitro MyoRep-expressing myoblasts do not respond to stress hormones as glucocorticoids.
Conclusions: Overall, since MyoRep can discriminate muscle loss due to pathological conditions from physiological ones anticipating muscle wasting, it represents an unprecedented tool to predict muscle atrophy in advance in a plethora of diseases. Moreover, MyoRep will enable us to identify early circulating markers of muscle loss or to test new drugs against muscle wasting, sparing mice in accordance with the 3R rules.

3-11

Impaired cAMP/PKA/CREB1 signaling drives mitochondrial dysfunction in skeletal muscle in cancer cachexia

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Introduction: Skeletal muscle wasting is a defining feature of cancer cachexia, a multifactorial syndrome that drastically compromises patient quality of life and treatment outcomes. Emerging evidence indicate that in the early stages of cachexia, a coordinated transcriptional program regulating mitochondrial biogenesis, dynamics, and function is suppressed in skeletal muscle, ultimately contributing to mitochondrial dysfunction and muscle wasting. In addition, very recent evidence indicates that tumour-induced remodeling of hepatic transcriptome and secretome drives skeletal muscle wasting.
Methods: In this study, we combined transcriptomic analysis in both skeletal muscle and liver, along with chromatin immunoprecipitation sequencing (ChIP-seq), Ser/Thr kinome activity profiling, and mitochondrial respirometry in the skeletal muscle of tumour-bearing male mice to dissect the molecular mechanisms underlying mitochondrial dysfunction in both muscle and liver of cachectic animals.
Results: We report that: (i) cancer impairs skeletal muscle cAMP-dependent protein kinase A (PKA) activity and the transcriptional function of cAMP response element-binding protein 1 (CREB1); (ii) tumour-driven disruption of PKA/CREB1 signaling contributes to the downregulation of a core transcriptional network that supports mitochondrial integrity and function; (iii) restoration of cAMP/PKA/CREB1 signaling in vivo through either pharmacological inhibition of the cAMP-hydrolyzing phosphodiesterase 4 (PDE4) or AAV-9 shRNA-mediated PDE4D silencing *in vivo*, rescue cAMP/PKA/CREB1 signaling, expression of mitochondrial-related genes, and mitochondrial function, thus mitigating skeletal muscle wasting;
Conclusion: Altogether, our data identify tumour-induced suppression of the cAMP/PKA/CREB1 axis as a central mechanism contributing to mitochondrial dysfunction in skeletal muscle and liver during cancer cachexia, and identify PDE4 isoforms as a potential therapeutic target to preserve muscle mitochondrial function and counteract muscle wasting in cachexia.

3-12

Effects of multicomponent interventions on physical function for people with cancer cachexia

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Introduction: Progressive functional decline is a defining feature of cancer cachexia. We evaluated the effects of multicomponent interventions on physical function outcomes for adults with cancer cachexia. We also explored whether changes in physical function outcomes, or overall quality of life, were different following interventions with or without components directly targeting physical function (e.g., exercise training).
Methods: We analysed quantitative data on physical function outcomes from the studies included in our published systematic review of multicomponent interventions for adults with cancer cachexia. We first conducted meta-analyses of change scores from randomised trials comparing physical function outcomes following multicomponent interventions versus standard care. We then conducted exploratory analyses of standardised effect measures, including studies of any design, comparing interventions based on whether or not they directly targeted physical function.
Results: We analysed data from 29 studies of multicomponent interventions, 16 of which included components directly targeting physical function. Hand grip strength was on average 2.10 kg greater (95% CI: 0.44 to 3.76 kg) and six minute walk distance was on average 17.34 metres greater (95% CI: -36.45 to 71.13 metres) following multicomponent intervention compared with standard care. Exploratory analysis showed improvement in fatigue was highest following an intervention with a specific fatigue self-management component (standardised mean change: 4.76). Standardised mean change in quality of life was on average lower following interventions with components directly targeting physical function (0.28 vs 0.59).
Conclusions: Multicomponent interventions appear to be superior to standard care for improving some measures of physical function for adults with cancer cachexia, namely hand grip strength and the six minute walk test. Alternative synthesis methods revealed that interventions targeting specific aspects of physical function (e.g., fatigue) may lead to greater improvements in those outcomes, but that improvements in overall quality of life may be lower following exercise-based interventions.

3-13

Body mass index but not percentage weight loss was associated with the race/ethnicity of patients with advanced lung cancer: A retrospective study.

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Background: Patients with cancer often experience weight loss which contributes to a decreased quality of life and signals a poor prognosis. The objective of this retrospective study is to investigate whether the self-reported race/ethnicity of patients undergoing palliative care is associated with weight loss.
Methods: The charts of 400 patients with advanced lung cancer, followed at a Supportive Care Clinic in the United States, during 2022, were screened at random and 94 Asian, 94 Black, 87 Hispanic and 91 Non-Hispanic-White patients were selected. Patient demographics, the Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), weight history, cancer treatments provided, prescription of appetite stimulants, and nutritional laboratory markers were collected. Univariate and multivariable regression linear analysis were performed to explore independent predictors of weight loss.
Results: Among the different racial/ethnic cohorts, no significant differences in age, gender and cancer treatments, and appetite stimulants received were noted. The Asian cohort had significantly lower weight and BMI at pre-diagnosis, Supportive Care consultation, and final recorded visit compared to all other groups ($p < 0.01$). Asian cohort had significantly less total weight loss (8.2 kg) compared to Black (13.4 kg), Hispanic (9.1 kg), and Non-Hispanic White (10.2 kg) cohorts ($p=0.04$), respectively; but all four groups experienced similar proportion of weight loss (%) (12.8 vs. 14.9 vs. 12.2 vs. 12.9; $p= 0.79$), respectively. In a multivariate analysis, the pre-diagnosis weight but not race/ethnicity was the only independent predictors of percentage weight loss.
Conclusions: In patients with advanced lung cancer, BMI and total weight loss but not percentage change in weight was significantly associated with race/ethnicity. On multivariate analysis, the percentage weight loss was significantly influenced by pre-diagnosis weight but not race/ethnicity. Racial and ethnic variations in BMI should be accounted for when screening for cachexia and more research is needed.

3-14

The influence of obesity on wasting during neoadjuvant chemotherapy in curative oesophagogastric cancer

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Introduction: Patients with gastro-oesophageal cancer lose significant weight throughout treatment. Cachectic wasting affects up to a third treated with curative intent. Cachexia limits treatment tolerance, quality of life, resilience and survival. Patients increasingly now present with obesity too, but the interface between cachexia and obesity is little understood. We sought to determine cachexia rates in obesity and explore its influence on wasting during neoadjuvant chemotherapy.
Methods: Retrospective analysis of 186 locally advanced (≥T2) gastric or oesophageal cancers treated with curative intent in South-East Scotland (2016-2020). Data included characteristics, weight, BMI, laboratory tests and CT-derived BCA using DAFS (staging; following NAC). Statistical analysis using R Studio 4.4.3.
Results: Over a quarter were obese (n=53 (28.3%), whilst just 5 (2.7%) were underweight. Low-muscularity affected 49.5% (n=92), with lowest rates in obesity (n=17 (32.1%) vs n=75 (56.4%); p=0.014). Inflammation rates were significantly lower in obesity too (n=7 (13.2%) vs n=35 (26.3%); p=0.069). Eighteen obese patients were cachectic according to Fearon criteria (24.0%), and five according to GLIM (9.4%). Following NAC, obese patients lost weight (median %change -2.13 (-5.5-0.0)), as mirrored by the whole cohort. Obese patients lost more muscle (%SMV change -2.5 (-7.0--2.1) than those with normal (-2.2 (-2.0--3.5); p=0.46) or low BMIs (-0.2 (-0.1--4.5)). Similarly, obese patients lost more visceral fat (%change VAT -5.1 (-37.8-52.6)) compared to normal (-1.18 (-87.7-396.2)) or low BMI (108.8 (-82.3-263.1) p=0.84). Following NAC, 105 exhibited low muscularity (56.5%), representing a 7% increase. Eighty-two exhibited a low-muscularity / high visceral-adiposity phenotype (44.1%) vs 30.6% at staging (n=57), constituting a 13.5% increase.
Conclusion: One in three patients presenting with curative OG cancer has clinical obesity. Despite lower levels of inflammation, cachexia still affects one in ten of those patients. Body composition deteriorates during NAC. Obese patients lose more skeletal muscle and visceral fat, appearing at higher risk of pre-operative deconditioning.

3-15

Body image distress associated with emotional distress but not cachexia in patients with advanced cancer

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Introduction: Cachexia in patients with advanced cancer can lead to psychosocial distress, such as body image dissatisfaction. The study objective was to determine the frequency of body image distress and association with weight loss and other symptoms.
Methods: Patients with cancer and their primary caregiver were prospectively enrolled to complete a cross-sectional one-time survey. We collected patient demographics, weight history and height, cancer history, Edmonton Symptom Assessment Scale (ESAS), the Patient Generated Subjective Global Assessment – short form (PG-SGA SF) - cut off ≥ 6 indication malnutrition risk, the Hospital Anxiety and Depression Scale, and a Body Image Scale (BIS).
Results: Of 165 patients that were approached, 99 (60%) completed the survey. The average (SD) age was 61.6 years old (11.5). Most patients were female gender (52%), Caucasian (75%), married (80%), and the most common cancers were gastrointestinal (22%) and genitourinary (21%). At the time of the survey, 28% had body image dissatisfaction (BIS ≥ 10). Body image dissatisfaction (BIS ≥10) was significantly more common in the female versus male gender (39% vs 17%, p=.01), younger patients (years, 56.3 vs. 25.9, p=0.004). Patients with body image dissatisfaction versus none were significantly more anxious (HADS-A (median (IQR); 3.0 (2.6) vs. 5.9 (3.6), p=0.001) and depressed (HADS-D; 6.8 (3.6) vs 3.0 (2.6), p=0.004). No significant difference in patients with versus without body image dissatisfaction was noted in patients at risk for malnutrition (PG-SGA (SF)) or cachexia, both 10% lifetime weight loss and 5% loss over 6 months.
Conclusion: Twenty-eight percent of patients with advanced cancer evaluated in an ambulatory supportive care clinic had body image dissatisfaction, which was associated with younger age, female gender, and psychological distress including anxiety and depression but not with malnutrition risk or cancer cachexia.

3-16

Volumetric muscle phenotyping and cytokine dynamics (IL-6, GDF-15) in advanced biliary tract cancer: secondary analysis of a randomized trial

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Introduction: Biliary tract cancer (BTC) carries a poor prognosis and is frequently accompanied by cachexia, characterized by systemic inflammation, metabolic dysfunction, anorexia, and progressive loss of skeletal muscle and adipose tissue. Cachexia reduces treatment tolerance and shortens survival. Interleukin-6 (IL-6) is a central mediator of inflammation and metabolic reprogramming, while growth-differentiation factor-15 (GDF-15) regulates appetite and contributes to wasting. Distinct IL-6– and GDF-15–driven phenotypes may underlie the heterogeneity of cachexia. Defining their respective roles in cachexia during treatment could provide mechanistic insight and inform supportive strategies in BTC.
Methods: We will perform a secondary analysis of the randomized phase II BILTRACTO trial (EudraCT 2018-004826-27), in which patients with metastatic BTC received gemcitabine-/cisplatin with or without the IL-6 receptor inhibitor tocilizumab. Plasma IL-6, GDF-15 and C-reactive protein (CRP) were measured during treatment until disease progression or death. Skeletal muscle volume from Th12–L5 is quantified using deep learning-based automated segmentation of CT scans obtained at baseline and every three months during treatment. Associations between cytokine trajectories and skeletal muscle volume dynamics will be evaluated.
Results: The BILTRACTO trial has been completed, but efficacy and survival outcomes are not yet reported. Data collection for this sub study is underway. Changes in IL-6, GDF-15 and CRP during treatment will be correlated with skeletal muscle volume change, and subgroup profiles stratified by baseline cytokine status.
Conclusion: This study will elucidate the relative contributions of IL-6– and GDF-15–driven pathways to cachexia in BTC. Integrating cytokine profiling with volumetric muscle phenotyping may identify modifiable inflammatory and metabolic targets, supporting precision supportive care in BTC.

3-17

Testosterone replacement tHerapy in hypOgonadal male advanced canceR patients: preliminary results of THOR trial

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Introduction: Male hypogonadism, defined by low testosterone and impaired spermatogenesis, is frequent in cancer patients (40–90%), due to chemotherapy, inflammatory cytokines, or therapies with opioids/glucocorticoids. Symptoms that negatively impact quality of life are fatigue, sexual dysfunction, muscle loss and mood changes. This study investigates the effects of testosterone replacement therapy (TRT) in hypogonadal men with advanced cancer.
Methods: In this prospective observational study, patients (18–75 years) with stage III–IV cancer, life expectancy ≥ 6 months, fatigue, weight loss or anorexia, and total testosterone (TT) <350 ng/mL were enrolled at first access to Palliative Care Department. Assessments included Phase Angle (PA) and Appendicular Skeletal Muscle Mass Index (ASMI) calculated from Bioelectrical Impedance Vector Analysis (BIVA), Handgrip Test (HGT), FACIT-Fatigue scale at baseline (T0), 3 (T3) and 6 months, and endocrinology consult for TRT (T0). Preliminary data were collected at T3.
Results: N. 23 patients completed T3, mean age 60.6 years (39–73). Mean data from T0-vs-T3 were: PA 5.0°-4.9° (-2%), ASMI 7.72-8.24 (+7%), ASMI < 7kg/m^2 in 5 vs 4 (22% vs 17%) patients, HGT 34.7-36.1 kgs (+4%), FACIT 36.4-39.2 (+7.5%).
At T3 data were improved: ASMI in 78% of patients, HGT in 65%, FACIT in 57% and PA in 48%.
FACIT at T0 indicated mild fatigue in 10 patients, moderate in 9, severe in 4. Among the 13 with moderate/severe fatigue, at T3 FACIT improved in 6, was stable in 6 and worsened in 1.
A significant moderate correlation was found between HGT and FACIT at T0-T3 variation (r=0.45, p-value 0.03).
Conclusions: Preliminary data from the THOR study suggest that TRT may improve symptoms of male hypogonadism in cancer patients, particularly muscle mass, strength and fatigue. These factors may enhance treatment tolerance and quality of life. The sample size remains limited; ongoing enrollment will help clarify specific correlations and clinical relevance.

3-18

Proposal of a tool for screening the risk of cachexia in cancer patients

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Rationale: The objective of this study was to develop a screening tool to identify the risk of cachexia in outpatients with cancer.
Methods: The tool was developed to detect the risk of cachexia in outpatients treated at an oncology center. The proposed screening tool was based on diagnostic criteria for cachexia; functionality; and symptoms that may reduce alimentation. The self-administered tool was also posted on the hospital website to enable access by health professionals from other hospitals and clinics, as well as by patients.
Results: Data were collected from 275 patients receiving outpatient care. The most prevalent diagnosis was breast cancer (26.2%). Metastatic cancer was present in 25.1% of the total sample. Risk of cachexia was identified in 37.8% of patients. Death within 30 days was experienced by 47.1% (41 of 87) patients treated in the emergency room and was significantly associated with the risk of cachexia (n=39; 57.4%) (p<0.001). Age, female sex, and metastatic disease were associated with the risk of cachexia (p<0.001, p=0.014, p<0.001, respectively).
Conclusion: Cachexia is a prevalent and underdiagnosed condition among cancer patients. The development of specific screening tools is extremely important to facilitate early detection of patients at risk, with the aim of initiating proactive interventions.

3-19

HFA-PEFF and H_2FPEF scores in advanced cancer patients

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Introduction: The risk scores HFA-PEFF and H_2FPEF are essential tools for diagnosing heart failure with preserved ejection fraction (HFpEF). This study aims to assess their potential use in oncological patients with left ventricular ejection fraction ≥50%.
Methods: We conducted an observational prospective study including 533 hospitalized patients with active cancer (61 ± 14 years, 50% female, 86% advanced cancer stage) without significant cardiovascular disease or antibiotic treated infection. All patients underwent comprehensive clinical assessment and echocardiography at baseline. HFpEF risk was assessed using the HFA-PEFF score and H_2FPEF score. Participants were followed longitudinally for all-cause mortality over up to 7 years.
Results: According to the HFA-PEFF score 21% of the study population had a low risk, 52% intermediate and 27% high risk of HFpEF. In contrast, the H_2FPEF score classified 56%, 43% and 1.5% of the patients into low, intermediate and high-risk categories, respectively. Significant correlations were observed between both scores and New York Heart Association class (HFA-PEFF: r_s= 0.252, p<0.001, H_2FPEF: r_s= 0.195, p<0.001). Both scores proved independent prognostic value for all-cause mortality (univariable analyses: HFA-PEFF ≥4 vs. HFA-PEFF <4: hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.38-2.09, p<0.001; H_2FPEF ≥1 vs H_2FPEF 0: HR 1.66 [95% CI 1.30-2.14], p<0.001; multivariable analyses: HFA-PEFF≥4 vs. HFA-PEFF<4: HR 1.40 [95% CI 1.10-1.79], p=0.006; H_2FPEF≥1 vs H_2FPEF 0: HR 1.81 [95% CI 1.39-2.34], p<0.001) adjusted for age, sex, systolic blood pressure, Eastern Cooperative Oncology Group performance status, anemia, cardiotoxic anti-cancer therapy, cancer stage, and cancer type. Moreover, regarding functional performance measures: 4-meter gait speed test negatively correlated with HFA-PEFF score (r_s= -0.357, p<0.001) and with H_2FPEF score (r_s= -0.258, p<0.001). Similarly, maximal handgrip strength negatively correlated with HFA-PEFF score (r_s= -0.290, p<0.001) and with H_2FPEF score (r_s= -0.158, p<0.001).
Conclusions: The HFA-PEFF and H_2FPEF scores may be considered as risk stratification tools in cancer patients as they hold independent prognostic value for all-cause mortality. Both scores show significant associations with dyspnea and functional performance status of patients with cancer.

3-20

Determination of a novel prognostic variable based on body composition radiodensity in gastric cancer

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Introduction: Prognostic assessment in gastric cancer remains largely dependent on TNM staging, yet outcomes vary considerably within the same stage. Body composition parameters, particularly adipose and muscle radiodensity, have recently emerged as independent prognostic markers. We hypothesized that combining these features could identify a high-risk metabolic phenotype associated with poorer outcomes.
Methods: This retrospective single-center study included 461 patients with gastric adenocarcinoma diagnosed between 2009 and 2018 at the University of Campinas Hospital, Brazil. Computed tomography images at the L3 level were segmented to quantify visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle (SM). Quantitative features, including radiodensity (Hounsfield Units, HU), were extracted. Candidate variables were generated through arithmetic combinations, categorized into tertiles, and their prognostic value was assessed using Kaplan–Meier and Cox regression analyses.
Results: Among the tested variables, difference between VAT median and SM median radiodensity (VAT–SM, VMD) was identified as a clinically reproducible variable with strong prognostic association. Patients in the highest VMD tertile had significantly shorter overall survival than those in the lowest tertile (13.8 vs 58.5 months, log-rank p < 0.001). In multivariable analysis adjusted for clinicopathological features, higher VMD values remained independently associated with mortality (HR 1.48, 95% CI 0.98–2.24, ptrend < 0.001).
Conclusions: The proposed VAT–SM variable integrates two established prognostic factors, capturing a phenotype of increased adipose radiodensity and reduced muscle radiodensity. This simple and reproducible measure significantly improves risk stratification beyond TNM staging. Validation in external cohorts is warranted, but VMD may represent a clinically useful biomarker in the context of sarcopenia and cancer cachexia research.
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3-21

Elevated Lipocalin-2 Levels are Associated with Weight Loss and Anorexia in Patients with Gastrointestinal Cancer

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Introduction: Cancer-associated anorexia is a frequent and debilitating condition that contributes to weight loss, sarcopenia, and poor prognosis. Lipocalin-2 (LCN2), a pleiotropic mediator of inflammation and metabolism, was identified as a key regulator of appetite. Experimental models showed that LCN2 deletion protects against anorexia and cachexia, but translational evidence in humans remains limited.
In this study, we investigated the association between circulating levels of LCN2 and anorexia in a cohort of naïve gastrointestinal cancer patients (GI-CP) and assessed their association with changes in body composition.
Methods: We conducted an observational study including 28 GI-CP at diagnosis, before anticancer treatments, and 10 healthy controls (C). Clinical, nutritional and biochemical data were collected. Anorexia was assessed by the FAACT questionnaire (cutoff ≤30). Serum LCN2 was measured by ELISA.
Results: LCN2 levels were significantly higher in GI-CP compared to C ($p<0.01$). LCN2 correlated inversely with BMI in GI-CP ($p=0.028$; $r=-0.430$). GI-CP with weight loss (n=16) showed significantly higher LCN2 levels than weight-stable GI-CP (n=12) ($p=0.031$) and vs C ($p=0.003$). Stratification by presence/absence of anorexia revealed that anorexic GI-CP (n=13) showed significantly higher LCN2 levels compared C (n=8) ($p=0.008$).
Conclusions: Our findings provide novel evidence linking circulating LCN2 with weight loss and impaired nutritional status in gastrointestinal cancer. The inverse association with BMI and higher levels in anorexic patients support hypothesis of LCN2 as an appetite-suppressing mediator in GI-CP. Further studies are warranted to clarify its role in the pathophysiology of cancer-associated anorexia.

3-22

Longitudinal Changes of Body Composition Parameters are Associated with Clinical Outcomes in HER2-Positive Metastatic Breast Cancer Receiving Trastuzumab Deruxtecan

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Introduction: Breast cancer represents a major global health issue, and HER2-positive metastatic cases remain particularly challenging to manage, even with recent targeted treatments such as Trastuzumab Deruxtecan (T-DXd).
This study aimed to assess how changes in body composition affect treatment-related toxicities, dose adjustments, and clinical outcomes in patients undergoing T-DXd therapy.
Methods: A retrospective study was conducted on 35 HER2-positive metastatic breast cancer to evaluate body composition parameters, including subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), skeletal muscle area (SMA), and skeletal muscle index (SMI). These parameters were assessed using CT scans performed at baseline (T0) and after a median follow-up of 4 months (T1). The percentage change between the two time points (ΔT0–T1%) was calculated for each parameter.
Results: Significant reductions overtime were observed in SAT (mean ΔSAT% =-5.7%, $p<0.05$) and SMA (mean ΔSMA% = -4.9%, $p<0.01$). 31% of patients experiencing severe (Grade 3-4) toxicities. Patients with higher ΔSAT% (above the median value) experienced more frequently grade 3-4 toxicities compared to those with lower ΔSAT% ($p<0.05$). Among patients without toxicities, a significant decrease in SAT was observed between T0 and T1 ($p=0.003$), while no significant change was detected in patients with grade 3-4 toxicities ($p=0.929$).
Greater reductions in SMA were associated with increased rates of treatment discontinuation (75% vs. 29%, $p=0.009$). Kaplan-Meier analysis confirmed that greater reductions in SMA significantly increased the risk of mortality (HR 5.1, 95% CI: 1.05–24.79) and showed a trend toward higher risk of disease progression (HR 2.58, 95% CI: 0.89–7.49).
Conclusions:
Changes in body composition, particularly reductions in SMA, were linked to higher rates of treatment discontinuation and mortality in patients with HER2-positive metastatic breast cancer receiving T-DXd. Conversely, increased SAT was associated with greater severe toxicities, underscoring its potential role in predicting treatment-related complications.

3-23

Histomorphological and Inflammatory Differences Between Subcutaneous and Visceral Adipose Tissue in Cancer Patients

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Introduction: We previously examined histomorphological features and inflammatory infiltrates in subcutaneous adipose tissue (SAT) of patients with cancer cachexia and observed decreased adipocyte size, increased fibrosis and inflammatory infiltration. The present study aimed to compare SAT and visceral adipose tissue (VAT) with respect to their histomorphological characteristics and inflammatory infiltration among cancer patients.
Methods: We enrolled gastrointestinal cancer patients undergoing surgery. Biopsies of SAT and VAT were collected for histomorphological analyses (cross-sectional area-CSA and fibrosis) and immunohistochemistry to characterize inflammatory cells. CT scans at L3 were used to quantify SAT, VAT, and total adipose tissue (TAT) areas.
Results: Biopsies were obtained from 15 patients (8 females) with a mean age of 65 ±11.9 years. Twelve presented with colon cancer and 3 with gastric. Cachexia was present in 8 patients. No differences were observed between cachectic and non-cachectic patients in histomorphological or immunohistochemical analyses. However, a trend toward an increased number of T lymphocytes in SAT was observed in cachectic (2.5; 0.6–6.4) vs non-cachectic patients (0.9; 0.5–6.7)($p=0.072$). In all patients, a higher number of macrophages and T lymphocytes were present in VAT vs SAT ($p<0.05$ and $p<0.03$, respectively). In non-cachectic patients, T-lymphocyte infiltration was higher in VAT vs SAT ($p=0.018$), while no differences were observed in the other parameters. According to adiposity measured by CT-scan, TAT positively correlated with the CSA of SAT (rho=0.671; $p=0.006$) and negatively with the number of CD3 in VAT (rho=-0.557; $p=0.031$). Also, CSA of VAT negatively correlated with the number of macrophages in VAT (rho=-0.670; $p=0.006$) and SAT (rho=-0.640; $p=0.006$).
Conclusion: VAT showed greater immune cell infiltration than SAT in cancer patients. While no significant cachexia-related differences were found, trends toward increased T-lymphocyte infiltration of SAT in cachexia and correlations between adiposity, adipocyte size, and immune infiltration suggest depot-specific roles of adipose tissue in cancer.

3-24

The GDF-15-neutralizing antibody visugromab induces immune modulation and metabolic reprogramming in cancer-induced cachexia.

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Introduction: Growth and differentiation factor 15 (GDF-15) is overexpressed in cancer cells leading to serum elevation in cancer patients. GDF-15 drives resistance to anti-PD-(L)1 checkpoint blockade and contributes to cancer-induced cachexia, two significant unmet medical needs for cancer patients. Visugromab is a GDF-15-blocking antibody currently under evaluation in patients with advanced cancers r/r to anti-PD-(L)1 therapy in combination with nivolumab (GDFATHER; NCT04725474). However, whether visugromab exerts anti-cachectic effects has not previously been reported.
Methods: GDF-15 neutralization by visugromab was assessed in GFRAL-based cell line systems as well as human cancer cell-immune cell co-culture assays. *In vivo*, the efficacy of visugromab in alleviating cancer-induced cachexia was evaluated across multiple tumor models, followed by post hoc analyses including transcriptomic and metabolomic analysis of skeletal muscle. The effect of visugromab on body weight was further evaluated in association with serum GDF-15 baseline levels in non-small cell squamous lung cancer (NSCLC), urothelial cancer (UC) and hepatocellular carcinoma (HCC) patients a patient subgroup of the GDFATHER Ph2a trial.
Results: Visugromab specifically blocked GDF-15-induced GFRAL-mediated ERK1/2 phosphorylation. Importantly, visugromab inhibited GDF-15-mediated immune suppression *in vitro*. In preclinical models of cancer-induced cachexia, visugromab reverted body weight loss, reduced food consumption and counteracted muscular atrophy. In the Ph2a trial visugromab treatment in combination with nivolumab increased body weight significantly in patients with cachexia-inducing GDF-15 serum levels (GDF-15 >1.5 ng/mL at baseline) at week 10.
Conclusions: Visugromab prevents GFRAL-mediated cachexia as well as alleviating tumor-induced immune suppression by effectively neutralizing GDF-15. In transcriptomic and metabolomic analysis of skeletal muscle, a reversal of cancer cachexia-induced muscle waste syndrome was observed. Clinical data from the GDFATHER Ph2a trial show body weight gain independently of clinical response. Collectively, we provide compelling evidence for visugromab as a new treatment option to overcome both immunosuppression and cancer-induced cachexia simultaneously.

3-25

Exploring experiences and impacts of changes in physical function among people with cancer cachexia

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Introduction: Progressive functional decline is a defining feature of cancer cachexia, but qualitative studies have focused on nutritional aspects of cachexia with limited exploration of functional concerns. This study aimed to explore people's experiences of changes in their physical function and the impacts on their quality of life.
Methods: In-depth qualitative interviews were conducted with a purposive sample of adults with cancer, recent unintended weight loss and a performance status of 1, 2 or 3, recruited from four hospitals across South London. Interviews were face-to-face or via video call, with an interpreter if required. Verbatim pseudonymised transcripts were analysed using reflexive thematic analysis.
Results: To date, 9 participants have been interviewed (6 women, 3 men; aged 37-85). Preliminary analysis shows that, alongside weight loss, participants noticed muscle loss and connected it with lower strength and energy, which restricted what they could do. Participants described changes in speed ("everything's slow motion now") and needing frequent rests, often causing frustration. Participants described feeling low because they couldn't do things that were important to them but also placed importance on mental strength and not giving up ("I'll play it right till the end"). Participants expressed a desire to keep doing things ("I want to do them while I can now"), but loved ones were often "over-protective", "preventing" or "querying" how much they should be doing. This caused tension and contributed to participants' sense of a loss of independence. Functional changes were "all-encompassing" and for some had "obliterated (their) quality of life".
Conclusion: Loss of strength and energy restricts what people with cancer cachexia can do, which directly impacts their mental and social wellbeing. Interventions aimed at improving quality of life should therefore support people to maintain independence and continue doing things which are important to them.

3-26

Meaningful within-patient change (MWPC) of PROMIS-Fatigue and PROMIS-Physical Function (PF) in patients with cancer cachexia in the phase 2 ponsegromab study

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Introduction: An MWPC threshold is the change in clinical outcome assessment scores that is considered meaningful to patients. MWPC was estimated for PROMIS-Fatigue 7a and PF 8c in patients with cancer cachexia using randomized phase 2 study data (NCT05546476).
Methods: Blinded data from adults with non-small-cell lung, pancreatic, or colorectal cancer and cachexia (Fearon criteria) were used. Raw scores ranged from 7 to 35 for PROMIS-Fatigue 7a and from 8 to 40 for PROMIS-PF 8c. T-scores were based on general US population values (mean: 50; standard deviation: 10). MWPC thresholds were estimated using an anchor-based analysis. For fatigue, Patient Global Impression of Severity (PGI-S) of fatigue and PGI of Change (PGI-C) in fatigue were anchors. For PF, PGI-S and PGI-C in limitations in patients' ability to do daily activities were anchors. Analyses were prespecified.
Results: Fatigue PGI-S and PGI-C analyses included longitudinal data from 148 patients. MWPC values (raw scores) were 4.63 (PGI-S) and 2.50 (PGI-C) based on a 2-category change in the anchor (7.15 and 3.83 on T-score metric). MWPCs were "large" (PGI-S) and "medium" (PGI-C) in terms of effect sizes. PF PGI-S and PGI-C analyses included longitudinal data from 148 and 151 patients, respectively. MWPC values (raw scores) were 5.22 (PGI-S) and 3.46 (PGI-C) based on a 2-category change in the anchor (6.30 and 4.13 on T-score metric). MWPCs were "large" (PGI-S) and "medium" (PGI-C).
Conclusions: For PROMIS-Fatigue, using a 2-point change in the anchor, values of 4.63 and 2.50 (original scores) and 7.15 and 3.83 (T-scores) can be considered MWPCs for cancer cachexia. For PROMIS-PF, using a 2-category change in the anchor, values of 5.22 and 3.46 (original scores) and 6.30 and 4.13 (T-scores) can be considered MWPCs.

3-27

Psychometric validation and meaningful within-patient change of the Functional Assessment of Anorexia-Cachexia Therapy 5-Item Anorexia-related Symptoms Scale (FAACT-5IASS) in patients with cancer cachexia

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Introduction: The FAACT-5IASS has demonstrated good internal consistency and responsiveness to changes in appetite among patients with non-small cell lung cancer (NSCLC). We further evaluated the psychometric properties of this scale in patients with other tumors and cachexia using randomized study data (NCT05546476).
Methods: Measurement properties (test-retest reliability, meaningful within-patient change [MWPC] estimation, known-group validity, ability to detect change, construct validity, and ceiling and floor effects) of the FAACT-5IASS were evaluated using data from the ponsegromab randomized, double-blind, placebo-controlled, phase 2 study in adult patients with NSCLC, colorectal, or pancreatic cancer and cachexia (Fearon criteria).
Results: Overall, patients (n=187) had a median age of 67 (IQR, 60-74) years; 36.9% were female, and 39.6%, 28.9%, and 31.6% had NSCLC, colorectal, and pancreatic cancer, respectively. Data are from all available patients at each timepoint (n=174 at baseline). Acceptable test-retest reliability (ICC=0.78) and internal consistency (Cronbach's alpha>0.70) were observed. No floor/ceiling effects were detected. Significant differences in mean FAACT-5IASS scores between groups with "no appetite loss" and "very severe appetite loss" supported known-group validity. FAACT-5IASS–Patient Global Impression of Severity (PGI-S; >0.6) correlations supported convergent validity. Confirmatory factor analysis supported the single-factor measurement structure of the FAACT-5IASS (Bentler's comparative fit index ≥0.95). MWPC values were 2.86 (Patient Global Impression of Change) and 3.58 (PGI-S) based on a 2-point change in the anchor measure. Ability to detect change was supported by the approximately linear relationship between changes in PGI-S and FAACT-5IASS.
Conclusions: The FAACT-5IASS demonstrated robust psychometric properties and an MWPC of 2.86 to 3.58, supporting the use of the scale in appetite and anorexia symptoms focused research in cancer cachexia.

3-28

An assessment of the healthcare resource use and cost impacts of cachexia among cancer patients in the United States: a Medicare claims study

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Introduction: Cachexia in patients with solid organ tumors is associated with substantial morbidity and mortality. Healthcare Resource Use (HCRU) is also an important, but understudied, element of cachexia burden of disease. This study addresses this evidence gap by comparing HCRU and cost outcomes between U.S. Medicare solid organ tumor patients with and without cachexia.
Methods: We conducted a retrospective cohort study using 2016-2022 Medicare fee-for-service claims. The cohort included adult patients with breast, colorectal, lung, pancreatic, or prostate cancer at any stage. Cachexia was defined as having associated ICD-10 diagnosis codes such as cachexia, abnormal weight loss, and sarcopenia. The index date was defined as the first cachexia diagnosis occurring in the 1-year before cancer diagnosis or any time in follow up after cancer diagnosis. The cancer cachexia cohort was compared to a propensity score-matched cancer cohort without cachexia for 1-year post-index date HCRU and cost outcomes.
Results: The study included 2,564,128 Medicare beneficiaries diagnosed with breast (N=645,564), colorectal (N=421,543), lung (N=520,693), pancreatic (N=112,137), or prostate cancers (N=864,191). Mean age at index date was 76.38 and 75.67 years for cachexia and non-cachexia patients, respectively. Standardized mean differences between cachexia and non-cachexia patients were <0.1 for demographic characteristics. In the 1-year post-index, median inpatient visits (3 vs. 1, P<0.001), median outpatient visits (1 vs. 0, P<0.001), median total cost ($56,550 vs. $18,976, P<0.001) were significantly higher among cachexia vs. non-cachexia patients. Similar results were found in the metastatic cancer subgroup.
Conclusions: Medicare cancer beneficiaries who met study cachexia criteria had significantly increased HCRU and cost outcomes. The substantial economic burden of cachexia demonstrates the need for innovative therapies that can modify the cachexia trajectory among cancer patients and thus lessen the economic burden.
Conflict of Interest Statement: Dr. Roth is an employee of Pfizer Inc. and holds stock in Pfizer Inc.

3-29

Accelerometer-determined physical activity and sarcopenic obesity risk in older European men and women

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Introduction: The extent to which time spent in light physical activity (LPA), or moderate-to-vigorous physical activity (MVPA) is associated with sarcopenic obesity (SO) risk in older adults remains unclear. Here we examined a) the association between the level of adherence to recommended amounts of MVPA and the risk of SO in older adults, and b) whether time spent in LPA is associated with SO risk independently of MVPA time.
Methods: Weekly time in LPA and MVPA were assessed by accelerometry (Actigraph GT3X) in 862 older adults (65 – 79 years). MVPA time was categorized as: Inactive (<75 min/week), Moderately active (75 – 149 min/week), Active (150 – 299 min/week), and Highly active (≥300 min/week). LPA time was expressed in tertiles. SO risk (High or Low) was determined based on DXA-derived appendicular lean mass, waist circumference, handgrip strength, and the 5-times sit-to-stand test. Logistic regression models determined the likelihood of high SO risk across levels of MVPA and LPA adjusted for covariates, including level of systemic inflammation and dietary protein intake.

Results: Compared to the inactive group, the likelihood of having a high SO risk were about 50% – 80% lower depending on the MVPA level ($p < 0.05$). The likelihood of high SO risk was about 50% lower among the highly active group compared to the active group ($p < 0.05$). LPA time was inversely associated with SO risk ($p < 0.05$) in participants spending < 150 min/week of MVPA, while no corresponding association was evident among active groups.
Conclusion: MVPA is strongly associated with a lower SO risk in older adults, independently of level of systemic inflammation and intakes of dietary proteins. LPA is related to SO risk in older adults who rarely engage in MVPA, which supports promotion of physical activity regardless of intensity for older sedentary adults.

3-30

Diet-derived Advanced glycation end-products (AGEs) worsen cancer cachexia. Identification of *Vaccinium macrocarpon* extract as an antiglycation strategy.

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Cancer cachexia (CC) is a multiorgan and unresolved paraneoplastic syndrome characterized by progressive loss of muscle mass and strength (i.e., muscle wasting; MW). High levels of advanced glycation end-products (AGEs) are contained in foods rich in sugars and fats, typically of the unhealthy Western diet (WD) style, which promotes several diseases by increasing systemic inflammation and oxidative stress. AGEs are dangerous non-enzymatic products, also formed endogenously in hyperglycemic conditions, inducing tissue damage by cross-linking proteins or activating their receptor, RAGE. High levels of AGEs are found in the plasma and tumor of cancer patients, and RAGE signaling contributes to CC. Recently, we demonstrated that endogenous and dietary AGEs (dAGEs) induce atrophy in C2C12 myotubes, and *Vaccinium macrocarpon* (VM) extract hinders AGEs. The direct role of dAGE-enriched WD in the onset and progression of CC is unknown. C2C12 myotubes exposed to tumor necrosis factor (TNF)-α or pro-cachectic factors secreted by Lewis lung carcinoma (LLC) or colon adenocarcinoma (C26) cells, also in the presence of cisplatin, mimicking CC in vitro, resulted in AGE accumulation in concomitance with myotube diameter reduction and myosin heavy chain (MyHC)-II degradation. LLC-injected WD- vs standard diet-fed mice showed a more severe CC, i.e., higher loss of body weight, presence of atrophic myofibers, MyHC-II degradation, and proteolytic system activation, in concomitance with greater muscle accumulation of AGE and hyperexpression of RAGE. VM counteracted MW in in vitro and in vivo models by abrogating AGE accumulation. Interestingly, in the presence of MyHC-II degradation, we observed a strong re-expression of AGEs and RAGE in rectus abdominis muscles derived from pancreatic carcinoma patients compared with healthy subjects. Collectively, our data suggest AGEs as determinant mediators of MW in cancer conditions, and identify a promising natural strategy for addressing cancer-induced MW, which is worsened by the consumption of an unhealthy diet.

3-31

The meaning of the EORTC Physical Functioning domain as a potential clinical endpoint in trials of patients with cancer cachexia: the association to direct physical assessments

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Background: The EORTC Physical functioning (PF) score, a subscale relying on five items in the EORTC QLQ-C30 questionnaire, is widely used in oncological trials and subsequently gains attention in cachexia research. The aim of this study was to assess how the PF subscale correlates with other performance assessments and how clinical features in patients with cancer cachexia may influence the PF result.
Methods: A mixed-type advanced-stage cancer cohort of 359 patients (stage III/IV 84%) was enrolled in a prospective study. Acute infections or cardiovascular diseases were counted as exclusion criteria. Cachexia was diagnosed as BMI <24kg/m² and weight loss of >5% over the past 12 months. Patients self-completed the EORTC QLQ-C30 questionnaire and physical performance was tested by hand grip strength (HGS), stair climbing power (SCP), and 6-minutes' walking distance (6MWD). Patients were followed-up over up to 84 months (median = 22.1). The PF subscale was calculated according to the EORTC's instruction. Linear regression was used to compare PF score with physical performance. Influence of clinical characteristics on the PF score was assessed as Cohen's d effect size estimates and with Pearson's or Spearman's correlation. Survival analyses were performed using Cox proportional hazards models adjusted for age, cancer stage, cancer type, anti-cancer therapy naïve, and CRP levels.
Results: In our study 27% of patients were diagnosed with cachexia. Although of similar age their PF was relevantly lower (56±29 vs. 67±29, p=0.001). PF subscale showed strong linear correlation to HGS (r=0.38, R^2=0.14, p<0.0001), SCP (r=0.32, R^2=0.100, p<0.0001), and 6MWD (r=0.52, R^2=0.265, p<0.0001). Common features of advanced cancer and cachexia like ECOG (Cohen's d -1.67, 95% CI [-1.91, -1.43]), cancer stage (Cohen's d -0.49, 95% CI [-0.77, -0.21]), previous anti-cancer therapy (Cohen's d 0.42, 95% CI [0.15, 0.70]), and blood parameters were associated with PF scores. In the cohort 1-year mortality was 41% (147 events) and 5-year mortality 63% (226 events). PF cut-points predicted different overall survival likelihood (log rank test, χ^2=37.69, p<0.0001) and the subscale proved to be an independent predictor in multivariable cox proportional hazards regression (Harrel's C 0.751, AIC 2328.18) with a HR of 0.95 (95% CI [0.92-0.99], p=0.004) per increase of 6.66 points.
Conclusions: Assessing reported performance through the EORTC PF score has good correlation with direct physical tests while being more feasible and predicting mortality. It makes for a promising endpoint for cachexia trials, though impact of patients' clinical characteristics must be carefully considered in trial designs.

4-01

Myostatin antisense administration prevents sepsis-induced muscle atrophy and weakness in male mice

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Background: Muscle atrophy and weakness are serious problems associated with sepsis. However, only few pharmacological interventions are available to date. In this study, myostatin antisense was used to prevent sepsis-induced muscle atrophy and weakness.
Methods: Sepsis was induced in 8-week-old male C57BL/6J mice via intraperitoneal injection of 1 mg/g cecal slurry (CS). Myostatin antisense was injected into the right tibialis anterior muscle. Myostatin mRNA was measured in the tibialis anterior and quadriceps femoris muscles on day 1. The body weight, grip strength, and cross-sectional area of the tibialis anterior muscle were measured on day 6.
Results: The administration of myostatin antisense decreased myostatin expression on day 1 in the injected side (0.023±0.010 in CS vs. 0.008±0.002 in CS+antisense) as well as in the noninjected muscles. It also decreased the myostatin protein level (2.0±0.3 in CS vs. 1.2±0.5 in CS+antisense, p = 0.04). Body weight reduction (94.9%±2.0% vs. 98.2%±1.8%, p < 0.01) and grip strength reduction (77.0%±12.3%vs. 89.8%±8.3%, p = 0.04) were suppressed by the injection. The cross-sectional area of the right tibialis anterior muscle increased after the treatment (1116±530 μm2 vs. 1435±648 μm2, p < 0.01).
Conclusion: Myostatin antisense suppressed the elevation of myostatin mRNA expression in whole muscles of mice with sepsis and prevented sepsis-induced muscle atrophy and weakness.

4-02

Bimagrumab preserves lean mass and sustains fat loss during semaglutide-induced weight reduction in diet-induced obese mice

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Introduction: Rapid weight loss promoted by incretin-based therapies, including semaglutide (GLP-1 receptor agonist), can result in concomitant loss of lean (muscle) mass leading to sarcopenia, impairing metabolic health, functionality, and quality of life. Hence, interventions preventing loss of lean mass while sustaining fat loss during weight reduction are warranted. The primary objective of this study was to assess whether Bimagrumab (human anti-activin II-receptor antibody) can prevent lean mass loss and concomitantly sustain fat mass loss during semaglutide-induced weight reduction in diet-induced obese (DIO) mice.
Methods: Male C57BL/6JRj mice were fed a high-fat diet (60 kcal-% fat) for 26 weeks. DIO mice were randomized to treatment based on body weight (n=10 per group). Semaglutide (30 nmol/kg, QD), Bimagrumab (20 mg/kg, QW) or vehicle was administered subcutaneously for 4 weeks. Vehicle-dosed age-matched chow-fed mice served as a lean control. Study endpoints included body weight, food intake, muscle weight, whole-body fat/lean mass (EchoMRI), plasma biomarkers, grip strength and muscle and adipose tissue histology.
Results: Semaglutide monotreatment reduced body weight with concomitant decrease in both fat and lean tissue mass. In contrast, bimagrumab monotreatment was weight-neutral, but reduced fat and increased lean tissue mass. Notably, the combination of semaglutide-bimagrumab treatment prevented loss of lean tissue mass with preserved reduction in fat tissue mass. Interestingly, semaglutide-bimagrumab combination treatment increased muscle weights, albeit did not improve muscle strength nor fiber type plasticity. Combination treatment with semaglutide-bimagrumab reduced skeletal muscle lipid accumulation and adipocyte size and number in DIO mice.
Conclusions: Bimagrumab preserves lean tissue mass and sustains fat loss during semaglutide-induced weight loss in DIO mice, implicating activin type II receptors in the adverse effects of weight loss drugs on muscle mass. Bimagrumab may serve as reference compound for exploring metabolic-dysfunction associated diseases aiming to profile drug candidates with therapeutic potential to prevent anti-obesity drug-induced sarcopenia.

4-03

Semaglutide inhibits proteolysis in skeletal muscle of obese mice

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Introduction: Semaglutide (SEMA) is widely used to treat obesity and its comorbidities, but its effects on skeletal muscle protein metabolism remain poorly understood.
Methods: We investigated these effects in obese male C57BL/6J mice (HFD, 16 weeks) treated with SEMA (120 μg/kg/day, s.c., 14 days) or vehicle, with lean mice as controls. In a separate experiment, lean mice were fasted for 48 hours and treated with SEMA (120 μg/kg/day) or vehicle (0.9% NaCl) along this period to exclude putative effects mediated by insulin. Total proteolysis was assessed ex vivo in soleus and EDL muscles by quantifying tyrosine release into the incubation medium. Tibialis anterior and soleus muscles were collected for molecular analyses. Data were analyzed using one-way ANOVA with Tukey's post-hoc test or Student's t-test, with statistical significance set at p<0.05. All procedures were approved by the Ethics Committee on Animal Use (CEUA 1393/2024).
Results: As expected, HFD increased energy intake, body weight, fat mass and lean mass, and impaired glucose intolerance in obese mice. SEMA reduced caloric intake and reestablished body mass, fat mass, lean mass and glucose tolerance to control levels. In soleus, SEMA treatment reduced overall proteolysis, activated the PKA/CREB pathway, and increased FoxO1 phosphorylation. Interestingly, under fasting conditions, SEMA also decreased proteolysis and enhanced CREB phosphorylation, even in the presence of reduced p-AKT content.
Conclusions: Semaglutide appears to inhibit proteolysis through direct effects on skeletal muscle, independently of insulin.

4-04

Liraglutide preserves soleus muscle mass in obese mice and modulates calcium handling in isolated single fibres

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Introduction: Liraglutide (LIRA), a GLP-1 receptor agonist, reduces food intake and enhances insulin secretion through cAMP signaling. Although widely used in diabetes and obesity therapy, its effects on skeletal muscle remain poorly understood. This study investigated the impact of LIRA on morphology, oxidative metabolism, protein balance, and Ca^{2+} handling in the soleus muscle of mice.
Methods: Male C57BL/6 mice were fed a normal diet (ND) or high-fat diet (HFD) for 16 weeks, followed by treatment with vehicle or LIRA (200 µg/kg, i.p., twice daily) for 10 days, generating six groups: ND, ND pair-fed, ND+LIRA, HFD, HFD pair-fed and HFD+LIRA. Body composition, glucose tolerance, cross-sectional area (CSA), fibre-type composition, OXPHOS content, anabolic/proteolytic markers, and Ca^{2+} handling in isolated single fibres were assessed. All procedures were approved by the Ethics Committee on Animal Use (CEUA 192/2020).
Results: HFD induced an increase in body weight, attenuated by LIRA treatment, accompanied by reduced fat mass and improved glucose tolerance. Despite a greater loss of body mass compared with the pair-fed group, LIRA preserved obesity-induced hypertrophy of muscle fibres. It also increased mitochondrial complexes IV and V and reversed the HFD-induced glycolytic shift. Moreover, LIRA stimulated anabolic signaling, as indicated by the S6 pathway, and attenuated the ubiquitin–proteasome system (UPS) through downregulation of the E3 ligases atrogin-1 and MuRF-1. In parallel, LIRA (10^{-6}M) reduced lysosomal and UPS activity and increased RyR1 Ca^{2+} in lean isolated single fibres.
Conclusions: LIRA promotes structural and metabolic adaptations on soleus, preserving muscle mass, enhancing oxidative capacity, inhibiting catabolic pathways, and modulating intracellular Ca^{2+} homeostasis. These effects occur, at least in part, independently of food restriction, unveiling novel mechanisms through which LIRA preserves the skeletal mass and function in obese mice.

4-05

Fracture risk in heart failure

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Introduction: Patients with heart failure (HF) have a high prevalence of osteoporosis and an increased fracture risk (FR). Although sarcopenia does not directly affect bone microarchitecture, it may contribute to FR in these patients through functional decline and reduced mobility. The coexistence of osteoporosis and sarcopenia represents a particularly hazardous yet often underestimated condition in individuals with HF.
Methods: We performed a retrospective analysis of 263 HF patients from the SICA-HF study with available T-Score values. Bone mineral density and muscle mass were assessed using dual-energy X-ray absorptiometry. Osteoporosis was defined as a T-score ≤ –2.5, and osteopenia as a T-score between –1.0 and –2.5. Sarcopenia was defined as an appendicular skeletal muscle mass index (ASMI) < 7.26 kg/m² for men and < 5.45 kg/m² for women. FR was calculated using the 3-year FR score for osteoporotic fractures developed by the German Society for Osteology (DVO).
Results: Of 263 patients with HF, 9 patients (3.4%) had manifest osteoporosis, 45 patients (17.1%) had osteopenia, and 46 patients (17.5%) were sarcopenic. Overall, 30 HF patients (11.4%) presented with a 3-year osteoporotic FR ≥10%. These patients showed a significantly higher prevalence of sarcopenia, lower ASMI, and reduced muscle strength (all $p < 0.05$), despite comparable T-scores to those with FR <10%. In univariate logistic regression using a FR >10% as dependent variable, lower ASMi and reduced handgrip and quadriceps strength were strongly associated with higher FR (all p <0.03), along with other comorbidities such as chronic kidney disease (p <0.02).
Conclusions: Our findings suggest that in HF, FR is closely linked to global frailty and age-related decline in musculoskeletal function rather than bone mineral density alone. Sarcopenia contributes to FR primarily through its overlap with low BMI and functional decline, highlighting the need for integrated muscle–bone–heart assessments in HF.

4-06

ExermiR-129-3p enhances muscle function by improving mitochondrial activity through PARP1 inhibition

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Introduction: Physical exercise has beneficial effects on various organs, including skeletal muscle. However, not all patients are capable of engaging in exercise to maintain muscle function, which underscores the importance of identifying molecular mechanisms of physical training that could lead to the discovery of exercise-mimicking molecules.
Methods: This study sought to identify molecular mediators of exercise that could improve muscle function. We focused on the exercise-induced microRNA (miR)-129-3p, investigating its role and effects on mitochondrial activity both *in vivo* and *in vitro*. The expression of miR-129-3p was analyzed in skeletal muscle following exercise, and its downstream effects on the poly(ADP-ribose) polymerase-1 (Parp1)-SIRT1-PGC1α signaling pathway were elucidated. Functional studies were conducted using muscle-specific overexpression of miR-129-3p in adult mice and intramuscular injection of AAV9-miR-129-3p in obese mice to assess exercise capacity and muscle strength.
Results: Exercise was found to upregulate miR-129-3p in skeletal muscle, which directly inhibits *Parp1*, a major NAD+-consuming enzyme. This inhibition leads to increased NAD^+ levels, activating SIRT1 and subsequently reducing the acetylation of PGC1α, thereby enhancing mitochondrial function. Muscle-specific overexpression of miR-129-3p in adult mice significantly enhanced exercise capacity, while AAV9-miR-129-3p injections ameliorated muscle weakness in obese mice. In human skeletal muscle myoblasts, miR-129-3p improved mitochondrial function via the PARP1-SIRT1-PGC1α signaling pathway.
Conclusion: Our findings suggest that miR-129-3p, induced by exercise, can mimic the beneficial effects of physical exercise. This highlights miR-129-3p as a potential therapeutic target for improving muscle health, especially in individuals unable to exercise.

4-07

Exercise-induced CLCF1 reverses age-related skeletal muscle and bone decline

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Introduction: Aging leads to progressive alterations in skeletal muscle, including declines in mass and function. While exercise

can counteract many of these changes, the role of muscle-derived cytokines (myokines) in mediating age-related adaptations remains unclear. Identifying myokines affected by aging may provide therapeutic strategies for musculoskeletal disorders.
Methods: We analyzed circulating myokines in humans and rodents across different ages and after exercise. CLCF1 levels were measured and experimentally manipulated in aged mice. Functional assessments included physical performance, glucose tolerance, mitochondrial activity, and bone remodeling. To determine causality, CLCF1 activity was either restored or inhibited.
Results: Circulating CLCF1 declined with aging but was significantly elevated by exercise in both species. Restoring CLCF1 in aged mice improved muscle function, enhanced glucose metabolism, and increased mitochondrial activity. In bone, CLCF1 inhibited osteoclastogenesis and promoted osteoblast differentiation, thereby preventing age-related bone loss. These effects paralleled benefits of exercise. Conversely, blocking CLCF1 abolished these improvements, indicating its essential role in mediating exercise-induced adaptations.
Conclusion: Our findings demonstrate that CLCF1 is a key regulator of muscle and bone health during aging. Exercise restores its levels, leading to improved metabolic and skeletal outcomes. CLCF1 may represent a promising therapeutic target to promote healthy aging and counteract musculoskeletal decline.

4-08

Establishment of a mouse model of disuse-induced muscle wasting and evaluation of the therapeutic efficacy of human Wharton's jelly-derived mesenchymal stromal cells

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Introduction: Disuse-induced muscle wasting, characterized by progressive loss of muscle mass and strength, commonly occurs following prolonged immobilization, aging, or disease. Despite its clinical significance, standardized animal models for studying this condition are limited, restricting mechanistic studies and therapeutic development. This study aimed to establish a simple, reproducible murine model of disuse-induced muscle wasting and evaluate the therapeutic potential of human Wharton's jelly-derived mesenchymal stromal cells (WJ-MSCs).
Methods: Muscle wasting was induced by flexing the hind paw of one hind limb in the plantar direction and immobilizing it using a surgical wire staple or suture. Muscle mass and grip strength were measured at baseline and 14 days post-immobilization. Histological analyses assessed myofiber structure and cross-sectional area. Molecular analyses evaluated expression of genes associated with muscle atrophy, inflammation, and regeneration, including *Trim63*, *Fbxo32*, *Tnf*, and *Myod1*. Human WJ-MSCs were administered intravenously to assess effects on muscle recovery and function.
Results: Immobilization significantly reduced muscle mass and strength, and histological examination revealed pronounced myofiber atrophy. Human WJ-MSC-treated mice showed significant recovery of muscle mass and grip strength, with partial restoration of *Trim63*, *Fbxo32*, *Tnf* and *Myod1* expression. No significant adverse effects were observed throughout the study.
Conclusions: We established a simple, reproducible murine model of disuse-induced muscle wasting suitable for preclinical research. Intravenous human WJ-MSC administration effectively ameliorated muscle wasting, improved molecular and functional phenotypes, and demonstrated potential as a therapeutic intervention. This model provides a reliable platform for evaluating novel treatments and investigating mechanisms underlying muscle atrophy.

4-09

Heterogeneity in mitochondrial adaptations to pulmonary inflammation and hypoxia across oxidative and glycolytic muscles

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Introduction: Chronic obstructive pulmonary disease (COPD) patients often experience skeletal muscle dysfunction and atrophy that may be partially explained by mitochondrial bioenergetics alterations. Among other factors, pulmonary inflammation and hypoxia may contribute to the COPD-associated muscle defects. Nevertheless, the precise molecular mechanisms and their effects across muscles with distinct metabolic profiles remain elusive. This study investigated the independent and synergistic effects of chronic pulmonary inflammation and chronic hypoxia on mitochondrial function in oxidative (soleus) and glycolytic (plantaris) muscles.
Methods: Twenty-eight male Wistar rats (20-27 weeks old; 530 ± 41 g) were assigned into one of the following four groups for 28 days until sacrifice: 1) Normoxia control (NC) 2) Chronic hypoxia (H) 3) Chronic pulmonary inflammation (I) and 4) H + I (HI). Following sacrifice, muscles were immediately weighed. To assess mitochondrial function, we measured rates of oxygen consumption, reactive oxygen species (ROS) emission (using H_2O_2 emission as a surrogate) and calcium handling capacity in isolated mitochondria.
Results: Chronic hypoxia led to a decline in adenosine diphosphate-stimulated complex I (CI) respiration ($p < 0.01$) and weight ($p < 0.05$) in plantaris. In contrast, chronic hypoxia increased respiratory complex I-derived ROS emission ($p < 0.01$) without any changes in mitochondrial respiration or mass of soleus. Finally, pulmonary inflammation caused a reduction in the mitochondrial calcium retention capacity of soleus
Conclusion: Using our original model of chronic hypoxia and pulmonary inflammation, we demonstrate a muscle-specific dichotomy. Hypoxia primarily impaired the glycolytic plantaris, inducing mitochondrial dysfunction and atrophy, while the oxidative soleus exhibited greater resilience, as indicated by the preservation of its mass and respiration, despite the elevated ROS emission. In contrast, inflammation specifically targeted soleus, increasing its mitochondrial permeability transition pore sensitivity. Conclusively, our findings suggest that chronic hypoxia predominantly affects glycolytic muscles, while chronic pulmonary inflammation compromises primarily oxidative fibres.

4-10

JUV-161 preserves muscle mass and function in a mouse model of cast immobilization atrophy

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Introduction: Prolonged muscle disuse due to injury, casting, or bed rest leads to rapid skeletal muscle atrophy, strength loss, and impaired mobility. There is a critical need for therapies that preserve muscle mass and function during these periods. JUV-161, a novel secreted protein developed by Juvena Therapeutics, is designed to enhance muscle regeneration and protect against disuse-induced muscle atrophy.
Methods: Fourteen-week-old male C57BL/6 mice underwent right hindlimb cast immobilization for 14 days to induce muscle disuse-induced. During this period, mice were treated daily with either vehicle (human serum albumin, HSA) or JUV-161 (12 mg/kg, subcutaneously). After cast removal, body composition was

assessed via EchoMRI, hindlimb grip strength was measured, and gait analysis (stance length) was performed. Tibialis anterior (TA) and gastrocnemius (GC) muscles were harvested and weighed to evaluate muscle preservation. The muscle mass ratio between the immobilized and contralateral limb was also assessed.
Results: JUV-161 treatment led to a 3.21% increase in body weight ($p < 0.05$) and a 2.4% increase in lean mass ($p < 0.05$) compared to vehicle-treated controls, indicating systemic anabolic effects. Hindlimb grip strength improved by 13.16% ($p < 0.001$), and stance length increased by 9% ($p < 0.05$), reflecting enhanced muscle function and locomotor stability. Muscle weights of the TA and GC muscles increased by 9.2% and 8.1%, respectively ($p < 0.05$). The casted/contralateral muscle weight ratio improved by 10.7% ($p < 0.01$), demonstrating reduced muscle loss in the immobilized limb.
Conclusion: JUV-161 significantly preserved muscle mass, improved functional strength, and enhanced mobility in a mouse model of immobilization atrophy. These findings support its therapeutic potential in preventing disuse muscle atrophy and promoting recovery during periods of immobilization or inactivity.

4-11

JUV-161 is effective in reversing skeletal muscle myopathy in mouse models of DM1 and Sarcopenia

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Introduction: Currently available animal models do not adequately model the multisystemic presentation of DM1 in humans.
Methods: Juvena developed a DM1 mouse (panCUG960/+) which addresses the genotypic and phenotypic characteristics of DM1 in humans. The panCUG960/+ model provides key genotypic, phenotypic and functional characteristics of DM1 not previously generated in a single animal. The panCUG960/+ murine DM1 model, through CUG repeat expansion in the 3' UTR region of the DMPK gene, reproduces the histopathologic changes seen in DM1 (including accumulation of RNA foci with splicing abnormalities, skeletal muscle loss, and shift to slow twitch fibers) while also demonstrating progressive functional consequences (e.g., decreased grip strength and impaired treadmill performance) that parallel disabilities noted in patients with DM1.
Results: Subcutaneous (SC) administration of JUV-161 at a dose of 12 mg/kg/day was associated with mitigation of histopathologic and functional consequences of CUG repeat expansion, including reversal of muscle fiber type changes, regain of lost muscle mass, reversal of grip strength losses and regain of treadmill performance. Similarly, in an age-related model of muscle degeneration (sarcopenia), SC administration of JUV-161 at 12 mg/kg/day enhanced muscle fiber size and promoted a conversion of slow to fast twitch muscle fiber type; these changes were associated with amelioration of muscle degeneration, improved muscle mass and mitigation of losses in functional muscle strength and performance.
Conclusions: Treatment with JUV-161 was effective at reversing skeletal muscle myopathy seen in DM1 and sarcopenia.

4-12

JUV-161 Accelerates Muscle Recovery and Attenuates Fibrosis in a Sarcopenic Mouse Model of Cardiotoxin-Induced Injury

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Introduction: Muscle injury in aged individuals is often compounded by sarcopenia, leading to impaired regeneration, increased fibrosis, and functional decline. Dysregulated repair mechanisms in the sarcopenic setting reduce protein synthesis and exacerbate tissue degeneration. JUV-161 is a novel secreted protein developed to promote muscle regeneration and recovery. This study evaluated the efficacy of JUV-161 in enhancing structural and functional repair in a cardiotoxin-induced tibialis anterior (TA) injury model in aged mice, mimicking muscle injury in sarcopenia.
Methods: Acute TA injury was induced in aged female C57BL/6 mice (20 months old) via intramuscular cardiotoxin injection (Day 0). Mice received intramuscular JUV-161 (20 µg/mL, 20 µL per TA, Days 2, 4, 6) or vehicle (HSA). On Day 8, muscle function was assessed with Aurora physiological testing (force–frequency response, fatigue resistance, contraction–relaxation kinetics). TA muscles were collected for weight measurement and histological analysis. Regeneration and fibrosis were quantified by H&E staining.
Results: JUV-161 significantly increased TA muscle mass versus vehicle. Aurora testing revealed improved force–frequency response, reduced fatigue, and faster contraction–relaxation rates, demonstrating enhanced muscle performance. Histological analysis showed a higher regenerative index and markedly reduced fibrosis in JUV-161–treated muscles.
Conclusions: In aged mice modeling sarcopenia, JUV-161 enhanced muscle regeneration, restored functional strength, and reduced fibrosis following acute cardiotoxin injury. These findings highlight JUV-161 as a promising therapeutic for sarcopenia and age-associated impairment in muscle repair, with translational potential for injury recovery in older adults.

4-13

JUV-161: Identification of a novel clinical candidate for the treatment of myopathy and sarcopenia

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Introduction: JUV-161 is the lead clinical candidate developed from a screening campaign of Juvena's platform to identify stem cell secreted proteins with the potential to treat myopathies. JUV-161 is a recombinant fusion protein of human serum albumin (HSA) linked to the human IGF-2 sequence (HSA-IGF-2-R61A). It retains the receptor binding capacity of IGF2, including relative receptor affinities as a potent and selective agonist of IGF-2R, IR-A / IR-B, and IGF-1R. JUV-161 has a higher potency (EC_{50} = 41.12 nM) relative to IGF2 (EC_{50} = 4.2 nM) in promoting IGF1R activation in cell-based potency assay, and activates the AKT signaling pathway in skeletal muscle.
Methods: Cell-based potency assays were used to evaluate receptor activation and downstream AKT signaling. Human muscle precursor cells (from healthy donors and patients with DM1, and sarcopenia) were treated with JUV-161 or IGF2 and assessed for myogenic progression from myoblast to myotube. In vivo efficacy was tested in mouse models of muscular dystrophy/myopathies and muscle loss by subcutaneous administration of JUV-161.

Endpoints included muscle regeneration, metabolism, and functional strength (grip test).
Results: In vitro data demonstrates that administration of JUV-161 drives myogenic progression of human muscle precursor cells through myoblast and myotube stages toward fiber formation comparable to the equimolar effects of IGF2. These effects are observed in muscle precursor cells derived from healthy individuals and those with myopathic disorders such as DM1, sarcopenia, or DMD. JUV-161's agonistic action at the IR-A / IR-B receptor drives glucose uptake and activation of the insulin-response pathway, such as PI3K. Collectively these pathways activate AKT-mediated signaling crucial for the survival and activation of the transcriptional cascade of muscle cell differentiation. In mouse models of myopathies, muscle loss, and dystrophies JUV-161 demonstrates promising therapeutic activity for improving muscle regeneration, metabolism, and muscle function (grip strength). Preclinical data indicate JUV-161 can be administered as a single weekly s.c injection. First-in-human studies in NHVs are currently ongoing.
Conclusion: JUV-161 has potential utility for the treatment of myopathies or sarcopenia.

4-14

Therapeutic Potential of JUV-161 in Enhancing Muscle Health and Insulin Sensitivity in Diabetic Myopathy and Sarcopenia

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Introduction: Type 2 diabetes (T2D) often leads to metabolic dysregulation, insulin resistance, and skeletal muscle wasting, collectively contributing to diabetic myopathy and sarcopenia. Effective therapies that improve insulin sensitivity while preserving or restoring muscle mass are urgently needed. JUV-161, a novel secreted protein, has been developed to enhance insulin signaling and promote muscle regeneration. This study assessed the effects of JUV-161 on systemic metabolism, muscle structure, and functional health in db/db mice, a well-established model of T2D-associated myopathy and muscle atrophy that mimics features of sarcopenia.
Methods: Male db/db mice received daily subcutaneous injections of JUV-161 (N=22) or vehicle (HSA) for 26 days. Insulin sensitivity was evaluated using the insulin tolerance test (ITT), and lean mass was quantified via EchoMRI. Serum markers of glucose homeostasis (glucose, HbA1c), liver function (AST, aspartate aminotransferase), kidney function (creatinine), and muscle integrity (CK, creatine kinase) were measured. Muscle health was further assessed by tibialis anterior (TA) and gastrocnemius (GC) weights, cross-sectional area (CSA), and fiber-type composition to determine regenerative capacity.
Results: JUV-161 significantly improved insulin sensitivity by 20% compared with vehicle ($p<0.001$) and reduced serum glucose, AST, CK, and creatinine levels ($p<0.05$–0.0001). HbA1c decreased from 10.1% to 8.2%. Lean mass increased by 4.6%, with notable gains in TA (0.00168 g/mm vs. 0.00135 g/mm, $p<0.001$) and GC (0.00497 g/mm vs. 0.00459 g/mm, $p<0.05$) weights. Histological analysis revealed increased GC CSA and expansion of type IIb fibers, indicating enhanced muscle regeneration.
Conclusions: JUV-161 improves insulin sensitivity (ITT), enhances lean muscle mass (EchoMRI), and protects against liver and kidney dysfunction in db/db mice with diabetic myopathy. These findings support JUV-161 as a promising therapeutic candidate for T2D-associated muscle wasting and sarcopenia, with potential applications in weight loss, injury recovery, and overall metabolic health.

4-15

High-throughput 3D imaging and quantification of mouse hindlimb muscles using light sheet fluorescence microscopy

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Introduction:
Accurate quantification of muscle mass in preclinical models of sarcopenia, obesity, and drug-induced atrophy remains challenging due to limitations in spatial resolution and anatomical specificity of conventional methods such as body composition scans. This study presents a scalable imaging and analysis pipeline utilizing light sheet fluorescence microscopy (LSFM) to enable micrometer-resolution, high-throughput quantification of individual hindlimb muscles in mice.
Methods: A fully automated workflow was developed, integrating optical tissue clearing, autofluorescence-based LSFM imaging, and image processing. Over 40 mouse hindlimbs were imaged at 1.5×1.5×10 µm XYZ resolution (downsampled to 10×10×10 µm for analysis). Samples were registered to an in-house developed custom 3D leg atlas, enabling segmentation of major calf muscles; gastrocnemius, plantaris, and soleus for volumetric analyses.
Results: The pipeline achieved reproducible anatomical alignment and high-throughput quantification of individual muscle volumes across samples. The micrometer-scale resolution allowed visualization of bones, fat, connective tissue, and distinct muscle fiber bundles. Compared to traditional lean mass assessments, the method detected subtle morphological features not otherwise resolvable. Although treatment effects are under ongoing investigation, the approach provides a mesoscopic bridge between MRI and histology, with potential for cross-modality benchmarking.
Conclusions: This LSFM-based pipeline offers a robust and anatomically precise tool for preclinical muscle research. Its scalability and resolution make it suitable for detecting fine structural changes in muscle tissue, positioning it as a valuable complement to existing imaging techniques. Future adaptations aim to extend its application to rats and to incorporate AI-assisted segmentation, advancing the development of translational pipelines that connect preclinical findings with clinical imaging phenotypes.

4-16

A MRI *vs* histology study of C57Bl/6J Rj, a murine model of muscle aging in a context of sedentary lifestyle.

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Introduction: Muscle aging is associated to a loss of muscle mass and modification of muscle structure. MRI can reveal these patterns as a decrease of contractile muscle Cross-Sectional Area (CSA) and an increase in the relaxation time T2. These features, which were observed in humans, were also noted in a mouse model, the C57Bl/6J Rj strain fed with high-energy diet. The aim of this preliminary study was to leverage muscle biopsies in mice to confront MRI with histology.
Methods: Six C57Bl/6J Rj male mice were studied: three at 8 months of age and three at 24 months. All animals underwent imaging on a 7T Bruker MRI system equipped with a surface cryoprobe. High-resolution anatomical scans and T2 mapping were performed to quantify maximal muscle CSA and muscle T2,

respectively. Following MRI, triceps surae (TS) muscles were collected. Cryosections (5 µm thick, snap-frozen) of the TS were analyzed by immunofluorescence to assess muscle architecture, including fiber CSA and the centronucleation index. Data are presented as mean ± SD, and group comparisons were performed using the Mann–Whitney test.
Results: In our small animal cohort, we observed a non-significant reduction in maximal muscle CSA across all compartments with aging. Muscle T2 values were elevated in every compartment with age (TS: T2 = 21.88 ± 0.62 ms at 8 months; T2 = 23.16 ± 0.23 ms at 24 months; $p < 0.05$). Immunofluorescence staining further revealed structural alterations in the TS muscle, notably a shift toward smaller fibers that was not associated with an increased proportion of centronucleated fibers (maximal fiber CSA: 8 months = 1000–1250 µm²; 24 months = 250–500 µm²; $p < 0.05$).
Conclusions: This combined MRI–histology study of aging mouse muscle revealed underlying histological changes that help explain the observed MRI features.

4-17

MicroRNAs altered during ageing affect mitochondria in skeletal muscle

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Introduction: As individuals age, skeletal muscle undergoes a process of atrophy known as sarcopenia. This leads to a diminished ability of the muscle to respond to stress, increasing the likelihood of developing comorbidities and mortality. Skeletal muscle ageing is characterised by impaired mitochondrial metabolism and function. Approaches that mitigate sarcopenia have been demonstrated to improve mitochondrial health, and more recently, it has been demonstrated that improving mitochondrial quality control can combat the effects of ageing. MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression at the post-transcriptional level and play a crucial role in age-related changes in skeletal muscle.
Methods: We integrated transcriptomic and bioinformatic approaches to identify miRNAs differentially expressed during skeletal muscle ageing in mice that are predicted to influence mitochondrial metabolism. We engineered skeletal muscle cells to modulate the expression of miRNAs altered during skeletal muscle ageing to assess mitochondria morphology and functionality, organelle interactions, and myogenesis. Subsequently, we analysed the transcriptional profile of cells overexpressing the miRNA, which predominantly affects mitochondrial function.
Results: We have identified miRNAs altered during muscle ageing and are predicted to affect mitochondrial function. Subsequently, we experimentally validated that miRNAs affect both mitochondrial dynamics and function in both myoblasts and myotubes. These miRNAs also influence myoblast differentiation since mitochondrial metabolism sustains myogenesis and muscle regeneration. The mechanism of action of the miRNA, which predominantly impacts mitochondrial functions, was assessed based on RNA sequencing results following its overexpression. We will evaluate whether the *in vivo* modulation of the miRNA will affect muscle metabolism and the ageing process.
Conclusions: We have identified miRNAs that regulate mitochondrial metabolism, which could be utilised to counteract the effects of ageing. This research aims to uncover potential RNA-based therapeutic approaches that could mitigate the decline in skeletal muscle performance associated with ageing.

4-18

Local TGF-β signaling causes impaired contractability and low-response to exercise in human skeletal muscle

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Introduction: Transforming growth factor-β1 (TGF-β1) impacts skeletal muscle-homeostasis, regeneration, and metabolism. Chronic activation of TGF-β1 impairs myogenesis and promotes fibrosis contributing to muscle dysfunction in conditions like muscular dystrophy and sarcopenia. Elevated TGF-β-signaling has also been implicated in impaired response to exercise training, reducing the improvement in glycemic control and mitochondrial function. Thus, elucidating the role of TGF-β1 in contracting skeletal muscle is essential for understanding maladaptation and variable exercise responses.
Methods: CD56-enriched primary human myoblasts isolated from vastus lateralis biopsies (n=3-10 donors) were used to generate functional myotubes utilizing a serum free IGF1-based differentiation medium in 2D or a 3D myobundle model capable of electrical-pulse-stimulated ex vivo exercise. Models were treated with TGF-β1 (1ng/ml) alone or in combination with the TGF-β signaling inhibitor SB431542 (10µM). Analysis included Video-based Motion-Tracking-Algorithms, qPCR, WB, Glucose- and Lactate-measurements, transcriptomics and proteomics. Transcriptomics was performed on tissue from vastus lateralis biopsies (n=42 donors).
Results: Our human muscle models showed robust contraction during exercise. Acute exercise induced *NR4A3* and *PGC1a* expression, AMPK-phosphorylation, elevated glucose utilization and lactate production. Down-regulation of TGF-β signaling is important for myotube development. Longitudinal analysis of contracting myobundles revealed that addition of TGF-β1, independent from maturity of differentiation, completely blocked contractability within only 24h . Local TGF-β1 signaling reduced the expression of several genes which are relevant for muscle energy metabolism or translation but have not been related to contractability yet. Interestingly, expression of these genes was also confirmed reduced in skeletal muscle of humans with low-response to exercise.
Conclusion: We revealed a fast and detrimental effect of local TGF-β signaling, present in low/non-responder individuals, on skeletal muscle function and contractability. Identifying specific mediators, will reveal strategies to overcome low-response to exercise, develop personalized interventions to prevent metabolic disease progression and preserve muscle function.

4-19

Myofiber aryl hydrocarbon receptor is essential for maintaining skeletal muscle integrity.

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Introduction: Sarcopenia profoundly impacts health span, yet the mechanisms driving skeletal muscle deterioration remain poorly understood.
Methods: We used murine models of muscle atrophy, whole-body AHR-deficient (*Ahr*$^{-/-}$) mice and generated myofiber-specific *AHR* transgenic mice (*Ahr*$^{myo-/-}$). Body weight, tissue weight, grip strength, muscle fiber cross-section, gene and protein expression, glucose tolerance test and micro-computed tomography were performed.
Results: Single-cell and single-nucleus RNA sequencing show that *AHR* is expressed in all cell populations inhabiting skeletal muscle (polynucleated and mononucleated cells) in both humans and mice. In addition, *AHR* transcript levels are downregulated in muscles from aged individuals with low muscle mass, strength and performance, whereas exercise training enhances *AHR* expression. These findings were reproduced in preclinical atrophic muscle models where dexamethasone-treated mice (excess glucocorticoid), *ob*/*ob* mice (sarcopenic obesity), and LPS-treated (infection) mice exhibited lower *Ahr* expression than control mice. Further, we found that *Ahr*$^{-/-}$ mice have decreased skeletal muscle mass, smaller myofibers and reduced muscle strength relative to *Ahr*$^{+/+}$ mice. Using *Ahr*$^{myo-/-}$ mice, we demonstrated that myofiber AHR is essential for maintaining skeletal muscle integrity. At 6-month of age, *Ahr*$^{myo-/-}$ mice have a significant decrease in muscle mass, which translates into a severe muscle strength reduction compared to control mice. This phenotype was conserved in 18-month-old mice, and these middle-aged *Ahr*$^{myo-/-}$ mice further developed age-related dysfunctions such as impaired glucose tolerance and bone loss.
Conclusions: Our findings reveal an essential role of myofiber AHR in maintaining skeletal muscle health.

4-20

Correlation of CT-measured myopenia with two-year overall survival in older adults with non-small cell lung cancer treated with immunotherapy in a third level hospital in Mexico.

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Introduction: Myopenia, defined as loss of skeletal muscle mass, is common among older adults with cancer and has been associated with impaired treatment tolerance and poor outcomes. In non-small cell lung cancer (NSCLC), the prognostic impact of myopenia in patients treated with immunotherapy is not fully established. This study aimed to determine the correlation between CT-measured myopenia and two-year overall survival in older adults with NSCLC receiving immunotherapy.
Methods: A retrospective cohort study was conducted at a third level hospital in Mexico, including patients ≥65 years with histologically confirmed NSCLC treated with immunotherapy between 2018 and 2024. Skeletal muscle index at the third lumbar vertebra was quantified using CT images. Patients were classified into groups with or without myopenia according to Prado and Zhuang cut-offs. Overall survival at 24 months was assessed using Kaplan–Meier curves and log-rank tests. Spearman's correlation and Cox proportional hazards models were applied to explore associations and adjust for confounders.
Results: Seventy-one patients were included (mean age 77 ± 6.3 years; 50.7% male). Myopenia was present in 76.1% (Prado criteria). At 24 months, survival was 65.9% in the myopenia group and 67.9% in the non-myopenia group (HR 1.06; 95% CI 0.41–2.78; p=0.898). Spearman's correlation showed a weak but significant negative association between myopenia and survival (rho –0.268, p=0.024). Myopenia was associated with lymphocytopenia (p=0.006), suggesting immunosenescence. Other predictors of mortality included delirium (HR 2.78, p=0.029), Karnofsky index <60 (HR 3.30, p=0.028), and CNS metastases (HR 3.03, p=0.048).
Conclusions: CT-determined myopenia correlated with reduced survival at 24 months, although not as an independent predictor in multivariate analysis. Its association with altered immune parameters and clinical vulnerability supports its role as a potential prognostic biomarker. Routine CT-based muscle quantification could enhance geriatric-oncology assessment and guide personalized therapeutic strategies.

4-21

Insights into the effects of platelet-based applications on skeletal myoblasts proliferation

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Introduction: Platelet-based applications have been proposed as therapies to address the continuous need for improved treatments to treat muscle injuries. This is due to their autologous nature, cost-effectiveness, and ease of access to multiple growth factors and cytokines that induce proliferation and regeneration. However, the evidence on the benefits of platelet therapies in skeletal muscle remains inconsistent. The aim of this study was to determine how different platelet products affect the proliferation of skeletal muscle cells *in vitro*.
Methods: Blood samples collected from healthy participants were used to prepare platelet-based products (platelet releasate, platelet-derived microparticles, washed platelets) through sequential centrifugation and/or chemical aggregation. Mouse skeletal myoblasts (C2C12) were cultured and treated with platelet-based products. The effects were assessed using proliferation assays (EdU), fluorescence imaging, and flow cytometry.
Results: Platelet-based products induced proliferation in a similar manner in both male- and female-derived samples. No significant differences were observed in the proliferative effects of washed platelets and platelet releasate. Proliferation increased in a dose-dependent manner up to a maximal concentration, after which the effect plateaued. The effect was observed to originate from platelet-derived microparticles rather than the soluble components of platelet products. Furthermore, these effects were prevented upon the inhibition of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors.
Conclusion: Altogether our results demonstrate that treatment with washed platelets, platelet releasate and platelet-derived microparticles similarly induce proliferation of skeletal myoblasts *in vitro* in a dose-dependent manner up to a maximal concentration, and this proliferation is mediated through the VEGF and PDGF signalling pathways.

4-22

Obesity reprograms adipose extracellular vesicles to induce muscle atrophy via miR-150-5p-mediated transcriptional silencing

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Introduction: Sarcopenic obesity, defined by excess fat with reduced muscle mass and function, is increasingly common in ageing populations and worsens physical and metabolic health. Adipose tissue-derived signals contribute to muscle decline, but mechanisms remain unclear. Extracellular vesicles (EVs), which transport regulatory cargo such as microRNAs (miRNAs), may mediate adipose–muscle communication.
Methods: EVs were isolated from adipose-conditioned media (ACM) of lean (BMI 20.7–24.4) and non-lean (BMI 25.3–39.3) human donors using ultracentrifugation. Donors were stratified by age (younger: 31–56; older: 60–84 years). EVs were characterised by NTA, ExoView, nanoscale flow cytometry, and TEM. Differentiated primary human myotubes were treated for 24 h with lean or non-lean EVs (1.3×10^9 particles/ml) or left untreated. Myotube thickness was assessed by immunofluorescence. Transcriptomic changes were measured by RNA-seq, EV miRNAs by small RNA-seq with qPCR validation, and miR-150-5p function by antagomir inhibition.
Results: Non-lean EVs significantly reduced myotube thickness versus untreated (8.7 ± 1.66 µm vs. 12.4 ± 1.72 µm, $p < 0.01$) and lean EV-treated cells (8.7 ± 1.66 µm vs. 13.2 ± 3.84 µm, $p < 0.05$). Effects were restricted to myotubes from older donors. MAFbx expression increased with non-lean EVs ($p < 0.05$). RNA-seq identified 471 DEGs vs. untreated and 293 DEGs between lean and non-lean EVs, enriched in inflammatory, oxidative, mitochondrial, and chromatin pathways. Seven EV miRNAs were differentially expressed, including miR-150-5p and miR-193b-5p, validated by qPCR. Inhibiting miR-150-5p partially restored myotube thickness and reduced MAFbx expression.
Conclusions: Non-lean adipose EVs induce age-dependent muscle atrophy and transcriptional changes, partly via miR-150-5p. EV miRNAs may represent targets to prevent obesity- and age-related muscle loss.

4-24

Large-Scale Screening Identifies Novel Compounds Promoting Myotube Hypertrophy Through Distinct Mechanistic Clusters

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Background: Sarcopenia and glucocorticoid-induced muscle atrophy are characterized by progressive loss of skeletal muscle mass and function, and they remain without effective pharmacological treatments. The identification of compounds that directly enhance myotube hypertrophy provides a promising strategy to counteract muscle wasting and to preserve muscle function in aging and disease.
Methods: To discover novel therapeutic candidates, a library of 6,494 small molecules was screened in differentiated C2C12 myotubes. Myotube hypertrophy was quantified using high-content imaging to assess diameter, cross-sectional area, and fusion index. Compounds that produced consistent hypertrophic responses across independent assays were classified as candidates, and each was further annotated according to its association with signaling pathways relevant to muscle biology.
Results: From this large-scale screen, twenty-three compounds were identified that reproducibly enhanced myotube hypertrophy compared with vehicle-treated controls. Mechanistic annotation revealed several distinct clusters of activity. Some compounds improved mitochondrial function and activated AMPK-PGC1α signaling, suggesting enhanced energy metabolism and oxidative resilience. Others modulated calcium-dependent pathways, which are central to excitation–contraction coupling and mitochondrial communication. Additional compounds stimulated protein synthesis through mTOR-S6K regulation, providing strategies to bypass anabolic resistance. One candidate acted through adrenergic modulation, a pathway that may help restore β-adrenergic drive in aged muscle. Finally, several novel compounds exerted hypertrophic effects through mechanisms that remain undefined but may represent unexplored pharmacological avenues.
Conclusion: This study identified twenty-three novel compounds that promote myotube hypertrophy in vitro through diverse mechanistic pathways. By targeting mitochondrial dysfunction, impaired calcium handling, anabolic resistance, and adrenergic decline, these candidates provide a foundation for translational research and highlight new therapeutic opportunities for muscle preservation in sarcopenia and cachexia.

4-25

ANGPTL3 as a Modulator of Catabolic Signalling in Insulin-Resistant Skeletal Muscle

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Introduction: Skeletal muscle (SM) wasting occurs when the balance between protein synthesis and degradation is disrupted, as seen in sarcopenia and cancer cachexia. A key driver of these alterations is insulin resistance (IR), which impairs anabolic signalling, promotes catabolism, and accelerates atrophy. Changes in the activity of Angiopoietin-like 3 (ANGPTL3), a liver-derived hepatokine, may contribute to the metabolic abnormalities occurring during SM wasting, including IR and ectopic lipid deposition. While its direct role in SM loss remains poorly defined, we hypothesized that ANGPTL3 may amplify catabolic pathways within SM. In this study, we investigated whether ANGPTL3 can directly modulate SM metabolism and atrophy pathways, using an *in vitro* coculture model of liver-muscle crosstalk under conditions of IR.
Methods: An *in vitro* muscle-liver crosstalk model was generated by co-culturing murine C2C12 myotubes with HeLa cells stably overexpressing ANGPTL3, under basal and IR conditions. Adipokine secretion was profiled using a proteome profiler array. Western blot was performed to evaluate SM intracellular signalling pathways regulating lipolysis, energy sensing, insulin signalling, and mitochondrial biogenesis.
Results: ANGPTL3 exposure induced IR-like features in myotubes, reduced secretion of adipokines involved in energy metabolism, insulin signalling, and increased pro-inflammatory mediators. In muscle cells, ANGPTL3 upregulated lipolytic proteins (pHSL, CGI-58, ATGL), activated AMPK and AKT, and increased PGC1-α expression. These molecular changes were observed both in basal and IR conditions.
Conclusion: Our preliminary data suggest that ANGPTL3 may act as a regulator of SM atrophy through lipolytic, energy-sensing, and IR-related pathways. In our model, by amplifying catabolic signaling under IR conditions, ANGPTL3 may bridge metabolic dysfunction with structural SM loss. Further analyses are ongoing to confirm these findings and clarify the role of ANGPTL3 in SM wasting.

4-26

Structural and Metabolic Muscle Changes with Age: An MRI and MRS Perspective on Mobility

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Introduction: In older adults, reduced mobility is a strong predictor of future disability in tasks required for independent living and self-care. A key contributing factor is the decline in mechanical power generated by the plantarflexor muscles during the push-off phase of walking, which represents a critical functional limitation in elderly gait.
Methods: We studied a cohort of healthy volunteers aged 20–84 years (38 females, 33 males). Participants underwent clinical assessments and gait speed evaluation, and were stratified into three groups: young (n=18), middle-aged (n=29), and older (n=24). Leg muscles were investigated using magnetic resonance imaging (MRI) and spectroscopy (MRS). Dynamic measurements were obtained with an amagnetic ergometer at 10–25% of maximal plantar flexion.
Results: Height-normalized gait speed and maximal plantar-flexion both declined progressively with age. Despite this, MRI-derived muscle mass was comparable across groups. Water T2, an MRI-based biomarker reflecting active muscle damage and sensitive to fluid changes, increased with age, and intramuscular fat fraction (FF) also rose; notably, physically active participants had significantly less FF than sedentary peers. End-exercise phosphocreatine (PCr) depletion did not differ between groups. During recovery, pH-normalized PCr recovery time was significantly longer in middle-aged and older adults. Post-exercise oxygenation was lower in older subjects, whereas maximal perfusion remained unchanged.
Conclusion: Although muscle mass is largely preserved with aging, reductions in plantar-flexor strength, gait speed, and metabolic efficiency point to qualitative rather than quantitative muscle changes. Increases in FF and altered water content highlight structural and functional remodeling that contributes to impaired mobility in older adults. Regular physical activity is associated with lower fat accumulation, underscoring its protective role for muscle quality and functional independence. The MRI data indicated an age-related blunted hyperemia or slower re-oxygenation during recovery, which might be related to shifts in intramuscular fat or connective tissue and possible differences in microvascular density.

4-27

Single-cell transcriptomics reveals cellular drivers of human skeletal muscle regeneration: implications for sarcopenia

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Background: Dysregulated skeletal muscle remodelling with ageing contributes to sarcopenia, characterised by the progressive loss of muscle mass and strength. However, the cellular and molecular mechanisms that underpin human skeletal muscle regeneration remain poorly defined. Here, we present the first single-cell transcriptomic characterisation of regenerating human skeletal muscle following acute traumatic injury, providing a novel framework for understanding muscle repair and identifying potential therapeutic targets.
Methods: Patient-matched skeletal muscle samples were obtained intraoperatively from injured and non-injured gluteus maximus/minimus sites following high-energy trauma (REC:21/WA/032) and cryopreserved in CS10 medium. Mononuclear cells were isolated and subjected to single-cell RNA sequencing (10x Genomics/Novogene) in a subset of patients (n = 4; injury severity score 10.2 ± 5.9; age 40 ± 10.9). Computational analyses were performed using the Seurat, Monocle3, CellChat, and NicheNet R packages to delineate changes in cellular composition and intercellular signalling during muscle remodelling.
Results: We identified 20 distinct mononuclear cell populations across injured and non-injured tissues. Injury induced marked infiltration of macrophage subsets and the emergence of activated fibroblasts from resident fibroadipogenic progenitors. Epiregulin and fibroblast growth factor-7 were identified as key ligands mediating crosstalk form these cell types with satellite cells. Macrophage subclustering revealed eight further subpopulations, including significant accumulation of TREM2+, APOC1+ lipid-associated and LDHC+, FN1+ metabolic macrophages previously undescribed in skeletal muscle. Pseudotime analysis of satellite cells mapped transcriptional trajectories from quiescence, through differentiation into myocytes, uncovering uncharacterised gene programs associated with regeneration.
Conclusions: Acute injury induces profound remodelling of the skeletal muscle niche, with dynamic crosstalk between immune cells, activated fibroblasts, and satellite cells likely orchestrating regeneration. These findings provide new insight into human muscle repair and highlight potential therapeutic targets to enhance remodelling, with implications for treating sarcopenia.

4-28

Therapeutic potential of human Wharton's jelly-derived mesenchymal stem cells in an aged mouse model of sarcopenia

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Introduction: Sarcopenia is an age-associated condition characterized by the gradual decline of muscle mass and strength. Current pharmacological interventions, such as myostatin and activin inhibitors, have shown limited clinical benefit, emphasizing the need for new therapeutic approaches. Mesenchymal stromal cell (MSC)-based therapies have gained interest for their regenerative potential. This study investigated the efficacy of human Wharton's jelly-derived MSCs (WJ-MSCs) in a murine model of sarcopenia.
Methods: C57BL/6 mice aged 20–24 months were used as a naturally aged model of sarcopenia. Animals received intravenous injections of 5 × 10^3 WJ-MSCs, either as a single dose or repeated at four-week intervals. Therapeutic outcomes were evaluated by grip strength measurement, protein expression of atrophy markers (MuRF1, Atrogin-1), and histological analysis of muscle fiber cross-sectional area.
Results: Aged mice exhibited reduced muscle strength and fiber atrophy, consistent with sarcopenic phenotypes. WJ-MSC administration significantly decreased MuRF1 and Atrogin-1 expression by approximately 60% ($p < 0.05$), while enhancing myosin heavy chain expression and increasing muscle fiber size. Grip strength improved following treatment, with peak effects observed at four weeks. Repeated administration provided greater efficacy than a single injection, resulting in progressive increases in muscle mass and functional performance.
Conclusion: Intravenous WJ-MSCs attenuated muscle degradation, promoted regeneration, and improved muscle function in aged mice. Repeated dosing further amplified therapeutic effects, suggesting a regimen-dependent benefit. These findings support WJ-MSCs as a promising regenerative strategy for sarcopenia and warrant further preclinical and translational studies.

4-29

Wharton's jelly-derived mesenchymal stem cells attenuate muscle atrophy in-vitro via secreted factor-mediated mechanisms

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Introduction: Sarcopenia, defined by progressive loss of skeletal muscle mass and strength, has no established pharmacological treatment. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) are known to influence surrounding cells through paracrine communication. This study aimed to evaluate the effect of WJ-MSCs on muscle atrophy in vitro and to identify specific mediators responsible for their protective action.
Methods: An in-vitro sarcopenia model was established using dexamethasone-treated mouse myotubes. Three groups were compared: untreated myotubes (control), dexamethasone-treated myotubes (atrophy model), and dexamethasone-treated myotubes co-cultured with WJ-MSCs. Expression of atrophy-related genes (MuRF1, Atrogin-1) was measured. We performed RNA sequencing analysis to identify therapeutic candidates secreted by WJ-MSCs. The candidates were further validated using qPCR and ELISA. Functional relevance of the identified factor was examined through gain-of-function (GOF) and loss-of-function (LOF) experiments.
Results: WJ-MSCs reduced MuRF1 and Atrogin-1 expression in the sarcopenia model, indicating promotion of muscle cell regeneration. Transcriptomic analysis revealed a key secreted candidate, and its expression was confirmed at both transcript and protein levels. When recombinant protein was directly applied to the sarcopenia cell model, MuRF1 and Atrogin-1 expression at both mRNA and protein levels decreased in a dose-dependent manner. Conversely, treatment with a blocking agent against the recombinant protein abolished the protective effect of WJ-MSC.
Conclusion WJ-MSCs exert a protective effect against dexamethasone-induced muscle atrophy, and a specific secreted protein was identified as a central mediator of this process. These findings provide mechanistic evidence supporting the therapeutic potential of WJ-MSCs for sarcopenia and suggest the secreted factor as a promising target for future intervention.

4-30

Automatic Muscle Segmentation for Faster and Easier Assessment of Muscle Trophicity in Sarcopenia and Neuromuscular Diseases Using MRI

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Introduction: MRI is the reference standard for determining muscle volume and composition, and when combined with other NMR approaches, it uniquely allows simultaneous investigation of muscle anatomy, physiology and energy metabolism. However, the need for manual segmentation of individual muscles has limited the widespread adoption of quantitative muscle MRI in the evaluation of sarcopenia and neuromuscular diseases.
Methods: We applied Convolutional Neural Network (CNN)-based techniques to automatically segment individual muscle groups and whole-segment muscle volumes from NMR images of patients of all ages, with varying degrees of fatty replacement and atrophy. The CNN architecture consisted of an encoder (MobileNet v2 without fully connected layers) and a decoder comprising up-sampling layers with a final softmax classifier. Four pairs of encoder and decoder layers were connected in a U-Net configuration. The CNN algorithms were integrated into a dedicated software suite, **MYOWEB**, available as a web service.
Results: The median Dice coefficient between CNN-based and manual segmentations for the muscle groups *Quadriceps*, *Hamstrings*, *Foot Extensors*, *Peroneal group*, and *Triceps Surae* ranged from 0.93 to 0.97. For whole-segment muscle volumes at the level of the legs and thighs, the median Dice coefficient reached 0.98. These results are comparable to the agreement observed between manual segmentations performed by two expert operators.
Conclusion: Our results demonstrate that AI-based automatic segmentation can accurately delineate muscle groups and quantify whole-segment muscle volumes, even in patients with substantial fatty replacement. This approach has the potential to make quantitative muscle MRI faster, more reproducible, and easier to implement in both clinical and research settings. It opens the door to more accurate monitoring of sarcopenia progression in natural history studies and to the objective assessment of therapeutic responses, among many other promising applications.

4-31

The adiponectin paradox and muscle mass in older adults: the influence of body fat distribution

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Introduction: The adipokine adiponectin has garnered significant attention for its insulin-sensitizing and anti-inflammatory properties. Unexpectedly, negative associations with muscle mass in older adults have lent credence to the adiponectin paradox. This study aimed to clarify the relationship between adiponectin levels and indicators of muscle and fat mass in older adults.
Methods: Body composition (BC) was assessed by DXA in 888 European older men and women (65-79 years). The following BC parameters were derived: Fat mass index (FMI; total fat mass/height^2), appendicular lean mass index (ALMI; ALM/height^2), regional body fat distribution (android/gynoid fat mass ratio). Levels of adiponectin and high sensitivity C-reactive protein (hsCRP) were assessed by Immunoassay. Associations (standardized β-coefficient) between adiponectin and BC parameters were determined using linear regression analysis stratified by gender and adjusted by covariates, including age, medication, smoking, alcohol consumption and hsCRP level.
Results: ALMI was inversely associated to adiponectin level in both women (β: -0.16, $P < 0.05$) and men (β: -0.24, $P < 0.05$) in models without adjustment for FM indicators. When adding FMI to the model, the influence of ALMI on adiponectin level was removed in women ($P > 0.05$) and attenuated in men (β: -0.15, $P < 0.05$). Importantly, when further adding android/gynoid FM ratio any remaining association between adiponectin and ALMI in men was removed. The android/gynoid FM ratio was the strongest BC parameter related to adiponectin level in both women (β: -0.48, $P < 0.05$) and men (β: -0.43, $P < 0.05$).
Conclusion: Adjustment by indicators of fat mass, with regional body fat distribution in particular, removed the observed inverse relationship between adiponectin and muscle mass in older adults. These findings suggest that adiponectin levels are largely reflected by variations in body fat distribution rather than muscle mass in older adults.

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Water distribution explains associations between phase angle and physical outcomes in older adults

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Introduction: Phase angle (PhA) is derived from BIA measurements and reflects the integrity of cell membranes. Higher PhA values are associated with better physical function. The aim of the study was to investigate PhA and body composition in sarcopenic and non-sarcopenic Icelandic older adults.
Methods: A cross-sectional study was conducted in 73 community dwelling older adults (65.8% women, 82±6 years, BMI=28.2±5.7; body fat%=42.8±9.0) who frequently used day-care services provided by the nursing homes in Reykjavik, Iceland. Bioelectrical Impedance Analysis (BIA) was used to measure body composition. Handgrip strength was tested as well as the short physical performance battery (SPPB) protocol was applied. Questionnaires were used to assess general characteristics of the participants. Sarcopenia was defined according to the revised European consensus on definition and diagnosis.
Results: Of the participants, 60.3% were sarcopenic. Sarcopenic participants had poorer physical function (7.3±2.5 vs.10.0±1.8, P=0.01), lower hand grip strength (19±7 vs. 25±8 kg, P=0.02), higher ECW/TBW ratio (52±4 vs 50±3%,P=0.038), a lower phase angle (3.5±0.5 vs 3.9±0.4, P=0.02) and took more medication (5.8±2.9 vs. 4.3±3.1, P=0.021) than non-sarcopenic participants, but did not differ significantly in skeletal muscle mass, age or gender distribution. After correction for age, gender and medication use, the difference in phase angle remained largely unchanged between both groups, however, after adjustment from BIA derived ECW/TBW ratio, the estimated difference disappeared and was no longer significant.
Conclusions: Sarcopenia is common in older adults who use day-care service provided by nursing homes in Iceland. Sarcopenic older adults have a lower phase angle derived from BIA which is also reflected by higher ECW/TBW ratio possibly indicating poor cell membrane integrity, loss of body cell mass and/or oedema.
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4-33

Sarcopenic patient-derived myotubes exhibit fusion dysfunction using an automated image analysis pipeline

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Introduction: Sarcopenia is a progressive age-related muscle disease, characterized by the loss of muscle mass and function, affecting a significant portion of the elderly population worldwide. This condition is associated with reduced quality of life and adverse health outcomes, imposing a substantial burden of healthcare systems. Human-specific in vitro skeletal muscle models are valuable for preforming mechanistic studies, disease modeling, muscle tissue engineering, and drug screening. Yet, there is a scarcity of human-specific models in sarcopenia research.
Methods: Patients who underwent curative elective colorectal surgery (cTNM stage 0-3) were screened for sarcopenia according to the clinical diagnostic criteria (AWGS 2019) and graded as non-sarcopenic (NS), sarcopenic (SA), and severely sarcopenia (SS). Muscle histology was examined using hematoxylin and eosin (H&E) and immunofluorescence staining. Patient-derived myoblasts were isolated and differentiated into myotubes in vitro. Myosin heavy chain (MYH2) positive cells were segmented using an interactive machine-learning software, Ilastik. Fusion index was analyzed using a self-developed pipeline.
Results: Sarcopenic patients with stage 3 cancer had longer hospital stays than non-sarcopenic patients ($p = 0.062$). SS muscle (n = 237) had significantly decreased fiber diameter compared to NS muscle (n = 63, $p = 0.018$). A high accuracy of fusion index was achieved using the self-developed automated pipeline, as comparable as manual annotation (r = 0.895). Sarcopenic-patient derived myotubes showed smaller diameter and reduced fusion index. There were also less multi-nucleated myotubes and myogenin-positive cells in SS than in NS.
Conclusions: Sarcopenia is associated with smaller muscle fibers and longer hospitalizations. Sarcopenic patient-derived myotubes exhibited fusion dysfunction. The developed automated pipeline can process large amounts of images with minimal human intervention. Together with high-content imaging that allows random selection of region of interest for analysis to reduce human selection bias, fusion index can serve as a novel in vitro biomarker for sarcopenia.

4-34

Association between intrinsic capacity and risk of dementia in older Mexican adults: analysis of the 2012 and 2015 waves of the Mexican Health and Aging Study

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Introduction: The World Health Organization (WHO) defines healthy aging as the ability to maintain intrinsic capacity (IC), a multidimensional construct that encompasses five domains: sensory, locomotion, psychological, vitality, and cognition. IC is strongly associated with adverse outcomes such as sarcopenia, frailty, disability, and mortality. However, the predictive value of IC for dementia risk has not been sufficiently evaluated in the Mexican population.
Methods: A prospective cohort study using data from the 2012 and 2015 waves of the Mexican Health and Aging Study. Participants aged ≥60 years at baseline were included, excluding those with dementia at baseline. IC was operationalized following the WHO ICOPE framework and the methodology of Beard et al. (2022), integrating five domains: vitality (weight/appetite loss, handgrip strength), locomotion (walking, climbing stairs, household tasks), sensory (vision and hearing), cognition (orientation and memory), and psychological status (CES-D 9). Cognitive performance was assessed using the Cross-Cultural Cognitive Examination, standardized by age and education. Dementia was defined as scores ≤−1.5 SD in at least two cognitive domains plus ≥1 limitation in instrumental activities of daily living. Sociodemographic and health covariates included age, sex, education, smoking, comorbidities, and marital status. IC was estimated through exploratory and confirmatory factor analyses, and associations with dementia were evaluated using survey-weighted logistic regression.
Results: The final sample included 7,263 participants (mean age 68.9±6.8 years; 56.4% women). Over three years, the cumulative incidence of dementia was 4.15% (95% CI 3.70–4.65). Higher baseline IC scores were associated with lower probability of dementia (OR=0.62; 95% CI 0.41–0.94; p=0.030), after adjustment for sociodemographic and health covariates.
Conclusion: Higher IC at baseline was associated with a reduced risk of developing dementia in Mexican older adults. Unlike frailty, which emphasizes deficits, IC highlights positive functional abilities and offers a promising framework to guide interventions that promote healthy aging in low and middle-income settings.

4-35

Towards a Body Composition–Oriented Definition of Maximal Healthy Weight Loss in Patients with Obesity

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Introduction: The advent of highly effective anti-obesity medications has renewed the debate on how weight loss targets should be defined. Weight reduction alters fat-free mass (FFM) composition, with a relative preservation of connective tissue from adipose stores and a disproportionate loss of skeletal muscle (SM). Consequently, achieving a “normal” BMI may result in too low SM in weight-reduced individuals. This study aimed to establish evidence-based criteria for a maximal weight loss target.
Methods: A cross-sectional dataset of 280 healthy adults (158 females, 122 males; age 41 ±14 y; BMI 28 ±6) was analyzed. Whole-body SM was measured by MRI, and FFM by densitometry. To model weight loss, we adopted evidence that 92–97% of FFM loss is attributable to SM, based on data from RYGB patients who lost 16–23% of their weight as FFM in the first postoperative year (Davidson et al., Obesity 2018;26:1130).
Results: SM was 45% and 49% of FFM in women and men ($p<0.001$). Stepwise multiple regression explained 87% of the variance in SM index (SMI, kg/m²):
SMI = 0.431×FFMI + 0.019×weight + 0.630×sex − 0.011×age −0.736 (female = 0, male = 1; SEE = 0.635).
This reference equation allows prediction of the normal SMI after weight loss. The observed SMI can then be compared with this predicted value, assuming ΔFFMI = ΔSMI. An SMI-standard deviation score (SMI-SDS) is calculated as: SMI-SDS = (SMI observed – SMI predicted) / SEE
An SMI-SDS of –0.67 corresponds to the 25th percentile of the reference population and may therefore define the maximal safe weight loss target.
Conclusion: A maximal weight loss target can be derived by predicting SM from FFM in a healthy reference population. This approach links simple data on 2-compartment model to percentile thresholds for SM and provides a framework for defining safe treatment goals in clinical practice.

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Risk of sarcopenia in people with long-term conditions and multimorbidity: a prospective UK Biobank study

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Introduction: Sarcopenia, defined as the progressive loss of skeletal muscle mass and strength, is a major contributor to frailty, disability, and mortality. While aging is a key driver, the role of long-term conditions (LTCs) and multimorbidity (≥2 LTCs) in the development of sarcopenia remains underexplored. This study examined the prospective association between individual LTCs, multimorbidity, and incident sarcopenia in the UK Biobank cohort.
Methods: We included 60,710 participants (mean age 56 years; 54% women) without sarcopenia at baseline. Sarcopenia was defined using EWGSOP2 criteria. Presence of 25 common LTCs was self-reported at baseline. Cox proportional hazards models estimated hazard ratios (HRs) for incident sarcopenia, stratified by sex and adjusted for sociodemographic and lifestyle factors.
Results: Over a median follow-up of 14.3 years, 1,863 participants (3.1%) developed sarcopenia. In women, baseline prevalence of gout (HR 4.23, 95% CI 1.57–11.43), type 2 diabetes (HR 3.08, 2.18–4.34), hiatus hernia, hypertension, and psoriasis were strongly associated with higher sarcopenia risk. In men, baseline prevalence of type 2 diabetes (HR 4.63, 3.44–6.21), gout (HR 3.78, 2.63–5.44), anxiety disorders, COPD, and hypertension showed the highest risks. A dose–response association was observed: each additional LTC at baseline was associated with higher sarcopenia risk by 29% in women and 36% in men. There was evidence of additive interaction between multimorbidity and sex ($P<0.0001$): risk was higher in men (HR 2.19; 95% CI 1.75–2.74) than in women (HR 1.96; 95% CI 1.66–2.32).
Conclusions: This large prospective study demonstrates that prevalence of specific LTCs and multimorbidity is associated with a substantially higher risk of incident sarcopenia, with stronger effects observed in men. These findings highlight the importance of integrating sarcopenia risk assessment into the clinical management of individuals with chronic conditions and support the development of targeted sarcopenia prevention strategies.

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Handgrip Strength <10 kg as a Saudi-Specific Cut-off for Sarcopenia in Women

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Background: Sarcopenia is defined by reduced muscle strength, often measured by handgrip strength (HGS). The European Working Group on Sarcopenia in Older People (EWGSOP2) recommends <16 kg as the threshold for probable sarcopenia in women. However, this value may not reflect ethnic and body composition differences in Saudi women.
Methods: This cross-sectional study included 134 Saudi women (premenopausal and postmenopausal). HGS and body composition were assessed. Probable sarcopenia was first defined using the EWGSOP2 cut-off (<16 kg). Saudi-specific cut-offs were then derived using the mean minus 2 and 2.5 standard deviations (SD) from healthy premenopausal women without obesity, resulting in thresholds of <10 kg and <8 kg. Prevalence was compared by menopausal and obesity status.
Results: Using the EWGSOP2 cut-off, probable sarcopenia was identified in 44% of postmenopausal and 33.89% of premenopausal women. With the Saudi-specific cut-off of <10 kg, prevalence dropped to 9.33% in postmenopausal and 5% in premenopausal women. Using the <8 kg cut-off, prevalence further decreased to 4% and 3.4%, respectively. Across all cut-offs, women with obesity had a higher prevalence of low HGS.
Conclusion: The EWGSOP2 threshold may overestimate sarcopenia in Saudi women. A Saudi-specific HGS cut-off of <10 kg provides a more accurate diagnostic criterion, reflecting ethnic and body composition differences. Adopting population-specific thresholds is essential for improving sarcopenia diagnosis and clinical decision-making in Saudi women.

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Handgrip strength and sit-to-stand performance as complementary markers of muscle function in patients with OSA and OHS

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Introduction: Weight reduction improves disease severity in obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), but may also promote skeletal muscle loss. We investigated muscle mass and performance parameters in these patient groups.
Methods: Consecutive obese OSA and OHS patients with complete data were prospectively enrolled between January and June 2025 at the University Clinic Golnik, Slovenia. Body composition was assessed by bioelectrical impedance analysis. Muscle performance was evaluated with handgrip strength (HGS) and the 5x Sit-to-Stand Test (5STS). Sex-stratified regression models were adjusted for age, diagnosis, and fat mass or BMI.
Results: Seventy-one OSA and 41 OHS patients were analysed, with OHS patients being older (57.8 ± 19.5 vs. 49.3 ± 21.7y), had lower HGS (35.8 ± 13.0 vs. 42.0 ± 16.1kg) and Z-scores (–0.11 ± 1.11 vs. 0.54 ± 1.13), larger waist circumference (133.3 ± 25.2 vs. 117.1 ± 18.8cm), and slower 5STS (12.9 ± 3.7 vs. 9.2 ± 3.0s). SMM, BMI, and FM did not differ. Twenty-three patients failed only one muscle performance test (8 HGS, 15 5STS), while only 4 failed both. In men, SMM predicted HGS (+1.7kg per 1kg SMM, p<0.001), and OHS diagnosis was associated with –12.5kg lower HGS (p<0.001). In women, HGS declined with age (–0.23kg/year, p=0.006). For 5STS, OHS was the main determinant (+4.3s in women, p=0.022; +6.0s in men, p<0.001). In men, higher HGS independently predicted faster 5STS (–0.16s per kg, p=0.003).
Conclusions: In obese OSA and OHS patients, HGS reflected skeletal muscle mass only in men, while 5STS captured OHS-related systemic burden and lower-limb function, independent of muscle or fat mass. The two tests identified different patient subsets: HGS served as a marker of muscle reserve, whereas 5STS detected functional limitation. Combined testing offers a more comprehensive assessment of muscle performance in this high-risk population.

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Sex-specific associations between hand-grip strength and inflammatory markers in the general population

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Introduction: Muscle atrophy is a complex process characterised by loss of muscle mass and function. While inflammation is important in muscle atrophy, the underlying biology is not fully understood. We analysed the association between hand-grip strength (HGS) and 47 cytokines in the general population.
Methods: We used data from 2.025 adults (48.7% woman), aged 20 to 83 years, from the Study of Health in Pomerania (SHIP-TREND-0). We used multivariable regression models adjusted for age, sex, body mass index, alcohol consumption, physical activity, smoking status, batch and storage time to relate 47 standardized (SD) cytokine concentrations with HGS in kg.
Results: In men, a higher interleukin-18 (IL-18) was associated with a 0.68 kg greater HGS (95% CI: 0.138, 1.23). More eotaxin (CCL11), macrophage-derived chemokine (CCL22), platelet-derived growth factor BB (PDGF-BB) and vascular endothelial growth factor A (VEGF-A) were related to 0.55 kg (95% CI: -1.07, -0.03), 0.96 kg (95% CI: -1.45, -0.47), 0.50 kg (95% CI: -0.98, -0.02) and 0.54 kg (95% CI: -1.02, -0.06) lower HGS, respectively. In women, higher concentrations of epidermal growth factor (EGF) and soluble CD40 ligand (sCD40L) were related to a 0.44kg (95% CI: 0.023, 0.855) and 0.48 kg (95% CI: 0.13, 0.84) higher HGS.
Conclusions: The identified relationship between several unrecognized cytokines and HGS in men and women suggests sex specific effects for low muscle strength. In men, higher levels of CCL11 (age-related inflammation), CCL22 (chronic immune response) and PDGF-BB (tissue remodelling) were related to low HGS. Hence, inflammatory signalling was linked to reduced muscle strength. In women, higher EGF and sCD40L, which are involved in tissue repair and remodelling was related to higher HGS. This also suggests immune signalling supporting muscle function in women. Hence, different inflammatory pathways are related to lower HGS in men and women.
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Predictive value of handgrip strength in muscle and malnutrition assessment

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Introduction: Malnutrition in oncology is common, prevalent at ~50% of patients even before antineoplastic treatment. The Global Leadership Initiative on Malnutrition (GLIM) is a recent initiative aimed to diagnose malnutrition in adults using phenotypic (weight loss/ low body mass/ low skeletal muscle mass) and etiologic (low food intake, or presence of disease/systemic inflammation) criteria.
Direct measurement of muscle mass is not readily available in clinical practice. Assessment of muscle function using handgrip strength (HGS) is commonly employed in the diagnosis of sarcopenia and frailty, but not of malnutrition.
Our aim was to examine whether HGS can predict muscle mass, measured automatically using diagnostic CT scans. Our secondary aim was to explore whether HGS can predict malnutrition confirmed by GLIM.
Methods: a retrospective study of 100 patients referred to nutritional consultation in Jusidman Cancer center, Tel-Hashomer was conducted. HGS was measured by handgrip dynamometer. Muscle mass was measured using diagnostic CT single-slice image at L3, taken adjacent to HGS measurement (±3 months), skeletal muscle index (SMI) was analyzed using automated software. Malnutrition was assessed using GLIM criteria.
Results: Data from 96 patients were analyzed, comprising 35 females (36.5%) and 61 males (63.5%). Mean age was 64 (±12.4), most patients were treated for pancreatic or bowel cancer, 59% presented with metastatic disease. Most patients had low SMI (62% for men, 71% for women). HGS correlated with SMI (r=0.35). Multivariate logistic regression for low SMI using age, gender and BMI achieved an AUC of 0.87 (sensitivity 83%, specificity 70%), with BMI as the strongest predictor; adding HGS lowered specificity to 69%. For severe malnutrition, a model including age, gender, BMI and HGS yielded an AUC of 0.80 (sensitivity 86%, specificity 56%).
Conclusions: HGS demonstrated limited predictive value for skeletal muscle mass compared to BMI, which remained the strongest predictor.

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Low Masseter Muscle Volume and Risk of Cognitive Decline in Older Adults: A Longitudinal Analysis from the Bunkyo Health Study

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Introduction: Cognitive decline is a growing concern in aging societies, but reliable biomarkers remain limited. Masseter muscle volume (MMV), which is less affected by aging and lifestyle factors, may serve as a potential indicator of neurocognitive vulnerability. This study examined whether low MMV predicts cognitive decline over five years, compared to appendicular skeletal muscle mass (ASMM).
Methods: This longitudinal study analyzed 1,009 community-dwelling older adults (median age 72 years) from the Bunkyo Health Study. MMV was measured via MRI, and ASMM via bioelectrical impedance. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) at baseline and follow-up. Multivariate ANCOVA and logistic regression analyses were conducted, adjusting for age, sex, BMI, physical activity, protein/alcohol intake, education year, Brinkman index, diabetes, cerebrovascular disease and baseline MMSE.
Results: MMV was not associated with age and only weakly associated with BMI. In contrast, ASMM was strongly correlated with both age and BMI at baseline and follow-up. Participants in the lowest MMV quintile (Q1) showed significantly greater MMSE decline over five years (mean −2.1 points; $p < 0.001$). Logistic regression showed that Q1 MMV was independently associated with cognitive decline (OR = 1.573; 95% CI: 1.065–2.323; $p = 0.023$), whereas ASMM was not ($p = 0.712$).
Conclusion: These findings suggest that masseter muscle volume, a craniofacial muscle less influenced by physical activity and aging, may serve as a novel and non-invasive biomarker for identifying older adults at risk of future cognitive decline, independent of conventional measures of muscle health.

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Sarcopenia in older individuals with hip fracture: study on the prevalence, correlation with obesity and ultrasonography of the rectus femoris

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Objectives: To determine the prevalence of probable sarcopenia in older patients with hip fractures and evaluate the correlation between ultrasound measurements of the rectus femoris, obesity, and sarcopenia diagnosis.
Methods: Sixty-five participants aged ≥60 years hospitalized with hip fractures were included. The SARC-F questionnaire was administered, and calf circumference and handgrip strength were measured. Bilateral rectus femoris thickness and cross-sectional area were assessed via ultrasonography.
Results: Probable sarcopenia was identified in 13 participants (20.6%). The mean rectus femoris thickness was 1.03 cm (SD=0.22) for the right and 1.03 cm (SD=0.23) for the left thigh. The mean cross-sectional area was 2.61 cm² (SD=0.71) on the right and 2.97 cm² (SD=0.69) on the left. Mean calf circumference was 31 cm (SD=4.29) for the right and 31 cm (SD=4.31) for the left leg. No correlations were found between rectus femoris ultrasound measurements and probable sarcopenia. Overweight individuals with hip fracture were four times more likely to have probable sarcopenia.
Conclusion: The prevalence of probable sarcopenia was 20.6%. No correlation was observed between rectus femoris ultrasound measurements and probable sarcopenia. Overweight was significantly associated with a four-fold increased likelihood of probable sarcopenia in this population.
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Effect of resistance exercise combined with β-hydroxy-β-methylbutyrate supplementation in older individuals with and without sarcopenia treated for hip fracture.

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Introduction: Sarcopenia affects the outcomes of older adults with hip fractures, such as mortality and length of hospital stay. This study aims to evaluate the influence of sarcopenia on length of hospital stay and one-year mortality in elderly patients with hip fractures, as well as determine the effect of a three-month program of resistance exercise and HMB supplementation on handgrip strength after one year.
Methods: We evaluated 65 participants aged 60 years or older who were hospitalized between March 29, 2023, and March 28, 2024, with a diagnosis of a proximal femur fracture. The EWGSOP2 criteria were used to diagnose sarcopenia. After discharge, one group received recommendations for a three-month program of resistance exercise and HMB supplementation, while the other received standard care. Data on length of hospital stay and one-year mortality were collected from medical records. Handgrip strength was measured one year after surgery. Adherence to the recommendations was not monitored.
Results: The average length of stay was 10.1 days for individuals with sarcopenia, compared to 7.9 days for those without ($p<0.05$). The one-year mortality rate was 23% for the sarcopenic group and 7.7% for the non-sarcopenic group. However, the sample size was too small to be statistically significant. Recommendations for resistance exercises and HMB supplementation were not associated with differences in handgrip strength after one year.
Conclusion: Older adults with hip fractures and a sarcopenia diagnosis had a longer hospital stay. Recommendations for resistance exercises and HMB supplementation without adherence monitoring did not correlate with changes in handgrip strength one year after fracture treatment.

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Role of Growth Hormone Resistance In IGF-I Deficient Sarcopenic Patients

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Introduction: Insulin like growth factor I (IGF-I) plays a key role in the onset of sarcopenia. It is unclear whether the pituitary gland, the liver as the main source of IGF-I production, or a dysregulation of the hypothalamic-pituitary axis is responsible for low IGF-I serum levels in these sarcopenic patients.
Methods: One hundred patients with IGF-I deficient sarcopenia/probable sarcopenia were recruited for an IGF-I generation test. Sarcopenia was diagnosed according to the European Consensus definition (EWGSOP2). On four consecutive days patients received 0.4mg growth hormone subcutaneously. Difference of IGF-I before and after the test was calculated. Patients with chances in IGF-I below 44.2% were regarded as growth hormone resistant. Further, in a subgroup of 17 patients the pituitary gland was stimulated with growth hormone releasing hormone (GHRH).
Results: Recruited patients had a mean age of 84 years. Fifty-two of the patients were female. Regarding the change of IGF-I concentration, 44% of the patients were below an increase of 44.2%. In the GHRH-testing only one patient did not show an adequate stimulation of the pituitary gland.
Conclusions: The pituitary gland seems to work adequately into old age. About one half of the patients have shown growth hormone resistance. All the other patients seem to suffer from a dysregulation of the hypothalamic-pituitary axis. Patients who react adequately to growth hormone application could profit from a therapeutic treatment with growth hormone.

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Low skeletal muscle mass and radiodensity are predictive of acute radiation-induced gastrointestinal toxicity in head and neck cancer patients

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Introduction: This study aimed to investigate the association between low skeletal muscle mass and radiodensity and acute radiation-induced toxicity in head and neck cancer (HNC) patients.
Methods: A prospective cohort was conducted at Pedro Ernesto University Hospital/State University of Rio de Janeiro, including HNC patients treated with radiotherapy (RT) from October 2023 to December 2024. Clinical and demographic data, and anthropometric measurements were collected on the day of the RT planning computed tomography (CT). CT images at the level of the third cervical vertebra (C3) were used to assess muscle area (normalized for height as skeletal muscle index – SMI) and skeletal muscle radiodensity (SMR). Patients below the sex-specific median were classified as having low SMI or SMR. Acute toxicities were recorded during treatment. Descriptive statistics and binary logistic regression were used to evaluate the predictive value of SMI and SMR.
Results: A total of 100 patients were included (mean age: 62.0 ± 10.7 years); most were elderly (67.0%), male (72.0%), and had a history of smoking (61.0%) and alcohol use (60.0%). The mean BMI was 24.0 ± 5.3 kg/m²; mean weight loss in six months: 9.0 ± 11.8%; mean RT dose: 67.2 ± 5.2 Gy; mean treatment duration: 55.7 ± 12.8 days. Most patients had advanced-stage disease (82.0%) and oropharyngeal tumors (38.0%). Common toxicities were dermatitis (89.0%), dysphagia/odynophagia (87.0%), xerostomia (66.0%), dysgeusia (66.0%), and mucositis (63.0%). In multivariate analysis, adjusted by age, sex, Karnofsky Performance Status, disease stage and site, RT dose and concurrent chemotherapy, low SMI was associated with a higher risk of mucositis (OR=3.099; 95% CI: 1.131-8.492; p=0.028) and low SMR with a higher risk of dysphagia/odynophagia (OR=6.497; 95% CI: 1.168-35.958; p=0.033).
Conclusions: Pre-treatment low skeletal muscle mass and radiodensity were independent predictive factors for acute gastrointestinal toxicity in HNC patients treated with RT.

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A Comprehensive Assessment of Sarcopenia and Sarcopenic Obesity in Prostate Cancer Patients on Androgen Deprivation Therapy Using a Range of Validated Diagnostic Criteria

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Introduction: Sarcopenia and sarcopenic obesity (SO) have both been linked to functional decline, poor quality of life and mortality, and are common in prostate cancer (PCa) patients undergoing androgen deprivation therapy (ADT). This study aimed to investigate the prevalence of sarcopenia and SO in men undergoing ADT for PCa treatment when different diagnostic criteria and cut-off values are used.

Methods: 47 men (age 71.53 ± 8.49 years, BMI 27.75 ± 3.98 kg/m^2) were assessed for hand grip strength (HGS), waist circumference (WC), adjusted calf circumference (aCC), along with Bioimpedance Spectroscopy (BIS) for measures including total skeletal muscle mass (TSMM), appendicular skeletal muscle mass (ASMM), and fat mass (FM) and calculated index values TSMMI, ASMI, and FMI in kg/m^2. Sarcopenia was assessed by combining low muscle strength (HGS) and low muscle mass, whilst SO was assessed by combining low HGS or low muscle mass and high adiposity.
Results: Prevalence of low muscle strength (mean HGS: 31.94 ± 7.97 kg) ranged from 27.66-63.80%, with the highest using the Sarcopenia Definitions and Outcomes Consortium (SDOC) criteria. Low muscle mass (mean TSMMI: 9.60 ± 1.19 kg/m^2 and ASMI: 7.95 ± 0.96 kg/m^2) prevalence ranged 28.89-86.67% when moderate and severe cases were combined, and 11.11-35.56% of severe cases. Sarcopenia prevalence ranged from 6.67-11.11% following the revised European Working Group on Sarcopenia in Older People (EWGSOP) definition, and 17.78-35.56% when applying UK-population and age-specific centile values. SO prevalence was 8.89-31.11% with HGS and WC combination giving the highest prevalence.
Conclusion: This is the first study to compare different diagnostic criteria and cut-off values to detect sarcopenia and SO in PCa patients undergoing ADT, and highlights their increased variability. A combined approach using affordable and accessible measures such as HGS, aCC, WC along with BIS assessment ensure significant screening until a harmonised, cancer-specific diagnostic criteria is established.

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Serum irisin in women with obesity and sarcopenic obesity: insights into a distinct metabolic phenotype

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Background: Irisin is a myokine induced by physical activity and also secreted by adipose tissue, classifying it as an adipo-myokine. Its role in metabolic regulation is established, but its circulating levels across obesity and sarcopenia phenotypes, particularly their overlap, remain unclear.
Objective: To assess serum irisin levels in relation to obesity, sarcopenia, and sarcopenic obesity in women.
Methods: This cross-sectional study included 79 women. Serum irisin was quantified via ELISA. Body composition was assessed using bioelectrical impedance analysis, and handgrip strength (HGS) was measured to define sarcopenia (HGS <16 kg). Obesity was defined as BMI ≥30 kg/m².
Results: Women with obesity had lower median irisin levels than those without obesity (p = 0.0663). Women with sarcopenic obesity exhibited the lowest levels, significantly lower than controls (women without obesity or sarcopenia) (p = 0.0076). Irisin inversely correlated with fat mass index (r = –0.38, p < 0.001), BMI (r = –0.36), and body fat percentage (r = –0.34). Among sarcopenia indices, only appendicular skeletal muscle index (ASMI) showed a significant inverse association (r = –0.28, p = 0.015).
Conclusion: Lower irisin levels are more strongly associated with adiposity than with sarcopenia. Sarcopenic obesity presents with markedly reduced irisin, suggesting a distinct metabolic profile. These findings highlight irisin's potential as a biomarker for adverse body composition in women.

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Role of osteosarcopenia in predicting overall mortality among older adults with cancer undergoing colorectal cancer resection

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Introduction: Osteosarcopenia is gaining attention as a predictor of clinical outcomes in oncology. We examined the associations between preoperative osteosarcopenia and overall mortality (OM) among older adults undergoing colorectal cancer (CRC) surgery.
Methods: This was a retrospective cohort study of patients aged ≥60 years who had undergone CRC surgery at the Our Lady of the Lake Medical Center in Baton Rouge, Louisiana, between October 2018 and February 2024. A preoperative computed tomography (CT) scan was used to assess vertebral bone density (VBD) and skeletal muscle index (SMI). VBD was assessed using the average trabecular attenuation in Hounsfield Units from the first to the fourth lumbar vertebrae. SMI was assessed by dividing the cross-sectional area of the skeletal muscle at the third lumbar vertebra by the patient's square of body height in meters. Patients were categorized as having: i) normal VBD and SMI; ii) low SMI only; iii) low VBD only; or iv) osteosarcopenia (low VBD and low SMI). Multivariable Cox regression analysis was used to examine the associations between osteosarcopenia and OM.
Results: Of the 250 patients (mean age: 71.9 years), 97 (38.8%) had normal VBD and SMI, 77 (30.8%) had low SMI, 29 (11.6%) had low VBD, while 47 (18.8%) had osteosarcopenia. Over a median follow up of 31 months, 61 (24.4%) participants died. In multivariable analysis, osteosarcopenia was significantly associated with a higher risk of OM (hazard ratio (HR)= 3.38, 95%CI: 1.55-7.39) compared to normal VBD and normal SMI status. Low SMI (HR: 1.66, 95%CI: 0.79-3.45) or low VBD (HR: 0.69, 95%CI: 0.19-2.47) alone were not significantly associated with OM. Additional predictors of OM included higher age, Charlson Comorbidity Index score, social vulnerability via the Vizient Vulnerability Index™, and AJCC stage.
Conclusions: Osteosarcopenia was significantly associated with an increased risk of OM among older patients undergoing CRC resection.

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Ultrasound assessment of quadriceps muscle architecture as a diagnostic and prognostic tool in hospitalized older adults with sarcopenia

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Introduction: Sarcopenia, characterized by loss of muscle mass, strength, and function, is prevalent in older adults. Muscle ultrasound (US) offers a practical alternative, but its usage in Malaysian inpatient settings is underexplored. This study aimed to assess the diagnostic and prognostic value of ultrasound-derived quadriceps parameters in relation to sarcopenia severity, functional outcomes, and hospital length of stay (LOS).
Methods: A prospective study was conducted at the University of Malaya Medical Centre (UMMC) from June 2021 to July 2022. Forty inpatients aged ≥65 years underwent sarcopenia assessment based on AWGS 2019 criteria. Ultrasound measurements included quadriceps muscle layer thickness (QMLT), cross-sectional area (CSA), pennation angle (PA), and

fascicle length (FL). Functional (MBI, EMS), nutritional (albumin, BMI), and frailty (CFS) domains were recorded. Correlation, regression, and ROC analyses were performed. Data were analyzed using SPSS version 30.0.
Results: Forty participants (mean age 74.3 ± 6.6 years; 62.5% female) were included, and 42.5% identified as having severe sarcopenia. These patients had significantly lower PA ($p = 0.013$), CSA ($p = 0.071$), and poorer scores in MBI and EMS, with higher CFS. CSA positively correlated with albumin ($p = 0.009$) and inversely associated with LOS ($p = 0.003$). The average hospital stay was 8.4 ± 5.1 days for sarcopenia and 11.0 ± 11.3 days for severe sarcopenia.
Diagnostic cut-offs for severe sarcopenia identified: QMLT ≤ 20 mm (sensitivity 65.2%, specificity 62.5%), CSA ≤ 30cm² (69.6%, 62.5%), PA ≤ 12.0° (73.9%, 56.3%), and FL ≤ 2.9cm (60.9%, 56.3%). CSA and PA showed the strongest predictive value.
Conclusion: Quadriceps ultrasound is a practical and informative tool for diagnosing sarcopenia and predicting clinical outcomes in hospitalised older adults. CSA and PA in particular demonstrate diagnostic relevance and prognostic utility, supporting the integration of bedside ultrasound into comprehensive geriatric assessment.

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A novel melanoma variant associated with myosteatosis

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Introduction: Myosteatosis, fat infiltration into skeletal muscle, has been linked to poor prognosis in various cancers. We have previously reported that myosteatosis is present in about half of stage III melanoma patients. We postulated that tumor-intrinsic molecular features of melanoma drive these systemic changes.
Methods: RNASeq was performed on tumor from 9 patients with myosteatosis and 10 patients without. Gene set variation analysis identified 225 pathways enriched in association with myosteatosis. A transcriptomic classifier of the myosteatosis-associated variant (MAV) phenotype was then applied to a melanoma cohort annotated by The Cancer Genome Atlas (N=466) as well as to an independent external dataset of patients receiving immunotherapy (N=72).
Results: The MAV phenotype was identified in 39 of 103 (38%) of primary TCGA melanomas and was associated with significantly shorter disease-free survival compared to MAV-negative tumors ($p=0.01$). The prevalence of the MAV phenotype was even higher in metastatic samples, with 40 of 68 (59%) of metastases being MAV positive. Based on gene set enrichment analysis, MAV tumors were characterized by accelerated proliferation, immunosuppressive environment, resistance to apoptosis and lipid metabolism reprogramming. Genes encoding secreted mediators, including AGRP (implicated in appetite regulation) and renin (inflammation and lipid metabolism), were upregulated, suggesting a role in tumor–host crosstalk. Application of the classifier to a cohort of patients receiving palliative immunotherapy confirmed the presence of the MAV phenotype and reproduced its association with worse progression free survival ($p=0.001$), as well as inferior response to Immunotherapy.
Conclusions: In melanoma, myosteatosis is associated with distinct tumor transcriptomic features and worse survival outcomes. Secreted proteins such as AGRP and renin are candidate mediators. The reproducibility of these findings in an external dataset validates the MAV phenotype as a clinically relevant feature of melanoma biology and highlights potential mechanistic links to systemic metabolic remodeling.

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Assessment of Sarcopenia Status in Post Metabolic Surgery Patients with Suboptimal Weight Loss Outcomes and the Effect of Subsequent Liraglutide 3.0mg

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Introduction: Sarcopenia risk in post-metabolic surgery populations and in patients subsequently treated with Glucagon-like peptide-1 (GLP-1) RA raises clinical concern due to potential long-term risks of muscle atrophy, frailty and disability. The aims of secondary data analysis from the BARI-OPTIMISE trial were to determine prevalence of baseline sarcopenia risk and examine the effects of 24 weeks of Liraglutide 3.0mg (LG) in patients with suboptimal weight loss post primary metabolic surgery (sleeve gastrectomy and Roux-en-Y Gastric Bypass) with a poor GLP-1 response versus placebo (PL).
Methods: 43 patients (46.4±9.8 years, BMI: 42.9±7.37 kg/m²) ≥12 months post metabolic surgery with suboptimal weight loss were given LG (n=22), or PL (n=21) adjunct to lifestyle intervention (500-kcal daily deficit) for 24 weeks. DEXA measures for appendicular lean mass (ALM), arm lean mass (ARMLM) and body fat mass (BFM), and hand grip strength (HGS) were assessed at baseline and 24 weeks. Different sarcopenia risk methodologies/criteria were applied (EWGSOP2, FNIH and SDOC).
Results: At baseline, using EWGSOP2 criteria for ALM, ALM index and HGS 0-36.4% of patients were at sarcopenia risk. Using FNIH and SDOC criteria for ALM/BMI, HGS/Body mass (BM), HGS/BMI, HGS/ALM, HGS/BFM up to 100% patients were at risk. Post trial PL and LG groups had significant reductions (% change) in ALM (-2.06% vs -7.31%) and ALMI (-2.50% vs -5.96%), whereas BFM only significantly reduced in LG group (+1.64% vs -9.51%). HGS measurements were maintained for the LG group, including absolute HGS, HGS/BM, HGS/BMI, HGS/ALM, HGS/BFM, ARMLM and HGS/ARMLM. In the PL group there was a significant reduction in the HGS/BFM ratio (0.81+/-0.21 vs 0.61 +/-0.28, $P<0.001$***).
Conclusions: Using measures of muscle mass and strength adjusted for BM, BMI and BFM, high levels of sarcopenia risk were identified at baseline. Although LG treatment significantly reduces total muscle mass, however, relative muscle function was preserved.

4-52

Effects of synbiotic supplementation on strength and physical performance in community-dwelling older Australians.

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Introduction: Age-related declines in muscle strength and physical performance have been linked with specific alterations in

the gut microbiome (GM). Altered microbial diversity and function have been linked to chronic low-grade inflammation, impaired nutrient metabolism, and anabolic resistance, all of which can negatively impact muscle health. Growing evidence supports a bi-directional 'gut-muscle axis', in which the GM influences host metabolism while physical activity, diet and medications shape microbial composition. This interrelationship highlights the potential of microbiome-targeted strategies to prevent or delay functional decline in older adults.
Objectives: To evaluate whether 16 weeks of synbiotic supplementation would result in statistically greater improvements in muscle strength and physical performance compared with placebo in community-dwelling older adults.
Methods: In a randomised, double-blind, placebo-controlled trial, 64 independently living, men and women aged 60-85 years were allocated to receive either oral synbiotic or matched placebo (n=32 per group) once daily for 16 weeks. Primary outcomes included hand grip strength (HGS), Short Physical Performance Battery (SPPB), and Timed Up and Go (TUG) were conducted at baseline and after 16 weeks.
Results: Baseline characteristics did not differ significantly between groups. After 16 weeks, participants receiving synbiotic supplementation showed significantly greater improvements than placebo in HGS (+1.2 kg, p = .024) and total SPPB score (+0.7, p = .006). Gait speed improved (Δ -0.21 s vs. Δ 0.18 s, p < .001) and TUG times decreased (-0.68 s, p = .001) significantly compared with placebo.
Conclusion: Sixteen weeks of synbiotic supplementation significantly improved muscle strength and physical performance in community-dwelling older adults compared with placebo. These findings support the potential of targeted microbiome interventions as a novel strategy to preserve muscle strength and functional capacity among older populations, warranting further mechanistic and long-term studies.

4-53

Change in Skeletal Muscle Mass among Patients with Cancer undergoing Chemotherapy or Immunotherapy: A Systematic Review and Meta-analysis

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Introduction: Skeletal muscle mass may decline during systemic cancer treatment, but the extent and variability across treatment modalities and cancer types remain unclear. This meta-analysis aimed to investigate changes in skeletal muscle mass during chemotherapy and/or immunotherapy in patients with cancer.
Materials and Methods: We conducted a systematic review and meta-analysis (PROSPERO CRD42022308388) of longitudinal studies reporting changes in skeletal muscle mass in patients undergoing chemotherapy and/or immunotherapy. PubMed, Embase, and Web of Science were searched. Standardized mean change scores (SMCR) were pooled using random-effects models with Hartung-Knapp adjustment. Risk of bias was assessed with the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.
Results: Seventy-nine studies (n=10,601; median age 65 years, range 34–77) were included, of which 58 (n=6,733) were eligible for meta-analysis. Across cancer diagnoses, skeletal muscle mass declined moderately (SMCR = –0.24, 95% CI: –0.29 to –0.19), corresponding to an average loss of 4.5% over a mean follow-up of 107 ± 63 days. Declines in skeletal muscle mass were most pronounced during chemotherapy (SMCR = –0.25, 95% CI: –0.30 to –0.21), whereas changes were not statistically significant with mono-immunotherapy or combined chemo- and immunotherapy. Declines in skeletal muscle mass were greatest among patients with pancreatic (SMCR = –0.35, 95% CI: –0.58 to –0.13), ovarian (SMCR = –0.31, 95% CI: –0.43 to –0.19) and lung cancer (SMCR = –0.30, 95% CI: –0.54 to –0.05). The prevalence of low skeletal muscle mass increased from 43% pre-treatment to 51% post-treatment. The overall risk of bias was low.
Conclusion: Skeletal muscle mass declines rapidly during systemic cancer therapy, particularly in patients receiving chemotherapy. This pattern is observed across cancer diagnoses and equal 4–5 years of normal age-related decline, underscoring the need for routine monitoring and targeted interventions to preserve skeletal muscle mass during treatment.

4-54

Case Report - Muscle Mass Assessment in Obese Hemodialysis Patient

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Background: Muscle mass (MM) assessment is a critical component in evaluating nutritional and physical status of patients with various morbidities. In hemodialysis patients, muscle mass evaluation is challenging as different assessment methods may be influenced by patients' hydration status. Calf circumference (CC) measurement is an easy and practical method to assess MM. However, it is unclear whether it is a reliable method for assessing muscle mass in obese hemodialysis patients
Case Presentation: We present a 61-year-old male receiving hemodialysis for 3.5 years at our dialysis unit. Post-dialysis weight was 114 kg with BMI 36.4 kg/m² (pre dialysis weight was 115.6 kg). The patient presented with mild edema in both legs.
Method: Three MM assessment methods were performed on the same day, approximately one-hour post- dialysis treatment. DXA scan and BIA method were performed using standardized protocols. MM from DXA and BIA was expressed by appendicular lean mass index (ASMI) with threshold values indicating lower mass for males < 7. CC was measured at the largest diameter of the dominant leg with values < 33 cm indicating low MM.
Results: ASMI values demonstrated similar values between DXA and BIA methods (9.73 kg/m² and 9.6 kg/m² respectively), CC was 42cm and 33cm after adjustment for BMI† and edemaβ.
Conclusions: In this case report DXA and BIA showed good concordance for MM according to ASMI standards with no sarcopenia indication, while CC revealed borderline MM at the lower threshold, likely due to over-adjustment. These findings highlight the substantial impact of anthropometric adjustments in obese patients and suggest considering alternative adjustment approaches for CC in obese hemodialysis patients.
*Kidney Disease Outcomes Quality Initiative
†Calf circumference adjustment for BMI: subtract 7 cm for a BMI of 30–39.9 kg/m²

βCalf circumference adjustment for edema: subtract 2 cm for male and 1.6 cm for female

4-55

Muscle Quality Index in patients on Peritoneal Dialysis: Associations with clinical, nutritional parameters, and outcomes

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Introduction: Patients undergoing peritoneal dialysis (PD) are at risk of reduced muscle strength and mass. The clinical usefulness of muscle quality index (MQI), which integrates muscle quantity and function remains unclear on PD. We evaluated the association between MQI, clinical, nutritional and physical function parameters, and outcomes, in patients on PD.
Methods: Longitudinal study involving adult patients initiating PD. MQI was calculated as handgrip strength (HGS) divided by appendicular muscle mass ((AMM) by multifrequency bioelectrical impedance); where higher ratio indicate better muscle quality. Association analyses with MQI was performed at baseline with age, sex, albumin, bicarbonate, creatinine, glycated hemoglobin (HbA1c), interleukin-6, leptin, C-reactive protein, body mass index, protein intake assessed by protein equivalent of nitrogen appearance (PNA), body fat, phase angle, gait speed (GS), sit-to-stand, and Short Physical Performance Battery (SPPB). The EWGSOP2 cut-offs were used for analyzing the physical performance tests. Clinical outcomes (infection, hospitalization, and mortality) were recorded over 12-months.
Results: 47 patients (58±15 years; 50% male) were included. AMM index was 7.3±1.6 kg/m², HGS 22 [16-30] kg, and MQI 1.2±0.4 kgf/kg. MQI was significantly correlated with age (r=-0.550), HbA1c (r=-0.450), interleukin-6 (r=-0.415), GS (r=-0.613), creatinine (r=0.343), phase angle (r=0.647), SPPB (r=0.481), and protein intake (r=0.312). In linear regression models adjusted for age and sex, HbA1c (β=-0.383; 95% CI: -0.132- to -0.033, R^2=0.414), phase angle (β=0.520; 95% CI: 0.90 to 0.304, R^2=0.446), and categorized GS (β=0.372; 95% CI: 0.104-0.653, R^2=0.374) remained associated with MQI (p<0.01). No association was found with clinical outcomes.
Conclusions: Patients initiating PD with higher age and HbA1c had lower MQI, while those with higher phase angle had higher MQI. Moreover, patients with low physical function had lower MQI. These results highlight the role of age, glycemic control, nutrition, and physical function in muscle quality, aggregating MQI as clinically useful parameter to patients on PD.

4-56

Low Relative Muscle Power in Patients on Haemodialysis: Poor Health Outcomes of the SARC-HD Cohort

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Introduction: In older adults, low skeletal muscle power (*i.e.*, powerpenia) is a novel predictor of adverse clinical outcomes. In patients on haemodialysis, this has yet to be explored. This study investigated the impact of powerpenia on adverse clinical outcomes in patients on haemodialysis.
Methods: A secondary analysis of the SARC-HD cohort study across 19 dialysis centers. Adults undergoing haemodialysis were assessed at baseline for relative muscle power with the five times sit-to-stand test (5-STS_{rel}) and the Alcazar's equation. Low relative muscle power (powerpenia) was classified as ≤2.5 $W \cdot kg^{-1}$ in males and ≤1.9 $W \cdot kg^{-1}$ in females. Sarcopenia was assessed by following the EWGSOP2 consensus. All-cause mortality, hospitalization, falls, and sarcopenia development/worsening were assessed through a 12-month follow-up period. Binary logistic regression and Cox proportional hazard regression were run adjusted for clinically relevant confounders.
Results: A total of 833 adults on haemodialysis were included (46% ≥60 years and 63% males), with 656 completing the follow-up. Powerpenia was observed in 31% (n=257) of the cohort, with 45% of older adults having the condition. It was associated with greater odds of having sarcopenia (adjusted odds ratio=2.17, 95% CI:1.41 – 3.36). Powerpenia increased the risk of all-cause mortality only in females (adjusted hazard ratio [aHR]=3.49, 95% CI:1.31–9.33), whereas no significant association with hospitalization. A borderline risk factor for falls was observed (aHR=1.40, 95%CI:0.99–1.99), which was confirmed only in older adults (aHR=1.63, 95%CI:1.03–2.59). Development/progression of sarcopenia was a major outcome (HR = 2.37, 95%CI: 1.50–3.77) in most subgroups (except in females).
Conclusions: *Powerpenia* affected one in three patients on haemodialysis. Powerpenia strongly associated with sarcopenia and increased the risk of adverse clinical outcomes in specific subgroups. The development or worsening of sarcopenia was the major adverse outcome. These findings emerge powerpenia as a relevant aging-related condition in this population.
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Cohort registration: RBR-82p87rq

4-57

Utility of Calf Circumference–Adjusted Body Mass Index for Assessing Muscle Wasting in Hemodialysis: Results from the SARC-HD Cohort

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Introduction: For individuals with body mass index (BMI) ≥25 kg/m², calf circumference (CC) adjustments have been proposed for the diagnose of muscle wasting to account for adiposity that may overestimate lean tissue in the calf area. This study aimed to assess the utility of BMI-adjusted CC in identifying muscle wasting in patients on hemodialysis (HD).
Methods: Multicenter cohort study (SARC-HD) from Brazil including patients on HD. Raw and BMI-adjusted CC were analyzed. The latter was applied when BMI was ≥25 kg/m², by subtracting 3 to 12 cm based on BMI range. Muscle wasting was defined by CC <32 cm for women and <33 for men. To assess the clinical relevance of CC, associations with clinical, nutritional, and physical function parameters were examined.
Results: 725 patients (57±15 years, 61% male) were included. The prevalence of muscle wasting using raw CC was 26% versus 49% with BMI-adjusted CC. Muscle wasting by BMI category was 13% (BMI25–29.9), 5% (BMI30–34.9), 0% (BMI35-39.9), and 13% (BMI≥40) using raw CC. For BMI-adjusted CC the prevalence was 49% (BMI25–29.9), 66% (BMI30–34.9), 30% (BMI35–39.9), and 50% (BMI≥40). When comparing groups with and without muscle wasting using raw CC values, patients were older, differed in HD modality, had lower weight, BMI, mid-arm muscle circumference, handgrip strength (HGS), gait speed, subjective global assessment, creatinine, and urea. Using BMI-adjusted CC, additional differences included dialysis vintage, HD frequency, %diabetes, and sit-to-stand test. When testing the determinants of muscle wasting; age and weight remained significant based on raw CC, while for BMI-adjusted CC, age, dialysis vintage, diabetes, weight, and HGS were associated with muscle wasting.
Conclusions: BMI-adjusted CC identified more patients with muscle wasting, and more associations with clinical, nutritional, physical function parameters as compared to raw CC, supporting the utility of CC adjustments in patients on HD.

4-58

Intramuscular sex hormone concentrations in healthy males and females across the lifespan

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Introduction: Plasma concentrations of androgens and oestrogens are moderated by sex and naturally fluctuate across the lifespan. Recent evidence suggests that sex hormones can also be synthesised locally in skeletal muscle. Previous research is however limited by small sample sizes and the use of immunoassays, which may yield unreliable results at low hormonal concentrations. To overcome these limitations, we aimed to develop a new liquid chromatography mass spectrometry-based technique to quantitate intramuscular hormone concentrations and apply it to a sample of 179 healthy males and females representing each decade of adulthood.
Methods: A muscle biopsy was obtained from the vastus lateralis and snap frozen in liquid nitrogen. Deuterated internal standards for the relevant androgens and oestrogens were added to ~20mg of muscle tissue. The steroids were extracted, and the samples analysed on a Vanquish LC coupled to an Orbitrap Exploris 240. A corresponding venous blood sample was obtained at the same time and analysed using gas chromatography mass spectrometry.
Results: Eighty-three males and 96 females aged 18 – 80 years participated in this study. In plasma, oestradiol decreased across menopause in females but remained unchanged in males. Testosterone remained unchanged in females and males, but free testosterone decreased across the lifespan in the males. In the muscle, underivatised hormones yielded low signals. However, derivatisation via either hydroxylamine hydrochloride (for androgens and progesterone) or dansyl chloride (for oestrogens) increased the peak area enabling quantitation.
Conclusions: Previous research suggests and that the intramuscular sex hormone concentrations may be more strongly associated with skeletal muscle mass and function, and that the intramuscular fraction is not proportional to the circulating hormone levels. Applying a mass spectrometry-based technique will be used to generate the first cross-sectional dataset on intramuscular sex hormone levels in adult males and females.

4-59

Maximum bite force as a simple screening tool for malnutrition and sarcopenia risk in older adults undergoing dental surgery

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Introduction: Chewing impairment may alter food quality and quantity, increasing the risk of malnutrition and sarcopenia in older adults. Maximum bite force (MBF) is considered the most reliable parameter of masticatory function. However, its potential use as a simple screening tool for nutritional risk in dental practice remains unexplored.
Methods: A pilot study was conducted in 38 older adults undergoing minor or limited/extended (LIM/EXT) dental surgery. Nutritional status was assessed with the Mini Nutritional Assessment–Short Form (MNA-SF), and weight changes over the previous 6 months were recorded. Body composition was estimated by bioelectrical impedance analysis (BIA), with sex-specific fat-free mass index (FFMI) cut-offs (≤16.8 kg/m² women, ≤19.1 kg/m² men). Muscle function was measured by handgrip strength (HGS) and the 6-minute walking test (6MWT). MBF was measured using a digital gnathodynamometer.
Results: MBF was significantly higher in normally nourished patients (n=30) compared to those at risk or malnourished (n=8, p=0.028). A combined effect of surgery type and nutritional status was observed: LIM/EXT patients with malnutrition (n=7) showed significant reductions in HGS (p=0.029), 6MWT (p=0.047), and MBF (p=0.004) compared to minor with normal status (n=18). MBF was also lower in LIM/EXT patients with low FFMI (n=7) versus minor with high FFMI (n=8, p=0.036), and in LIM/EXT patients with weight loss (n=6) compared to MILD with weight stability (n=15, p=0.014).
Conclusions: Older adults with malnutrition, low FFMI, or weight loss exhibit marked reductions in MBF and muscle function after surgery. MBF may represent a practical early tool to identify patients at nutritional risk during dental visits, supporting timely referral to Clinical Nutrition specialists. Larger studies are ongoing to validate these preliminary findings and to define clinical thresholds for risk stratification.

4-60

Exploratory study of factors associated with respiratory sarcopenia in patients with non-small cell lung cancer

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Introduction: Respiratory sarcopenia (RS), characterized by reduced respiratory muscle mass and strength, may precede systemic sarcopenia and is linked to poor prognosis in NSCLC. However, its preoperative prevalence and associated factors in Chinese patients with early-stage resectable NSCLC remain understudied. This study aimed to evaluate the prevalence of RS, identify related factors, and examine its relationship with systemic sarcopenia in stage I–II NSCLC.
Methods: This two-center cross-sectional study enrolled 320

patients with resectable stage I–II NSCLC between October 2024 and May 2025. Pectoralis muscle area was assessed using preoperative chest computed tomography scans at the level of the fourth thoracic vertebra using Slice-O-Matic software (v5.0, Tomovision, Canada) and adjusted with BMI. RS was diagnosed using sex-specific thresholds for peak expiratory flow rate (PEFR: males <7.5 L/s, females <4.5 L/s) in combination with BMI-adjusted pectoralis muscle index (PMI: males <1.2, females <0.87). Systemic sarcopenia was defined according to the 2019 Asian Working Group for Sarcopenia criteria. Univariable and multivariable logistic regression analyses were performed to identify factors independently associated with RS. Phenotypic overlap between RS and systemic sarcopenia was visualized using Venn diagrams.
Results: Preoperative prevalence of RS and systemic sarcopenia was 15.6% and 11.6%, respectively. Multivariable analysis revealed six factors independently associated with RS: older age (OR=1.045 per year, *P*=0.012), squamous cell carcinoma histology (OR=10.316, *P*=0.010), higher body fat percentage (OR=1.053 per %, *P*=0.029), elevated lymphocyte count (OR=1.917 per $\times 10^9$/L, *P*=0.034), increased handgrip strength (OR=0.928 per kg, *P*=0.006), and unilobar involvement (OR=0.325, *P*=0.047). Among RS patients, 74.0% (37/50) exhibited components of systemic sarcopenia, predominantly functional impairment (94.6%).
Conclusions: RS is prevalent in early-stage NSCLC and closely linked to systemic sarcopenia. Both modifiable (e.g., body fat, muscle strength) and non-modifiable (e.g., age, histology) factors were identified, providing opportunities for targeted prehabilitation and facilitating early risk stratification.

4-61

Functional tests and SARC-F score as predictors of sarcopenia in elderly people

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Introduction: The gold standard for diagnosing sarcopenia is the appendicular lean mass index (ALMI), evaluated by the Whole-body densitometry using dual-energy X-ray absorptiometry (DEXA). The escore of strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire is a screening test for sarcopenia. The aim of this study were to evaluated the accuracy of the SARC-F score and functional tests to predicted sarcopenia in elderly people; and to investigate the association between the ALMI, SARC-F score and functional tests.
Methods: This is an observational and cross-sectional study. All individuals were evaluated by DEXA (ALMI <7.26 kg/m^2 for men and <5.45 kg/m^2 for women were diagnosed as sarcopenia), SARC-F questionnaire and functional tests: muscle force (handgrip), gait speed and sit to stand test. A discriminative power analysis by receiver operator characteristic curve (ROC) and Pearson's correlation coeficiente were used.
Results: Seventy-five patients were included in the analysis. The SARC-F questionnaire predicted sarcopenia in elderly people with a cutoff score of 5 (area under the curve, AUC=0.75 and p=0.02) with good sensitivity (87%) and specificity (71%). Functional tests were not predictors of sarcopenia (p>0.05). Lower values of ALMI were associated with lower muscle force (p<0.0001; r=0.46), higher time in speed gait test (p=0.01; r=-0.31) and higher SARC-F score (p=0.01; r=-0.29).
Conclusion: The SARC-F questionnaire was a good predictor of diagnosis sarcopenia, and could be used as an alternative to the gold standard (DEXA). Despite, the functional variables and the SARC-F score were associated with the ALMI, only the SARC-F score was a good predictor of sarcopenia.

4-62

Worse Self-Rated Health as a Marker of Sarcopenia in Older Adults: Preliminary Findings from a Prospective Cohort

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Introduction: Early detection of frailty is essential to prevent adverse outcomes and typically combines subjective and objective measures. This study examined the association between self-rated health and objective indicators of sarcopenia We investigated whether self-perceived health correlates with physical performance and frailty indices, aiming to identify feasible clinical markers for sarcopenia risk.
Methods: We conducted a cross-sectional analysis within a prospective cohort study in São Paulo, Brazil, including adults aged 65 years or older. Assessments comprised self-rated health (categorized as “good” or “poor”), handgrip strength measured with a Jamar® dynamometer, gait speed, the Timed Up and Go (TUG) test, and the 10-minute Targeted Geriatric Assessment (TAGA). Associations were analyzed using logistic regression models for categorical outcomes (odds ratios, OR) and Pearson correlation coefficients (r) for continuous associations between self-rated health and functional parameters.
Results: Initially, data were collected from 127 older adults aged 65 years or older. A predominance of females was observed, representing 70.4% of the sample (n = 88), while males accounted for 29.6% (n = 39). Most participants (62%) rated their health as poor. Poor self-rated health was significantly associated with worse TUG performance (p = 0.0107; OR = 3.5;IC 95%), indicating reduced mobility. Handgrip strength and gait speed showed non-significant trends toward poorer performance among those with worse health ratings. A strong positive correlation was observed between poor self-rated health and the TAGA frailty index (r = 0.579; p < 0.001), suggesting that unfavorable health perceptions align with increased frailty risk.
Conclusions: Older adults reporting poorer self-rated health exhibited lower functional performance and higher frailty scores, particularly in mobility-related domains measured by TUG and TAGA. These findings support self-rated health as a complementary marker for early frailty detection.

4-63

The impact of EWGSOP2-defined sarcopenia on treatment tolerance and survival in patients with lung cancer – preliminary data from a prospective cohort study

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Introduction: Low muscle mass is linked to negative outcomes in patients with lung cancer, but prospectively collected data on muscle strength and function during systemic oncological treatment remains scarce. We aimed to assess the association between EWGSOP2-defined sarcopenia and treatment-related complications and prognosis in patients with lung cancer undergoing chemotherapy.
Methods: In this prospective cohort study, we measure muscle mass (bioelectrical impedance analysis and CT scans at L3), muscle strength (handgrip dynamometry), and muscle function (5-times and 30-second sit-to-stand test, and 10-meter gait speed) at diagnosis and at 3-month follow-up. Chemotherapy-induced toxicity will be evaluated using the CTCAE 5.0 template, and 1-year survival by medical record audit.
Preliminary results: We included 285 participants during the first 9 months of inclusion (95% recruitment rate), from the diagnostic pathway at department of pulmonary medicine, Zealand University Hospital, Næstved, Denmark. Lung cancer was confirmed in 203 patients, and 114 received primary systemic treatment (target: n=180) and were included for follow-up. Median age was 72 years (65-77) and BMI 25 kg/m² (22-29). At baseline, handgrip strength for 85% was in the age- and sex-standardized normal range, while 10% were reduced and 5% severely reduced. For 30-second sit-to-stand, all of 32% were reduced and 16% severely reduced. We performed follow-up (median 86 days) for 60 patients, and found substantial decreases in all parameters, including a 5% decrease (-7 to -3) in skeletal muscle mass and 21% decrease (-35 to -15) in sit-to-stand performance.
Conclusion: Preliminary results illustrate the poor physical health of patients with lung cancer and alarming declines at 3 months follow-up. The high inclusion rate and large target study population holds promise as the largest prospective study for this group of patients and results may have substantial impact on clinical practice and future research in the field.

4-64

Validation of anthropometric sarcopenia scores in brazilian elderly: A preliminary study of Lee equations versus DEXA

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Introduction: Sarcopenia, a critical geriatric syndrome, demands precise diagnosis for timely intervention. While Dual-energy X-ray Absorptiometry (DEXA) is the gold standard for muscle mass assessment, its limited accessibility in developing countries necessitates validated anthropometric alternatives like the Lee equations. Their applicability and appropriate cutoffs in diverse populations, such as in Brazil, remain uncertain.
Methodology: This cross-sectional study included 52 fragile Brazilian older adults. We compared sarcopenia diagnosis by DEXA (Baumgartner criteria) with Lee's full equation (using arm and calf circumferences) and an adapted equation (using only calf circumference). Key metrics included Pearson correlation, Kappa concordance, Bland-Altman analysis, and ROC curves.
Results: DEXA diagnosed sarcopenia in 13.5% of the cohort. Applying original Lee cutoffs significantly underestimated this prevalence: full Lee found 1.9%, while adapted Lee found 5.8%. Both Lee equations showed good linear correlation with DEXA ASMI (Pearson's r=0.632 for full; r=0.642 for adapted). Diagnostic concordance was weak for full Lee (Kappa=0.224) but moderate for adapted Lee (Kappa=0.565), indicating improved classification. Bland-Altman analysis showed adapted Lee consistently overestimated ASMI by +2.08 kg/m² versus DEXA. The adapted Lee also exhibited moderate predictive performance (AUC=0.695), with a local optimal cutoff of approximately 8.2 kg/m² to maximize sensitivity and specificity.
Conclusion: Original Lee cutoffs inadequately diagnose sarcopenia in this Brazilian cohort, leading to significant underestimation. While the adapted Lee equation shows greater potential as a simpler screening tool due to its moderate performance, its systematic bias necessitates rigorous local calibration. This study highlights the urgent need for population-specific and locally validated anthropometric tools and cutoff points in ethnically diverse developing countries.

4-65

Socioeconomic impacts and sarcopenia: Evidence from a brazilian cohort

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Introduction: This study investigated the influence of socioeconomic factors on functional outcomes in older adults, focusing on Brazil's context of profound social inequalities. It was hypothesized that disadvantaged individuals would present poorer physical performance, thus increasing their risk of sarcopenia and functional decline.
Methods: A cross-sectional analytical study utilized primary data from 127 participants (aged 65+) of a São Paulo cohort. Sociodemographic and socioeconomic variables (e.g., social support, social benefits, private health insurance) were assessed alongside functional capacity using handgrip strength (HGS), gait speed, and the Timed Up and Go (TUG) test. Statistical analysis employed $p<0.05$.
Results: The mean age of participants was 72.2 years. Average performance scores were: HGS 23.5 kg, gait speed 0.94 m/s, and TUG 12.8 seconds.
Among the socioeconomic variables evaluated, only the receipt of social benefits (LOAS) showed a statistically significant association with handgrip strength. Older adults who were beneficiaries of governmental assistance programs exhibited lower muscle strength compared with non-recipients, a difference confirmed by the Kruskal-Wallis test ($p = 0.0067$)
Other socioeconomic variables including education, social support, private health insurance, sex, and marital status did not achieve statistical significance. Nevertheless, some demonstrated consistent positive trends suggesting potential influence on functional outcomes. The lack of significance may be partially explained by the sample size, highlighting the need for larger studies to further clarify these relationships.
Conclusions: The significant link between social benefit receipt and poorer muscle strength underscores the direct impact of socioeconomic vulnerability on older adults' functional capacity. These findings emphasize the importance of incorporating social determinants into geriatric care and public policy, advocating for integrated strategies that combine health and social assistance to promote equitable aging in Brazil.

4-66

Trajectories of skeletal muscle index in patients with endometrial cancer after surgery: A group-based trajectory modeling analysis

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Introduction: Physical activity in patients with endometrial cancer often declines after surgery due to lower limb lymphedema and chemotherapy-induced peripheral neuropathy (CIPN), potentially leading to sarcopenia. This decline may affect activities of daily living (ADL), instrumental ADL (IADL), health-related quality of life, and work ability. Preserving skeletal muscle mass is crucial for maintaining postoperative physical function. This study aimed to identify the postoperative trajectories of changes in skeletal muscle mass and explore factors associated with each trajectory.
Methods: We retrospectively analyzed 322 patients with endometrial cancer who underwent total hysterectomy and bilateral salpingo-oophorectomy at Keio University Hospital. Computed tomography images were obtained preoperatively and at 6 and 12 months postoperatively. Skeletal muscle index (SMI) was calculated at the third lumbar vertebra level. Group-based trajectory modeling (GBTM) was applied to identify patterns in SMI change. Multinomial logistic regression was conducted to evaluate associations between patient characteristics (age ≥ 55 years, BMI ≥ 25 kg/m^2, menopause status, FIGO (2008) stage II to IV, open surgery, chemotherapy, CIPN, lymphedema, and preoperative myopenia) and trajectory groups.
Results: The median age was 55 years (IQR 49–67). GBTM identified six SMI trajectories: early increase (n=27, 8.4%), late decline (n=81, 25.2%), early decline (n=71, 22.0%), transient increase (n=27, 8.4%), late increase (n=27, 8.4%), and steep decline (n=84, 26.1%). Compared with transient increase, early increase was significantly associated with advanced disease (FIGO stage: OR 8.67, 95%CI 1.82–41.31, p=0.01), while steep decline was significantly associated with preoperative myopenia (OR 0.29, 95%CI 0.08–0.99, p=0.05).
Conclusions: Six trajectories of skeletal muscle change were identified up to 12 months postoperatively. Patients with advanced-stage disease showed early muscle mass gain, whereas those without preoperative myopenia experienced a sharp decline. These results suggest that individualized supportive care strategies are needed for patients with endometrial cancer in both preoperative and postoperative phases.

4-67

Correlation Between Sarcopenia and the Risk of Falling, Assessed Using the FES-I Scale, in Older Adults

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Introduction: Sarcopenia is a progressive and generalized condition of skeletal muscle, characterized by accelerated loss of muscle mass, function, and strength. Recent evidence demonstrates an association between this condition and the fear of falling, measured using the Falls Efficacy Scale-International (FES-I). This study aims to explore the correlation between these two conditions in older adults and potential variations depending on the method used to assess sarcopenia.
Methods: This cross-sectional study evaluated 93 older adults from a prospective cohort in the city of São Paulo, including individuals aged 65 years or older. The criteria for sarcopenia were defined as: SARC-F ≥11 or handgrip strength <16 kg in women/ <27 kg in men in the dominant hand or sit-to-stand time >15 seconds or Baumgartner Index < 5 in women/ <7 in men. For fall risk assessment, the FES-I cut-off points were ≥23 for sporadic fall risk and ≥31 for recurrent fall risk.
Results: The study showed that sarcopenic older adults had significantly higher scores on the FES-I scale (31.8±14.0 vs 23.4±6.0; p=0.004), according to Welch's t-test: t=2.95; p=0.004 and Cohen's d=0.52 (moderate effect), indicating greater fear of falling. When analyzing the functional tests individually, the sit-to-stand test was significantly associated with higher FES-I scores (29.4±12.3 vs 24.4±7.3; p=0.017), according to Welch's t-test t=2.43; p=0.017; Cohen's d=0.46 (moderate effect), while reduced handgrip strength showed only a non-significant trend. Taken together, these findings reinforce that sarcopenia, and particularly impaired functional mobility, are associated with increased fear of falling in older adults.
Conclusion: Sarcopenia and limitations in mobility and functionality demonstrated a significant association with greater fear of falling in older adults, underscoring the importance of strategies aimed at preserving muscle strength and function in this population.

4-68

Functional decline and risk of falls in elderly people: cross-sectional findings from a prospective cohort in São Paulo

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Introduction: Sarcopenia is characterized by the progressive decline in skeletal muscle mass, muscle force, and physical performance, which leads to a greater predisposition to falls among elderly people. This study aims to identify individuals with sarcopenia and analyze its relationship with episodes of falls.
Methods: A cross-sectional study was conducted of elderly individuals the Center for Health Promotion, Rehabilitation, and Social Integration in São Paulo, from February 2024 to April 2025. Individuals over the age of 65, without disabling musculoskeletal disorders, who were able to attend the clinic independently and had preserved communication skills were included. Cases undergoing treatment in specialties conflicting with the study protocol were excluded. To identify sarcopenia, the following instruments were applied: SARC-F + CC (Stair Climb and Falls Scale + Calf Circumference), Timed Up and Go (TUG), and whole-body densitometry (DXA).
Results: Among the 105 elderly individuals assessed, 20.95% were diagnosed with sarcopenia. Worse performance on the TUG test was associated with older age and higher scores on the SARC-F + CC scale. Individuals over 80 years olde presented an average time of 15 seconds at the TUG, while younger participants presented 11 seconds (p = 0.008). That result showed a reduction in functional mobility in the older group. Additionally, 43% of elderly participants with sarcopenia reported falls, compared to 31% among those without the condition; however, there was no statistically significant difference between groups classified by SARC-F + CC (chi-square: p = 0.61; Fisher's test: p = 0.38).
Conclusion: The data indicate that aging is associated with reduced functional capacity, even without a diagnosis of sarcopenia, and that individuals aged 80 years or older are at

increased risk of falls and functional impairment—factors related to both advancing age and sarcopenia.

4-69

Low sarcopenia prevalence but consistent declines in strength, muscle, and bone across menopausal stages in healthy females

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Background: Sarcopenia is a major risk factor for functional decline, yet its prevalence and related changes across the lifespan remain poorly characterised in healthy female cohorts. This study examined sarcopenia prevalence and related characteristics across pre-, peri-, and post-menopausal females.
Methods: One hundred and fifty-one participants were categorised as pre- (n=37), peri- (n=41), or post-menopausal (n=73). Body composition, appendicular lean mass index (ALMI), bone mineral density (BMD), and fat mass were assessed using DXA. Lean mass was adjusted for height in line with EWGSOP recommendations. Muscle strength and performance were measured via handgrip strength, chair stand test, and gait speed. Sarcopenia prevalence was determined using EWGSOP 2010 and 2019 criteria. Lifestyle data were collected through validated questionnaires.
Results: Significant declines were observed in total lean mass ($p<0.001$), lean mass adjusted for height ($p=0.002$), ALMI ($p=0.024$), handgrip strength ($p=0.002$), relative handgrip strength ($p=0.006$), and chair stand repetitions ($p=0.002$) from pre- to post-menopause, while gait speed was unchanged. Fat mass increased progressively ($p=0.002$), together with significant declines in total bone mass and BMD (all $p<0.001$). Using EWGSOP 2019 criteria, sarcopenia prevalence was 0% across groups. In contrast, EWGSOP 2010 identified 2.4–4.1% as pre-sarcopenic and 1.4% as sarcopenic, suggesting earlier definitions may have been more sensitive to early changes. Protein intake (g/kg BW) was significantly lower in peri- and post-menopausal women compared with pre-menopause ($p=0.014$), and leisure physical activity declined in post-menopause ($p=0.028$).
Conclusions: Despite no sarcopenia diagnosed by EWGSOP 2019 criteria, consistent declines in strength, lean mass, and bone health were evident across menopausal stages, alongside increased fat mass and lower protein intake. These findings suggest that current criteria may underestimate early risk in females. While limited by its observational design and modest sample size, this study highlights the need for preventive strategies targeting musculoskeletal health before overt sarcopenia develops.

4-70

Mitochondrial protein modulation as a therapeutic approach to counteract muscle wasting in cancer cachexia, steroid use, and disuse conditions

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Introduction: Muscle atrophy from steroid use, cancer cachexia, and immobilization contributes to sarcopenia and poor clinical outcomes, largely driven by mitochondrial dysfunction. This study investigates the role of pyruvate dehydrogenase kinase 4 (PDK4), a metabolic enzyme elevated in skeletal muscle, in regulating muscle atrophy and explores its potential as a therapeutic target to prevent muscle loss in various disease conditions.
Methods: We utilized three established muscle atrophy models: steroid-induced (glucocorticoid (GC) 25 mg/kg, intraperitoneally, for 10 days), cancer cachexia (CT-26 cells (3×10^6 cells per mouse) was subcutaneously injected into the left flanks of male BALB/c mice.), and disuse atrophy (hindlimb immobilization using tape and microcentrifuge tube positioning for 14 days). Muscle function was evaluated in both wild-type and PDK4 knockout mice, as well as with pharmacological PDK4 inhibition. In vitro experiments were conducted using C2C12 myotubes, and human gluteus maximus samples from hip replacement patients—with or without steroid treatment—were analyzed to assess key myogenic genes and proteins.
Results: Knockdown or pharmacological inhibition of PDK4 protects against muscle atrophy and dysfunction in C2C12 myotubes under steroid and cancer cachexia conditions. This effect is linked to increased myogenin and myosin heavy chain expression, reduced MAFbx levels, and improved mitochondrial function. PDK4 was found to phosphorylate myogenin at S43 and T57, promoting its degradation via MAFbx. Blocking this phosphorylation through a non-phosphorylatable myogenin mutant preserved muscle fibers in dexamethasone-treated mice. Overall, targeting PDK4 enhances muscle strength and fiber size in various muscle atrophy models.
Conclusion: This study reveals PDK4 as a key driver of muscle atrophy across multiple conditions. Its inhibition improves muscle strength, promotes growth markers, reduces atrophy-related genes, and restores mitochondrial function, positioning PDK4 as a potential therapeutic target for muscle-wasting diseases.

4-71

DNA methylation as a driver of long-term muscle transcriptome alterations in critical illness survivors

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Introduction: Critically ill patients requiring intensive-care-unit (ICU) admission suffer from muscle weakness that persists for years. We recently documented altered RNA expressions in muscle of former ICU patients that suggested disrupted mitochondrial function, disturbed lipid metabolism and fibrosis, of which many associated with lower long-term muscle strength. We now hypothesized that altered DNA methylation may drive these abnormal RNA expression patterns, contributing to prolonged muscle weakness.
Methods: Genome-wide DNA methylation (Infiniumv2® HumanMethylationEPIC BeadChips) was assessed in skeletal muscle biopsies from 118 patients 5 years post ICU admission and from 30 controls. Differentially methylated positions (DMPs) in patients versus controls were identified, adjusting for age, sex and BMI (minfi R package, Benjamini Hochberg false discovery rate<0.05), followed by pathway over representation of affected genes. DMP's methylation status was correlated with RNA expression (Spearman correlation). Finally, risk factors for abnormal DNA methylation were identified with multivariable linear regression.
Results: Former ICU patients showed 7379 DMPs as compared with controls. These DMPs were associated with 1334 unique genes, enriched for muscle contraction, vascular development, cell

differentiation and signal transduction. When correlating DMP-methylation with RNA-expression, a higher percentage of correlations reached a |rho|>0.3 for differentially expressed RNAs (DERNAs, 18.1%) than for non-DERNAs (1.7%). This percentage was even higher for DERNAs associated with lower muscle strength (24.2%). Focusing on DERNAs involved in mitochondrial function, lipid metabolism or fibrosis, the percentage of correlations with |rho|>0.3 was consistently higher for DERNAs associated with muscle strength than for DERNAs not associated with strength. Several potentially avoidable in ICU treatments were associated with more abnormal DNA methylation, most notably glucocorticoids, benzodiazepines and early parenteral nutrition.
Conclusion: Altered DNA methylation in muscle 5 years after critical illness, partly attributable to possibly avoidable risk factors, contributes to abnormal RNA expression related to lower muscle strength.

4-72

Role of inflammatory macrophages in skeletal muscle impairment in COPD

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Introduction: Muscle wasting and impaired regeneration are a hallmark of chronic obstructive pulmonary disease (COPD). As macrophages, recruited by injured tissues via chemotactic pathways such as the CXCL12-CXCR4 axis, play an important role in skeletal muscle homeostasis and pathology, they may be involved in muscle impairment in COPD. The aim of our study was to investigate macrophage-muscle interactions in an experimental COPD context.
Methods: The effect of conditioned medium (CM) from pro-inflammatory macrophages (THP-1 human monocytes differentiated into M1 macrophages with PMA followed by LPS and IFN-γ stimulation; M1-CM) and naïve macrophages (THP-1 cells with PMA only) was compared on proliferation and differentiation of immortalized human skeletal muscle cells (HSM), as well as on HSM cytokine and chemokine expression. We also tested the effect of COPD-like conditions (HSM pre-exposed to hypoxia (4% O_2) and TNFα (10 ng/mL)) on adhesion of THP-1 to HSM under static and perfused conditions, in conventional and muscle-on-chip culture models.
Results: M1-CM enhanced HSM proliferation and expression of myf5, but decreased expression of myogenin and myosin heavy chain isoforms. M1-CM did not alter fusion of myoblasts to myotubes in healthy conditions, but decreased fusion when myotubes were pre-exposed to both hypoxia and TNFα. M1-CM increased the expression of inflammatory cytokines (IL-1β, IL-6) and chemokines (MCP-1, CXCL8, CXCL12) in myotubes. In direct co-culture in both static and perfused conditions, monocytes spontaneously adhered to HSM. Such adhesion was enhanced when HSM were pre-exposed to hypoxia and TNFα, and was accompanied by expression of CXCL12 at HSM cell surface.
Conclusions: Inflammatory macrophages promote HSM proliferation but inhibit later phases of muscle cells differentiation, and enhance the expression of pro-inflammatory cytokines and chemokines in muscle cells. Recruitment of such macrophages might be favoured in COPD context by increased chemotaxis following inflammation and hypoxia in muscle cells.

4-73

Decreases in RyR1 content extend beyond recessive RYR1-related myopathies and trigger ER and metabolic stress.

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Background: Decreased ryanodine receptor type 1 (RyR1) protein levels are a well-established feature of recessive RYR1-related myopathies. Emerging evidence suggests that the reduction in RyR1 content is more extensive and detrimental to muscle cells. In this study, we investigate myopathies linked to reduced RyR1 levels and the mechanisms by which this deficiency leads to muscle pathology
Methods: We analyzed publicly available datasets and muscle samples from human inflammatory, mitochondrial, and congenital myopathies, along with an inducible muscle-specific RYR1 recessive mouse model and RyR1 knockdown in C2C12 cells and human primary muscle cultures, to assess RyR1 content and ER stress markers. We employed proteomics, lipidomics, molecular biology, calcium imaging, and transmission electron microscopy to investigate the alterations associated with reduced RyR1 levels.
Results: RYR1 transcript and protein levels were reduced in muscle samples from patients with inflammatory myopathies, muscular dystrophies, and congenital myopathies. This was accompanied by shared metabolic alterations. RyR1 reduction was consistently associated with increased ER stress markers in all human myopathy samples. Using in vitro systems and a muscle-specific RyR1-depleted mouse model, we demonstrated that reduced RyR1 directly triggers ER stress and metabolic disturbances, impairs endoplasmic reticulum (ER)-mitochondria tethering, disrupts mitophagy, and leads to mitochondrial dysfunction, accumulation, with altered glucose metabolism. Ongoing studies are investigating the role of ER stress in RyR1-related pathologies and testing a novel strategy to restore RyR1 expression in human muscle cells.
Conclusions: Decreased RyR1 is more frequently associated with myopathies than expected. It is linked to endoplasmic reticulum (ER) stress and metabolic alterations in vitro, in mouse muscle, and in human myopathy muscles. This suggests that RyR1 depletion-induced ER stress may play a significant role in the development of myopathies. Targeting this axis may be promising for developing new therapeutic approaches for myopathies.

4-74

Molecular mechanisms mediating exercise-induced maladaptations *in vitro*

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Introduction: Physical training stimulates mitochondrial biogenesis and protein synthesis in skeletal muscle. If training load is too demanding and prolonged, an overtraining syndrome may develop. Reported overtraining symptoms include recurrent respiratory infections, sleep disturbances, with potential alterations at the skeletal muscle level such as soreness, and atrophy. The aim of the present study was to investigate skeletal muscle (mal)adaptations in overtrained athletes, developing an *in vitro* model to delve deeper into the molecular mechanism.
Methods: Electrical stimulation was applied to C2C12 myotubes to mimic endurance exercise. For the simulated training (s-T), stimulation was applied once daily for three days. In the simulated overtraining (s-OT), stimulation was applied three times daily for three days. Proteomics highlighted bulk differences. Oxygen consumption rate was assessed in Oroboros. Confocal imaging was used for mitochondrial localization and live-cell imaging. Western blot was used to validate protein content.
Results: In s-T, we observed the expected beneficial adaptations, including myotube hypertrophy, increased expression of myosin heavy chain proteins, and enhanced mitochondrial respiration. In contrast, s-OT showed myotube atrophy, reduced myosin heavy chain content, and impaired mitochondrial respiration. Consistent with these respiratory findings, proteomics analysis revealed a decreased abundance of proteins involved in the mitochondrial respiratory chain in s-OT. Interestingly, mitochondria appeared aggregated in s-OT myotubes, a feature also reported in athletes with the overtraining syndrome, suggesting possible impairments in mitochondrial quality control. Live-cell imaging revealed possible autophagy alterations in the s-OT condition but not in s-T.
Conclusions: This *in vitro* model provides a molecular platform for further investigations of skeletal muscle maladaptations to overtraining, in a clinical setting. Collection of human muscle biopsies is currently in progress, and the combination of both tools will help to clarify the molecular mechanisms underpinning muscle maladaptations to excessive physical exercise, which may be then translated to patients suffering from overtraining.

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Body Composition Shapes MicroRNA Signatures in Newly Diagnosed Breast Cancer Patients

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Introduction: Metabolic changes in skeletal muscle (SM) and adipose tissue (AT) are frequent in women newly diagnosed with breast cancer (BC) and represent negative prognostic factors. However, the underlying mechanisms are not fully understood. Growing evidence indicates that microRNAs (miRs), which act as key post-transcriptional regulators of genes involved in tissue remodelling, metabolism, and inflammation, may contribute to BC-related changes in tissue compartments.
This study aimed to assess the expression of circulating and tissue-specific miR in BC patients (BCP) and explore their associations with changes in body composition.
Methods: We studied newly diagnosed BCP and healthy controls (C). Body composition was estimated by bioelectrical impedance analysis (BIA). BCP were stratified according to fat-free mass index (FFMI, internal cut-off: 17 kg/m²) as low (LMM) and high (HMM) muscle mass. Blood samples and SM biopsies were collected prior surgery. miRs were quantified by RT-qPCR. Associations with changes in body composition and clinical parameters were evaluated.
Results: In 46 BCP, circulating levels of miR-29a and -29b were upregulated vs C (n=16) ($p<0.05$). Circulating levels of miR-133a were significantly downregulated in LMM vs HMM BCP. Also, plasma levels of miR-21 were overexpressed in BCP vs C ($p<0.05$), while its expression in SM tissue of BCP was significantly lower in LMM compared with HMM ($p<0.05$) and positively correlated with BMI values ($p=0.038$, $r=0.661$). We observed significant upregulation of plasma miR-133a in BCP with BMI (kg/m^2) ≥25 and concomitant presence of metabolic syndrome (MetS) or dyslipidemia (Dys) vs those with BMI<25 without MetS or Dys ($p<0.05$).
Conclusions: Our preliminary findings indicate that BCP display distinct patterns of miR dysregulation according to body size, body composition, with differences related to muscularity, adiposity, and metabolic status. Further studies are ongoing to clarify their role in SM and AT remodeling associated with BC.

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AI-driven ultrasound radiomics for predicting sarcopenia, muscle strength and nutritional risk in hospitalized geriatric patients

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Introduction: Ultrasound (US) approach to sarcopenia diagnosis relies heavily on subjective visual interpretation. Automated radiomics extraction from US may capture subtle, objective muscle composition patterns. This study explored the utility of US radiomics for predicting sarcopenia risk (SARC-F), maximal handgrip strength, and nutritional risk in hospitalized patients.
Methods: We included 31 inpatients (mean age 87 ± 6 years; 45% female) from Lausanne University Hospital. Rectus femoris, vastus lateralis, and gastrocnemius were imaged bilaterally in longitudinal and transverse planes using a 12MHz linear probe. Muscle aponeuroses were segmented via deep learning, and 300 radiomic features were extracted per image with PyRadiomics and aggregated across muscles and planes. Outcomes included: SARC-F (n=29; <4.5 = 17, ≥4.5 = 12), maximal handgrip strength (n=30; <21 kg = 15, ≥21 kg = 15), and Nutritional Risk Score-2002 (n=31; <3.5 = 22, ≥3.5 = 11). Information gain ratio was applied for feature selection, and four classifiers (SVM, kNN, RF multilayer perceptron) were tested with leave-one-out cross-validation.
Results: For sarcopenia screening, the RF model yielded the best accuracy of 79% (sensitivity 82% ; specificity 78%), with features reflecting muscle brightness and roughness as key predictors. Handgrip strength was best predicted using kNN (accuracy 80%; sensitivity 80%; specificity 79%), where sex and muscle uniformity contributed most. Nutritional risk was most accurately classified using SVM (accuracy 81%; sensitivity 81%; specificity 80%), combining BMI with entropy-related texture features. These radiomic markers align with what clinicians visually assess on US, muscle echogenicity, uniformity, and structural heterogeneity.
Conclusions: Ultrasound radiomics shows promise as a non-invasive tool for predicting sarcopenia risk, muscle strength, and nutritional risk in older adults. By quantifying visual characteristics such as echogenicity and heterogeneity, radiomics provides an objective and reproducible complement to traditional ultrasound assessment. These preliminary single-center findings warrant external validation in larger cohorts and may support the development of automated, bedside screening approaches.

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C-Peptide promotes myogenic differentiation *in vitro* and its low serum levels associate with sarcopenia in adults and the elderly

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Introduction: Sarcopenia is an emerging public health concern, driven by aging, reduced physical activity, and inadequate nutrition, with high prevalence also among cancer patients. Currently, no effective pharmacological therapy exists, although several studies suggest a potential role of insulin C-peptide in regulating muscle mass and metabolism. Building on this premise, our study aimed to investigate the effects of C-peptide in an *in vitro* sarcopenia model and to explore the association between serum C-peptide levels, sarcopenia, and fracture risk.
Methods: We performed in vitro experiments on C2C12 cells to examine the role of C-peptide in myogenic differentiation and protection against nutrient-deprivation–induced muscle damage, assessed by H&E staining, western blot, and qPCR. In parallel, a cross-sectional study was conducted in 191 individuals aged ≥50 years, assessing serum C-peptide levels, appendicular skeletal muscle mass (bioelectrical impedance analysis), and incidence of falls and fractures during follow-up.
Results: *In vitro*, C-peptide accelerated C2C12 differentiation, increasing myotube diameter and expression of *MyHC IIx*, *Pax7*, and *BMP4*, thereby enhancing maturation and regeneration. Under nutrient deprivation, C-peptide prevented MyHC loss and reduced muscle damage. In humans, participants in the lowest C-peptide tertile had significantly lower appendicular skeletal muscle mass ($p<0.001$) and a higher risk of sarcopenia (OR=0.31; $p<0.001$) compared with those in the highest tertile. They also experienced more falls (32% vs 14%) and fractures (17% vs 0%). Fractures were associated with both falls and low C-peptide levels (OR=0.29; $p=0.01$).
Conclusion: C-peptide promotes myogenic differentiation and protects against muscle damage in vitro. Higher endogenous C-peptide levels are associated with reduced sarcopenia prevalence and lower fracture risk in older adults. These findings highlight C-peptide as a promising therapeutic target for sarcopenia and fracture prevention, warranting further clinical investigation. A novel drug combining C-peptide with a bisphosphonate has recently been patented for osteosarcopenia (n.24169036.1-1109/4445909).

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Sex-specific reference ranges for CT body composition analysis in healthy adults: comparison with published cut points

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Introduction: Body composition changes indicative of malnutrition are associated with poor clinical outcomes. CT-based assessment at the third lumbar vertebra (L3) is the *de facto* gold standard for evaluating body composition. Most published cut-points are based on older or clinical populations. This study aimed to establish sex-specific reference ranges body composition metrics in a healthy cohort and to compare cohort-derived 5th percentile cut-points with published thresholds.
Methods: Skeletal muscle radiation attenuation (SMRA) and skeletal muscle and adipose tissue cross-sectional areas (CSA) were extracted from the uEXPLORER Healthy-Total-Body-CTs dataset (Selfridge et al., 2023) scans of healthy adults, using DAFS body composition software. CSAs were normalised for height, to generate skeletal muscle index (SMI) and subcutaneous, visceral and intermuscular adipose tissue indices (SATI, VATI, IMATI). Sex-specific (M/F) 5th/95th percentile cut-points were compared to cut-points from oncology populations (Martin et al. 2013; Ebadi et al., 2017; Doyle et al., 2013) and healthy kidney donors aged 20-82 years (van der Werf et al., 2018).
Results: Of 30 scans, 28 were evaluable using DAFS. Mean age was 47 years (range: 26-78), mean BMI 28 (range: 19.5-37.2 kg/m^2). Mean (percentile cut-off) values were: SMRA (HU) F:41 (5^{th}:32); M:48 (5^{th}:42), SMI (cm²/m²) F:45 (5^{th}:37); M:60 (5^{th}:48), SATI (cm²/m²) F:88(95^{th}: 192); M:68 (95^{th}:104), VATI (cm²/m²) F:33 (95^{th}:68); M:48(95^{th}:79) and IMATI (cm²/m²) F:4(95^{th}:6); M:3 (95^{th}:5). Compared to 7% being classed as abnormal using the cohort-derived sex-specific 5^{th} (SMI)/95^{th} (SATI/VATI) percentile cut-points, 11%, 21%, 75% and 46% were classed as having low SMRA, low SMI, high SATI and high VATI, respectively, using oncology-derived cut-points, whereas all were classed as having normal SMRA and SMI, using kidney donor-derived cut-points.
Conclusions: Choice of cut-points, particularly clinical vs. population-derived cut-points significantly influences prevalence estimates for body composition abnormalities. These findings highlight the importance of deriving body composition cut-points from healthy, non-aged populations for clinically meaningful interpretation.

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Impact of Nutritional and Radiomic Index of Sarcopenia in Retroperitoneal Sarcoma

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Background: Sarcopenia, characterised by loss of skeletal muscle mass, strength, and function, negatively impacts surgical outcomes in oncology, including complications, prolonged hospitalisations, and reduced survival. This study investigated the relationship between nutritional and radiomic indices and tumour burden in sarcopenic versus non-sarcopenic patients with retroperitoneal soft tissue sarcoma (STS).
Method: A retrospective analysis was conducted on patients with retroperitoneal STS treated at the Midlands Abdominal Retroperitoneal Sarcoma Unit (MARSU) between June 2023 and December 2024. Nutritional status and sarcopenia were evaluated using body mass index (BMI), Prognostic Nutritional Index (PNI), Skeletal Muscle Index (SMI), and Total Psoas Index (TPI). Correlations were explored between sarcopenia, tumour burden (volume and weight), and clinical outcomes including survival.
Results: The study included 73 patients: 57 with liposarcoma (LPS) and 16 with leiomyosarcoma (LMS). Most had an ECOG performance status of 0. Sarcopenia was present in 57.9% of LPS and 37.5% of LMS patients preoperatively. Among LPS patients, sarcopenia was significantly associated with a lower PNI (p=0.05), suggesting poorer nutritional status. Sarcopenia showed no significant correlation with tumour volume or weight in either cohort. Similarly, it did not significantly affect hospital stay length in LPS (p=0.475) or LMS (p=0.328). Median follow-up was 14.6 months (range: 6.5–37.8). Recurrence was more common in sarcopenic patients; however, disease-free survival (DFS) in sarcopenic LPS cases did not reach statistical significance (p=0.117). Survival analysis in LMS was limited due to censored data.
Conclusions: PNI serves as a reliable marker for identifying sarcopenic patients and may guide preoperative nutritional and physical rehabilitation strategies to enhance surgical outcomes. Although early recurrence trends were observed, larger cohorts and extended follow-up are necessary to validate associations with overall survival (OS) and further define prognostic implications.

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Novel sex-specific cut-offs for subcutaneous adipose tissue radiointensity in patients with cirrhosis: a post-hoc analysis

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Introduction: While several recent studies have addressed the prognostic impact of sarcopenia and myosteatosis in cirrhosis, less is known about the role of subcutaneous adipose tissue radiointensity (SAT-r). The aim of this study is to prospectively assess the prognostic value of high SAT-r in a heterogeneous cohort of patients with cirrhosis.
Methods: This is a post-hoc analysis of the prospective multicentre EpatoSarco study, in which 433 patients with cirrhosis were enrolled after CT scan for clinical indication. SAT-r was evaluated using SliceOmatic software at the L3-L4 level and its prognostic impact was assessed by the Fine and Gray model for competing risks.
Results: The median SAT-r was 95 HU (IQR -115 to -83 HU), significantly lower in patients with no muscle changes than in those with other muscle changes (-96±13 vs -90±15, p=0.0015). Fifty-one patients died during the 1-year follow-up: mean SAT-r was significantly lower in alive than in deceased patients (-92±15 vs -87.1±15, p 0.025). We failed to validate the Ebadi's cutoffs (>-83 Hounfield Unit - HU - for men and >-74 HU for women) and found that in our population the best discriminant cutoff for death-risk was -89.5 HU for men and -98.4 HU for women. With these cut-offs, 188 patients had high-risk RSAT-r, with a significantly higher cumulative incidence of death (p=0.006; death and OLT competing; figure, left).The SHR for mortality of high-risk SAT-r, adjusted for the MELD score was 1.9(CI 1.006 to 3.6). When type of muscle damage and its interaction term with high-risk SAT-r was added to the model, the interaction was almost significant (p. 0.06) and allowed to identify 4 different risk groups (figure, right).
Conclusion: New sex-specific cut-offs for high SAT-r may identify patients at high risk of death, especially when combined with other muscle changes.

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Sarcopenic Obesity in Men with Castration Sensitive Prostate Cancer treated with Androgen Deprivation Therapy

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Background: It is estimated that over 45% of patients with castration sensitive prostate cancer (mCSPC) receive androgen deprivation therapy (ADT). Although ADT is associated with excellent prostate cancer (PCa) control, the hormonal shifts from ADT cause marked, unfavorable changes in body composition leading to a body phenotype, sarcopenic obesity (SO). ADT-induced SO is characterized by simultaneous presentation of sarcopenia and excess adiposity and is uniquely characterized by poor quality of muscle, with an increase in fatty infiltration in muscles or myosteatosis - a cardinal symptom of SO. The adverse effects of SO in this patient population has been consistently shown to lead to multiple metabolic disorders compared to sarcopenia alone, and include cardiovascular disease and insulin resistance, diabetes mellitus and ultimately to poor PCa prognosis and all cause- related mortality. Myosteatosis has been consistently shown to contribute to poor prognosis in almost all cancers as well as all-cause mortality.
Methods: The goal of our study is to retrospectively evaluate the prevalence of SO and myosteatosis in castration sensitive prostate cancer (mCSPC) patients. To date, the prevalence and prognostic value of SO or myosteatosis in mCSPC patients treated with ADT has not been characterized.
Results: We have approval to conduct this study and will present the results at this meeting.
Conclusion: Future studies must first characterize the prevalence of SO in this patient population using a single composite biomarker that is indicative of the cardinal symptom of SO, myosteatosis. With the multidimensional nature of the adverse effects of ADT, there is a paucity of well-powered, "bundled", evidence-based intervention trials that target the underlying mechanisms t0 mitigate the impact of ADT on the cardinal symptom of SO, myosteatosis and its effects on functional status, metabolic abnormalities, and biomarkers of mCSPC progression

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Association between sarcopenia, body composition, functionality, and blood biomarkers in elderly individuals with obesity: cross-sectional findings from a prospective cohort in São Paulo

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Introduction: Sarcopenic obesity is a significant health concern as it combines the negative impacts of excess body fat with the loss of muscle mass in older adults. This condition increases the risk of falls, fractures, functional decline, and metabolic complications. This study aimed to investigate the associations between sarcopenia, body composition, functional performance, and blood biomarkers in older adults with obesity.
Methods: This was an observational, cross-sectional study from a Prospective Cohort in São Paulo. Individuals aged ≥65 years with obesity (BMI ≥27 kg/m²) were included. Participants with acute illness, physical disability, or conditions that could interfere with body composition assessment were excluded. Participants were assessed for body composition using body mass index (BMI) and whole-body densitometry via dual-energy X-ray absorptiometry (DEXA). Sarcopenia was screened using the SARC-F questionnaire. Functional performance was evaluated through handgrip strength, gait speed, and the sit-to-stand test. Laboratory blood tests included hemoglobin, C-reactive protein (CRP), vitamin D, calcium, phosphorus, magnesium, creatinine, and parathyroid hormone (PTH). Pearson's correlation coefficient was used for statistical analysis.
Results: Seventy-one participants were included. BMI showed significant correlations with fat mass index (FMI) ($p = 0.0007$; $r = 0.52$), fat mass percentage ($p = 0.0001$; $r = 0.66$), Baumgartner index ($p = 0.01$; $r = 0.33$), CRP ($p = 0.001$; $r = 0.43$), vitamin D ($p = 0.04$; $r = -0.26$), and PTH ($p = 0.02$; $r = 0.32$). Fat mass percentage was negatively associated with handgrip strength ($p = 0.007$; $r = -0.54$) and hemoglobin ($p = 0.002$; $r = -0.49$) and positively associated with PTH ($p = 0.006$; $r = 0.44$). **Conclusion:** BMI was positively associated with adiposity, C-reactive protein, and PTH levels, and inversely associated with vitamin D and the Baumgartner Index. Fat mass was associated with reduced muscle strength, lower hemoglobin and higher PTH. These findings suggest that older adults with sarcopenic obesity present inflammatory, metabolic, and functional alterations that may contribute to adverse health outcomes.

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***Vaccinum macrocarpon* extract abolishes the aging-like effect of Western diet consumption by hindering the advanced glycation end-products (AGEs)/RAGE axis.**

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The diffusion of a Western-like diet (WD) is considered a major risk for Sarcobesity (SO), a chronic metabolic disorder characterized by ectopic fat deposition (obesity) and concomitant progressive loss of muscle mass and strength (sarcopenia). WD foods rich in saturated fats and refined sugars contain high amounts of advanced glycation end-products (AGEs), a heterogeneous group of glycated proteins formed *via* the Maillard reaction. AGEs and their receptor, RAGE, promote ageing and several chronic diseases by sustaining inflammation and oxidative stress. We recently demonstrated that dietary AGEs induce muscle atrophy *in vitro,* and *Vaccinium macrocarpon* (*VM*) extract blunts AGEs. Adult WT and RAGE-null (*Ager*$^{-/-}$) mice were fed with with high-AGE WD for 20 weeks in the absence or presence of *VM*. We found AGEs accumulation in muscles and sera of WT mice, in concomitance with muscle RAGE upregulation, loss of muscle performance, reduction of myofiber areas, excessive activation of proteolytic systems, and degradation of the sarcomeric protein, myosin heavy chain (MyHC)-II. Besides muscle, WD-fed WT mice showed hepatomegaly with fat deposition and fibrosis, spleen weight increment and histological alterations, and visceral fat deposition, establishing a chronic low-grade inflammation causing sarcopenia. The ability of *VM* to abrogate dietary AGE accumulation in muscle and serum tissues of WT mice rescued muscle force, downregulated atrogenes and autophagy-related genes, thus preventing MyHC-II degradation, and restrained WD-dependent body composition changes. Remarkably, WD did not induce sarcopenia in RAGE-null (*Ager*$^{-/-}$) mice. By *in silico* target fishing, potential targets of *VM*'s metabolites underlying its antiglycation properties were identified. Collectively, our data unravel the AGEs/RAGE axis as a determinant mediator of SO and identify a promising natural strategy for inhibiting dietary AGE-associated sarcopenia.

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Preoperative screening for sarcopenic obesity in bariatric surgery: diagnostic challenges

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Introduction: Sarcopenic obesity (SO) may be common among candidates for bariatric surgery (BS) and reflects significant alterations in body composition with potential adverse health outcomes. Accurate identification is essential for timely interventions, and alternative screening methods to dual-energy X-ray absorptiometry (DXA) have been proposed to improve clinical accessibility. This study aimed to determine the prevalence of SO and evaluate the performance of different screening tools.
Methods: In this cross-sectional study, adults scheduled for BS with BMI ≥ 30kg/m² were assessed using the SARC-F questionnaire and two adapted versions of the SARC-CalF, incorporating calf circumference (CC) as either raw or BMI-adjusted. Adjusted CC was obtained by subtracting 7 cm for BMI 30–39 kg/m² and 12 cm for BMI ≥ 40 kg/m². Low CC was defined as ≤ 33 cm for women and ≤34cm for men. Screening was considered positive with SARC-F ≥ 4 or SARC-CalF > 10. SO was confirmed by appendicular lean soft tissue percentage (%ALST) measured by DXA (< 23.47% for women; < 28.27% for men) combined with muscle strength assessed by the five-times-sit-to-stand test (5STS), using sex- and age-specific cut-offs. Sensitivity and specificity of the screening tools were calculated.
Results: Eighty-seven participants were included (87.4% women; mean age 42.0±9.7 years; BMI 46.0±5.8 kg/m²; body fat 50.3±5.2%). Screening positivity was 25.3% with SARC-F and 18.4% with the BMI-adjusted SARC-CalF, while the raw version identified no cases. Reduced ALST and low muscle strength were observed in 82.8% and 56.3% of participants, respectively, yielding an SO prevalence of 47.1%. Sensitivity and specificity were 34.1% and 82.6% for SARC-F and 26.8% and 89.1% for BMI-adjusted SARC-CalF.
Conclusion: SO appears highly prevalent among bariatric surgery candidates, emphasizing the need for preoperative screening. Screening tools showed limited sensitivity, reflecting sample-specific characteristics and cut-off challenges, highlighting the need for improved or complementary screening strategies.

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Distinct microRNA and ANGPTL Signatures in Sarcopenic Obesity Associate with Muscle Loss and Metabolic Dysfunction

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Introduction: Sarcopenic obesity (SO) is a metabolic disorder characterized by reduced skeletal muscle (SM) mass with excess ectopic lipid accumulation, leading to impaired function and increased cardiovascular disease risk. The mechanisms underlying SO remain poorly defined. Angiopoietin-like (ANGPTL) proteins, central regulators of lipid trafficking and energy metabolism, and microRNAs (miRs), key modulators of SM homeostasis and remodelling, may interact to promote SM wasting and metabolic dysregulation in SO. In this study, we characterized the circulating profile of SM-associated miRs and ANGPTL3/4 in patients with SO and explored their relationships with SM mass and clinical metabolic parameters.
Methods: Sixteen patients with SO and 16 obese (Ob) patients were studied. Body composition was estimated using dual-energy X-ray absorptiometry (DEXA), including ASM/BW ratio to diagnose SO. Fasting blood samples were collected to profile miR levels by RT-qPCR and ANGPTL3/4 using ELISA. Associations with ASM/BW, lipid profile, glucose metabolism, and anthropometric parameters were evaluated.
Results: SO patients exhibited significant upregulation of miR-15b (p=0.025) and downregulation of miR-133a (p=0.028) vs Ob. ANGPTL3 tended to be elevated in SO (p=0.060), while ANGPTL4 variedly increased. In SO, miR-206 inversely correlated with ANGPTL3 (r=-0.50, p=0.048). miR-27b was negatively associated with ASM/BW (r=-0.42, p=0.016) and blood glucose (r=-0.43, p=0.016), while miR-181a correlated positively with blood triglycerides (r=0.37, p=0.041). A borderline positive correlation was also observed between miR-206 and arm circumference (r=0.34, p=0.056). ANGPTL3 showed trends for negative correlation with ASM/BW and positive with total cholesterol.
Conclusion: These preliminary results indicate that miRs and ANGPTLs are differentially regulated in SO and associate with muscle depletion and metabolic alterations. The inverse miR-206-ANGPTL3 relationship and miR-27b and miR-181a associations with energy metabolism highlight novel molecular pathways in muscle-metabolic impairment observed in SO. Further investigations are ongoing to validate these findings.

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Unravelling metabolic dysregulation in heart failure with frailty: insights from plasma metabolomics

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Introduction: Altered metabolism is a hallmark of heart failure (HF). The aim of this study was to provide novel findings on how frailty and muscle weakness may alter metabolic pathways in HF, utilizing high throughput plasma metabolomics.
Methods: Frailty was defined by low physical activity combined with reduced handgrip strength and/or 30-second chair stand test, per the EWGSOP2 criteria. Plasma gas chromatography-mass spectrometry was performed to explore metabolic differences among patients with HF and frailty (HF-Frail), patients with HF without frailty (HF-NonFrail), and NonHF (NonHF-Frail and NonHF-NonFrail) controls. Biomarkers (GDF-15, myostatin, activin A, follistatin-3, TNF-α) were measured using ELISA assays. Statistical analyses were conducted via MetaboAnalyst and SPSS.
Results: Twenty-five outpatients with HF (67.9 ± 10.0 years; 19 males, 7 females) and 29 NonHF controls (67.8 ± 11.1 years; 14 males, 15 females) participated in this study. Of 25 patients with HF, 18 were classified as HF-Frail, while out of 29 NonHF controls, 8 were classified as NonHF-Frail. Compared to NonHF-NonFrail, HF-Frail had a lower appendicular lean soft tissue index to body mass index ($p = 0.03$), reduced 6-minute walk distance, timed-up-and-go, 30-second chair stand, and grip strength ($p < 0.05$). Additionally, HF-Frail had higher GDF-15 levels ($p < 0.01$). HF-Frail showed higher glucose, TNF-α, GDF-15, amino acids (e.g., alanine, isoleucine, glutamic acid), and carbohydrate metabolites (e.g., galactose, galacturonic acid-1-phosphate) compared to NonHF controls. Compared to HF-NonFrail, HF-Frail showed lower galacturonic acid-1-phosphate, methionine, indole-3-acetamide, and energy metabolites (e.g., pyruvic acid, malic acid), but elevated 2-hydroxy-glutaric acid ($p < 0.05$), isoleucine ($p = 0.02$), and valine levels ($p < 0.01$).
Conclusions: HF-Frail patients exhibit altered amino acid and carbohydrate metabolism, with elevated TNF-α and GDF-15 compared to HF- and NonHF-NonFrail groups. These findings highlight the potential role in screening for frailty and targeting catabolic signaling as a treatment strategy.

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Circulating microRNA-22-3p as a potential diagnostic tool in patients with primary sarcopenia

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Background: Primary sarcopenia is a progressive, age-related loss of skeletal muscle mass and strength, contributing to increased frailty and reduced survival. Growing attention has focused on molecular biomarkers. In preclinical models, microRNA-22-3p (miR-22), a key regulator of muscle differentiation and function, has been linked to sarcopenia. We aimed to assess the diagnostic potential of miR-22 in patients with primary sarcopenia.
Methods: Circulating miR-22 levels were measured in community-dwelling adults aged ≥70 years with physical frailty enrolled in the evaluator-blinded, randomized controlled trial "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT). Serum levels were quantified using miR-specific TaqMan real-time quantitative polymerase chain reaction (qRT-PCR).
Results: Among 61 participants, sarcopenia was present in 33 (54.1%). Sarcopenic and non-sarcopenic participants were similar in age, sex, BMI, and comorbidities. Patients with sarcopenia had a slower gait speed (0.7 [0.6–0.8] vs 0.8 [0.7–1.0] m/s; $p<0.001$). Serum miR-22 levels were lower in sarcopenic participants (relative CT value 13.5±2.6 vs 11.6±1.9; $p=0.001$). ROC analysis demonstrated that miR-22 discriminated sarcopenic from non-sarcopenic participants (AUC 0.733, 95% CI 0.607–0.859; $p=0.002$), with an optimal CT cut-off of 13.1 yielding moderate sensitivity (60.6%) and high specificity (82.1%). In univariate logistic regression, miR-22 was significantly associated with sarcopenia (OR 0.680, 95% CI 0.525–0.880; $p=0.003$). Multivariate logistic analysis, adjusted for age, BMI, renal function markers (creatinine and urea), heart failure status, and prior cancer, confirmed an independent association between miR-22 (adjusted OR 0.637, 95% CI 0.441–0.920; $p=0.016$) and sarcopenia.
Conclusion: Circulating miR-22 levels are associated with sarcopenia and may serve as a diagnostic biomarker in older adults with sarcopenia and physical frailty.

4-89

Sarcopenia and Hypotension in Heart Failure

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Background: Hypotension is often overlooked in clinical practice and might discourage the uptitration of heart failure (HF) medication. Sarcopenia, the loss of muscle mass and function, has

been linked to orthostatic hypotension, but its association with low resting blood pressure in HF is not well established.
Methods: We conducted a retrospective analysis of 112 male HF patients under 70 years of age. Hypotension was defined as systolic blood pressure (SBP) <100mmHg. Sarcopenia was defined by an appendicular skeletal muscle mass index (ASMI) <7.26 kg/m², assessed via dual-energy X-ray absorptiometry.
Results: Prevalence of hypotension was 13.4% in our cohort. Compared to patients with SBP ≥100 mmHg, hypotensive patients showed no significant differences in mean age (58.7 vs. 60.0 years, p=0.7), HF treatment (ACEi/ARB: 96% vs. 93%, p=0.5; beta-blockers: 91% vs. 93%, p>0.9), or NYHA class III–IV (47% vs. 32%, p=0.26). However, hypotensive patients had significantly lower mean body weight (78.9 vs. 95.1 kg) and BMI (25.5 vs. 30.5 kg/m², both p<0.001). All hypotensive patients had HF with reduced ejection fraction and ASMI values below the cohort median. Sarcopenia was more prevalent among hypotensive patients (33.3% vs. 9.3%, p=0.021), who also exhibited lower mean ASMI (7.6 vs. 8.5 kg/m², p=0.004) and higher median NT-proBNP levels (1088.2 vs. 476.2 pg/mL, p=0.041). In a multivariate linear regression model for ASMI as dependent variable, hypotension remained independently associated with reduced muscle mass (β = -0.69; 95% CI: -1.20 to -0.17; p=0.011), adjusting for age, LVEF, handgrip strength, and iron deficiency.
Conclusion: In male patients with HF under 70 years of age, resting hypotension is associated with lower skeletal muscle mass and a higher prevalence of sarcopenia. Sarcopenic patients often present with hypotension, which might represent an obstacle in the implementation of therapeutic strategies in a cohort of patients that are already at higher risk.

4-90

Quorum Sensing Peptides in Sarcopenia: Insights from iAM373

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Introduction: Sarcopenia is a prevalent and clinically relevant condition, yet the development of predictive biomarkers and effective pharmacological interventions remains limited. Bacterial quorum sensing peptides (QSPs) have recently emerged as bioactive molecules with diverse functions, including potential roles as biomarkers and therapeutic agents in muscle wasting. However, their presence in humans and pharmacodynamic properties are poorly understood.
Methods: In a cohort of 193 older adults, we used LC-MS/MS to determine the plasma concentrations of five QSPs, previously reported to have cellular and/or preclinical effects on muscle wasting: iAM373, CSP-7, PInA, LamD, and CSP-21 [10.1016/j.bbadis.2019.165646; 10.1016/j.bbadis.2024.167094; 10.1002/ctm2.1053]. Concentrations were estimated using maximum likelihood methods for censored data. To further explore iAM373, we investigated its cell-penetrating properties in C2C12 myoblasts using fluorescence microscopy. Mechanistic insights were obtained through assays assessing cellular redox status and related pathways.
Results: All five QSPs were detected in human plasma at concentrations within the pico- to nanomolar range, with estimated mean values ranging between 0.1 and 10 pM. iAM373 exhibited the highest prevalence (12% above LOD). *In vitro*, iAM373 penetrated C2C12 cells and significantly altered the redox balance, suggesting at least a direct intracellular mode of action.
Conclusion: This study demonstrates for the first time that multiple QSPs are present in the circulation of older adults, with iAM373 emerging as the most prevalent. Its ability to enter muscle cells and disrupt redox homeostasis highlights iAM373 as a promising biomarker and effector in sarcopenia pathophysiology.
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5-01

The anti-inflammatory effects and safety of omega-3 fatty acids regarding dose, active ingredients, ratio and source in patients receiving haemodialysis: a systematic review and meta-analysis

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Introduction: There is limited information available on the anti-inflammatory effects and safety profile of omega-3 fatty acid supplementation in patients receiving haemodialysis (HD) regarding eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) dose, content, ratio and source.
Methods: We searched PubMed (n=345), CENTRAL (n=148) and EMBASE (n=706) to July 2025, screened using Covidence reference management software, assessed risk of bias assessed using the Cochrane risk of bias tool (ROB 1) and analysed data using Review Manager version 9.5.1. C-reactive protein (CRP) was the outcome of interest. Pre-planned sub-group analyses included: formulation type, total daily dose, total daily dose of active ingredients and DHA vs. EPA ratio. We combined data in meta-analyses using random-effects models to derive pooled standard mean differences (SMD); I^2 scores were used to assess heterogeneity. A sensitivity analysis was conducted. The protocol is registered with the Open Science Framework (https://doi.org/10.17605/OSF.IO/JCBHN).
Results: Thirteen studies (n=678 participants) were included (n=12 usable for meta-analyses). There were Two studies were judged at overall high risk of bias, one study as unclear risk of bias and the others as low risk of bias. Eight studies did not report adverse events. CRP concentrations were reduced more in the omega-3 fatty acid group than in comparator groups across the triglyceride formulations (SMD -0.62, 95% CI -1.22 to 0.03; P = 0.04, I^2 = 74%); the total daily dose <2000 mg subgroup (SMD -0.32, 95% CI -0.61 to -0.04; P = 0.02, I^2 = 29%) and the <2000 mg active ingredient subgroup (SMD -0.36, 95% CI -0.59 to -0.13; P = 0.003, I^2 = 31%). In sensitivity analyses no significant changes were observed.
Conclusion: Findings indicate that a low dose (under 2000mg) of omega-3 fatty acids in natural triglyceride form appears more effective than synthetic ethyl ester forms for reducing CRP in patients receiving HD.

5-02

glp-1 receptor agonists and skeletal muscle mass preservation: insights from bis monitoring during initial 12-week weight loss course

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Introduction: A 12-week prospective monitoring period, including dietary and exercise interventions with GLP-1 therapy, used non-invasive BIS to guide the patient.
Methods: We prospectively monitored a single patient at home over 12 weeks using bioimpedance spectroscopy (BIS) to assess skeletal muscle mass, fat mass, and total body water. BIS measurements were taken at baseline, then twice daily (am/pm) for 8 weeks; afterward, at least once daily. Clinical parameters including weight, BMI, physical activity, and dietary intake were recorded. Blood Pressure and blood sugar were measured weekly. Primary outcomes were changes in body weight, skeletal muscle mass, fat mass, and total body water.
Results: Home-based BIS monitoring was feasible and well-tolerated. Standardizing measurement times improved consistency and interpretability of body composition trends. Overall weight decreased by 7.49% (6.4 kg). The patient experienced a fat mass reduction of 4.8 kg (3.2% of initial body weight). Skeletal muscle mass was preserved, with a 0.1 kg increase (2% of total body weight). Total body water loss was 1.1 liters (2.5%). BMI decreased from 33.3 to 30.9.
Conclusion: This case report shows home-based BIS monitoring is feasible and informative for tracking body composition during GLP-1 therapy. BIS enabled continuous detection of muscle mass preservation and fat mass reduction. These findings support non-invasive monitoring's role in guiding personalized interventions to mitigate muscle mass loss during pharmacologic weight loss.

5-03

Real-World Impact of Nutritional Support on Hospital Readmissions and Costs in Elderly Patients: Evidence from Brazil's Private Healthcare Sector

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Introduction: Malnutrition is a common condition in hospitalized elderly patients, with a reported prevalence of 35 to 70%. It is associated with frailty, sarcopenia, falls and functional decline, increasing mortality during hospitalization and after discharge.
Our study aimed to analyze the clinical outcomes and cost-effectiveness of oral nutrition supplementation (ONS) in elderly patients who were malnourished at hospital discharge.
Methodology: This is a retrospective study. Nutritional status was evaluated using the Mini Nutritional Assessment (MNA), muscle function and risk of sarcopenia using the SARC-F scale, in addition to weight variation. Elderly patients identified as being at nutritional risk or diagnosed with malnutrition received ONS for a period of 90 days. Outcomes included 30-day hospital readmissions and the economic impact related to the intervention.
Results: Fifteen patients with a mean age of 87.4 years were evaluated, with an average of 4 comorbidities. 53% were malnourished, 47% at risk of malnutrition, 6% had a normal SARC F score, 93% presented a predictive score for sarcopenia. Patients received ONS for 90 days. Paired Wilcoxon tests were performed to compare baseline and final SARC-F, MNA, and weight scores, revealing a statistically significant improvement in SARC-F, indicating a positive effect on muscle function. No hospital readmissions occurred. Based on published data reporting an average 30-day readmission rate of 20% among elderly individuals, we estimated an absolute risk reduction of 20 percentage points (NNT=5). Considering an average cost of BRL32,000 per readmission, the intervention could prevent 200 readmissions per 1,000 elderly individuals, yielding potential savings of BRL6.4 million.
Conclusion: ONS in malnourish elderly patients post discharge demonstrated positive effects on sarcopenia, improved functional outcomes and reduced costs related to hospital readmissions.

5-04

Taste and smell changes and quality of life among ambulatory cancer patients receiving systemic treatment

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Introduction: Taste and smell alterations (TSAs) are common side-effects of anti-cancer treatment and can negatively affect patients' food choices, food intake, nutritional status and quality of life (QoL). This study aimed to assess the prevalence of TSAs and identify associated factors among a cohort of Irish cancer patients.
Methods: n=1,015 patients were enrolled in the SARCONC study– a prospective cohort study conducted at two Irish university teaching hospitals between 2012-2017. The SARCONC study investigated the nutritional status, QoL (EORTC-QLQ-30 validated questionnaire) and treatment outcomes of patients receiving systemic anti-cancer treatment (Ní Bhuachalla et al., 2018; Sullivan et al., 2022). This study is a secondary analysis of the patients recruited from 2015-2017, after which additional survey questions on TSAs were introduced following ethical approval. Quantitative analyses included chi-squared tests, Independent Samples T-tests, and logistic regression models. Statistical significance was determined at $p<0.05$. Qualitative responses underwent qualitative content analysis.
Results: TSA data was available for a total of 292 patients, of which 50.3% reported taste changes and 20.8% reported smell changes. TSAs were significantly more likely to present within symptom clusters, including anorexia, constipation, nausea, dyspnoea and fatigue. 'Metallic'(34.9%) and 'bland'(25.3%) were the most commonly described changes in food taste. Compared to those without taste changes, patients with taste changes were significantly more likely to be female (46.9% vs. 63.3%), have breast cancer (13.1% vs. 29.3%), be receiving Paclitaxel (12.4% vs. 27.2%), and not enjoy prescribed Oral Nutritional Supplements (39.4% vs. 63.2%). Taste changes were associated with lower QoL scores (OR:0.979 [95%CI: 0.967-0.992], p=0.001), and the drug Paclitaxel (OR:2.376 [95%CI: 1.168-4.834], p=0.017), independent of age, sex and cancer type.
Conclusions: TSAs are common and associated with specific demographic, clinical and treatment-related factors, including the drug Paclitaxel. These findings may improve identification of patients at risk and guide targeted nutritional interventions to improve nutritional status and quality of life.

5-05

Leptin as a biomarker for nutritional status in patients with onco-hematological diseases undergoing chemotherapy

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Introduction: In onco-hematological diseases, nutritional and inflammatory changes affect the synthesis of hepatic proteins and the regulation of adipokines, such as leptin. Understanding these interactions may support patient monitoring and the development of nutritional strategies. The project was approved by the Research Ethics Committee under protocol number 7.324.529. This study aimed to investigate the association between leptin, albumin, inflammation, and body composition in patients with hematological malignancies undergoing chemotherapy of different intensities.
Methods: This cross-sectional study included 31 patients (77.4% men and 54.8% obese). The diagnoses comprised acute leukemias (48.4%), multiple myeloma (25.8%), and lymphomas (25.8%). Anthropometric parameters, body composition by bioelectrical impedance spectroscopy, and serum markers (leptin, albumin, and C-reactive protein [CRP]) were also assessed. Correlations were analyzed using Spearman's coefficient, with significance set at $p < 0.05$. **Results:** Leptin levels were positively correlated with albumin levels ($r = 0.38$; $p = 0.05$), suggesting that higher leptin levels are associated with better protein preservation. No significant association was found between leptin and CRP levels ($r = -0.27$; $p = 0.18$). In body composition analysis, leptin correlated positively with phase angle ($r = 0.49$; $p = 0.015$) and reactance ($r = 0.44$; $p = 0.033$), both indicators of cellular integrity. Leptin also showed a strong correlation with the fat mass index ($r = 0.61$; $p = 0.002$), confirming its relationship with adiposity.
Conclusion: In patients with onco-hematological diseases, leptin is associated with fat reserves, albumin, and functional bioimpedance markers, reflecting not only energy balance but also cellular integrity. Elevated leptin levels may indicate unfavorable inflammatory profiles and alterations in body composition, reinforcing its potential as a biomarker for nutritional assessment in the context of intensive chemotherapy.

5-06

The burden of malnutrition in patients with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF): a systematic literature review

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Introduction: Malnutrition is a significant determinant of clinical outcomes in chronic diseases, compromising vitality and accelerating progression to frailty, cachexia and mortality. It is particularly common in individuals with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF). This systematic literature review investigated the burden of malnutrition and its association with clinical outcomes among patients with COPD or IPF.
Methods: Searches were conducted in Embase, Medline, and Cochrane databases for peer-reviewed manuscripts published between January 1, 2020–June 1, 2025. Titles, abstracts and full-texts were screened by one reviewer with 20% independently verified. Studies with ≥50 patients were retained.
Results: Thirty-nine full-texts were screened, of which 14 met eligibility criteria (11 COPD; 3 IPF), encompassing 3489 patients. Eleven different measures of nutritional status were utilized, including fat-free mass index, Geriatric Nutritional Risk Index, Prognostic Nutritional Index (n=2 each) and Controlling Nutritional Status (n=3). Seven different measures were used in 1 study each. Reported outcomes included mortality (all-cause/cardiovascular-related), hospitalization, composite of mortality and hospitalization, length of stay (LOS), activities of daily living, exacerbations, frailty, and disease severity. All-cause mortality was assessed in 7 studies; 6 used multivariable analysis (MVA). Malnutrition was significantly associated with higher mortality in 4/6 MVAs and all univariable analyses (UVAs). Significant associations were also reported for hospitalizations (1/3 MVAs; 2/2 UVAs), exacerbations (1/2 MVAs; 1/2 UVAs), and severity (3/4 UVAs). Malnutrition was associated with higher mortality (all-cause/cardiovascular-related), hospitalization, composite of mortality and hospitalization, and hospital LOS in all studies assessing these outcomes. In all studies, malnutrition was statistically significantly associated with ≥1 adverse outcome.
Conclusions: In COPD and IPF, malnutrition is consistently associated with higher mortality, greater healthcare utilization, and worsening disease severity. These findings highlight the need to systematically assess and address malnutrition as a modifiable determinant of vitality in the management of chronic disorders.
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5-07

Territorial differences in vitamin d status and gait performance among chilean older people: a multi-regional analysis across 30 degrees of latitude

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Background: Chile's extreme latitudinal range (17°S to 53°S) provides a natural laboratory for examining how geographic factors influence vitamin D synthesis and functional outcomes in older adults. This study investigated relationships between territorial context, 25(OH)D concentrations, gait speed, and dietary patterns across three distinct Chilean regions.
Methods: A cross-sectional analysis included 208 community-dwelling adults aged 60–90 years from North 23.65°S (n=51), Center-South 33.46°S (n=84), and South-Austral 53.15°S (n=73) regions. Comprehensive geriatric assessment incorporated multidimensional questionnaires, functional performance testing (gait speed, handgrip dynamometry, TUG, SPPB), serum 25(OH)D measurement, and detailed dietary frequency analysis. Statistical analysis employed ANOVA and post-hoc comparisons.
Results: Center-South participants demonstrated significantly superior gait speed (1.1±0.3 vs 0.7±0.4 and 0.7±0.3 m/s, $p<0.001$) and higher 25(OH)D concentrations (35.6±9.2 vs 22.0±6.8 and 19.1±9.4 ng/ml, $p<0.01$) compared to North and South-Austral regions. Dietary analysis revealed South-Austral participants consumed significantly more bread (68.0±1.8 vs 40.0±1.1 and 48.0±2.0s g/day, $p<0.001$) and meat products (25.2±1.2 vs 19.4±0.9 and 15.0±2 g/day, $p<0.01$) than North and Center-South respectively, while maintaining suboptimal fruit and vegetable intake across all territories. Despite these regional variations in gait speed and vitamin D status, no significant differences emerged in

handgrip strength, TUG performance, or SPPB scores between regions.
Conclusions: This latitude-dependent study demonstrates that Center-South Chilean older adults exhibit optimal functional and biochemical outcomes despite similar multidimensional performance measures across regions. The distinct dietary pattern in South-Austral regions, characterized by elevated bread and meat consumption, may contribute to differential health outcomes. These findings underscore the importance of latitude-specific interventions addressing both vitamin D optimization and culturally-adapted dietary modifications in aging populations across diverse geographic territories.

5-08

Optimising amino acid availability in older adults: contrasting the effects of essential amino acid supplementation and a standard protein-content breakfast in a randomised crossover trial

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Background: Older adults often fail to meet protein recommendations, contributing to muscle loss and sarcopenia. Essential amino acids (EAAs) stimulate muscle protein synthesis with minimal appetite suppression, offering a practical strategy to support muscle health. However, poor palatability can limit adherence. This study compared plasma amino acid responses and palatability of two EAA supplements versus a standard protein-content breakfast placebo.
Methods: In a randomised, placebo-controlled, crossover trial, ten older adults consumed one of three supplements (Gel A, Gel B, or an isocaloric placebo) before a standardised breakfast containing ~10 g protein. Gel A and Gel B both provided 7.5 g EAAs with differing relative compositions. Plasma amino acids were measured at baseline, 15 min, and every 30 min for 3 h using LC-MS/MS. Palatability, appetite, and food preference were assessed by visual analogue scales. Repeated measures ANOVA evaluated condition, time, and interaction effects; AUC analyses compared total and individual amino acid availability.
Results: The standard breakfast placebo produced only a modest plasma EAA rise (+19%), insufficient to sustain levels above baseline. In contrast, both Gel A and Gel B rapidly increased plasma EAAs and BCAAs within 15 min (all $p < 0.001$), with concentrations elevated by 102–108% above baseline. AUC analyses confirmed greater EAA and BCAA exposure with both supplements ($p < 0.001$). Palatability ratings showed Gel B was significantly less acceptable than placebo ($p = 0.018$), whereas Gel A did not differ.
Conclusions: A standard protein-content breakfast produced negligible changes in plasma amino acid availability, highlighting the limitations of typical diets in older adults. In contrast, EAA supplementation enhanced availability, with Gel A providing better palatability. These findings support tailored EAA supplementation as a practical strategy to overcome dietary protein gaps, improve adherence, and help prevent sarcopenia.

5-09

Optimising Patient Treatment with Immuno-Nutrition: A Study Protocol Evaluating the Impact of an Omega-3-Enriched Nutritional Supplement in Cancer Patients at Risk of Malnutrition

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Background: Cancer cachexia is a complex, progressive and clinically significant syndrome. It is characterised by involuntary weight loss, skeletal muscle wasting, and systemic inflammation. It impairs treatment tolerance, physical function, and quality of life in patients with advanced malignancy. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may help modulate inflammation and preserve lean body mass. Growing evidence supports the potential of targeted nutritional therapies to enhance patient outcomes.
Objective: This study aims to evaluate the impact of an Omega-3-Enriched Nutritional Supplement on nutritional status in cancer patients at risk of malnutrition.
Methods: This is a multicentre, randomised controlled, open-label trial. We will recruit adults at nutritional risk with lung or colorectal cancer (stage III–IV cancer receiving treatment with non-curative intent) and systemic inflammation. Once eligibility is confirmed and informed consent obtained, participants will be randomised in a 1:1 ratio, with stratification by study centre and modified Glasgow Prognostic Score (mGPS 1 or 2). The intervention group will receive dietary counselling plus two daily servings of FFS for eight weeks. The control group will receive dietary counselling in line with standard clinical care, with standard oral nutritional supplements (ONS) provided only if clinically indicated by the treating dietitian. Outcomes will be assessed at baseline (pre-randomisation), midpoint (week 4), and end of study (week 8). The primary outcome will be change in body weight (kg). Secondary outcomes include nutritional status (PG-SGA SF), quality of life (EORTC QLQ-C30), physical activity (step count), and inflammatory status (biochemical markers). Lean body mass will be assessed via bioimpedance analysis. These outcomes will be analysed using multiple or multilevel regression models. A sample size of 118 was calculated to detect a 2 kg difference in body weight with 90% power and a 5% significance level. This study is funded by Danone Global Research.
Conclusion: This trial is among the few RCTs in cancer cachexia to integrate EPA-enriched supplementation with specialist dietetic input. By evaluating nutritional, functional, and inflammatory outcomes, it aims to generate new insights into multimodal strategies for managing cancer-associated weight loss and systemic inflammation.

5-10

Effects of nutrition combined with exercise on inflammation and muscle damage in older adults: systematic review and meta-analysis

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Introduction: This systematic review and meta-analysis evaluates the additional effect of nutritional interventions to exercise on biomarkers of inflammation and muscle damage in older adults above 65 years.
Methods: Pubmed, Embase and Web of Science were evaluated, and 30 studies were included. A random-effects meta-analysis was performed on inflammatory and muscle damage biomarkers, to compare the effect of exercise plus diet with exercise alone.
Results: Exercise interventions consisted of walking, resistance training, aerobic, combined, or multicomponent exercise, and duration varied from one single exercise session to 18 months. The nutritional interventions consisted of caloric restriction, protein supplementation, multi-nutrient protein based drinks, soy milk, omega-3 fatty acid rich healthy diet, omega-3 fatty acid supplementation, milk fat globule membrane supplementation, creatine supplementation, L-carnitine and leucine supplementation, fungus-derived exopolymer supplementation, and vitamin C, D, or E supplementation. Meta-analysis could be conducted for caloric restriction, protein supplementation, and omega-3 fatty acid supplementation. A reduction in circulating basal IL-6 compared to the exercise condition only was observed in studies with caloric restriction in addition to aerobic or combined aerobic and resistance exercise (MD: -0.53 pg/ml; 95% CI: [-0.90, -0.16]). Omega-3 fatty acid supplementation in addition to resistance exercise did not reduce IL-6 (MD: -0.25 pg/ml; 95% CI: [-0.53, 0.03]) or TNF-a (MD: 0.07 pg/ml; 95% CI: [-0.45, 0.60]) compared to exercise alone. Muscle soreness decreased (MD: -0.50; 95% CI: [-0.67, -0.33]) upon protein supplementation during a long-distance walking program, compared to the exercise condition only, while we did not find an effect on creatine kinase (MD: -87.2 U/L; 95% CI: [-274.3, 99.9]).
Conclusions: Caloric restriction in addition to aerobic or combined exercise reduced circulating basal pro-inflammatory cytokine IL-6 in older adults, compared to exercise alone. Protein supplementation reduced muscle soreness upon prolonged walking exercise, while there was no effect on muscle damage biomarker creatine kinase.

6-01

Gait speed and associations with muscular imbalance in community dwelling older adults

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Introduction: Muscular imbalance (MI) between the left and right sides of the body is common in older adults. The aim of the study was to investigate associations between MI, muscular strength and physical function in older adults.
Methods: A cross-sectional study was conducted in 73 community dwelling older adults (65.8% women, 82±6 years, BMI=28.2±5.7, SPPB = 8.6±2.4) who used day-care services provided by the nursing homes. Bioelectrical Impedance Analysis (BIA) was used to measure body composition and MI in the lower limbs. Physical function was assessed using the short physical performance battery (SPPB).
Results: The mean skeletal muscle mass per leg was 3.6±1.2 kg in women and 5.0±1.2kg in men. More than 70% of the participants had an asymmetry greater than 100 g and the mean MI between legs was 0.27±0.32kg with a range from 0.02 to 1.81 kg. In a gender and age adjusted analysis, MI was associated with lower SPPB (B=-0.32 per 0.1 kg MI, P=0.001). Additional adjustment for cognitive function, BMI, medication did only marginally change the observed associations. Further statistical correction for physical activity reduced the strength of the association by around 25% but was still significant (B=-0.25 per 0.1 kg MI; P=0.11). Within the three components of SPPB (balance, chair raise test, gait speed), MI was mainly related to chair raise test and gait speed, but nor balance.
Conclusions: Muscular imbalance is frequently observed in older adults who use day-care services provided by nursing homes. This is related to poorer physical function, mainly to lower gait speed and poorer performance on the chair raise test. It seems that this lower physical function is only partly associated with a lower physical activity of participants with MI and our results indicate that older adults with muscular imbalance might benefit from specific training to correct the imbalance.
Conflict of Interest: None Disclosed.
Funding: No funding to report.

6-02

Selfperception of health and short physical performance battery in Icelandic older adults.

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Introduction: Self-rated health (SRH) in older adults is a widely used subjective measure that reflects an individual's perception of overall health. It serves as a reliable predictor of various health outcomes. The aim of the study was to investigate the relation between physical activity, physical function and SRH in pre-frail older adults.
Methods: A cross-sectional study was conducted in 73 community dwelling older adults (65.8% women, 82±6 years, SPPB = 8.6±2.4, SRH=70±21) who frequently used day-care services provided by the nursing homes in Reykjavik, Iceland. Physical function was assessed using the short physical performance battery (SPPB) protocol, cognitive function was assessed using MMSE. Questionnaires were used to assess SRH (score from 0-100) and general characteristics of the participants.
Results: Participants in the lower half of SRH (score: 53±15) were older (85±6 vs. 80±6 years, P=0.001), had a lower SPPB score (7.6±2.8 vs. 9.1±2.2, P=0.013) and tended to be less physically active (2.7±3.1 vs 3.5±2.8 hours/week, P=0.065) when compared to participants in the upper half of SRH (score: 87±9). Gender distribution, number of medication, cognitive function and BMI were similar between the groups. According to age and gender adjusted analysis, SPPB remained associated with SRH (B=3.0, P=0.001). Further adjustment for medication, cognitive function and BMI attenuated this association although SPPB remained significant (B=2.1; P=0.040). Physical activity was also associated with SRH (B=1.62 per hour/week, P=0.046), however not independently from physical function.
Conclusions: In our cross-sectional study in older pre-frail Icelandic adults, physical activity and in particular physical function were related to SRH. Although the study design does not allow to define the direction of a given association, it seems feasible to pay attention to the maintenance or improvement of physical function in consideration of SRH in this age group.
Conflict of Interest: None Disclosed.
Funding: No funding to report.

6-03

Aerobic exercise effect of belt electrode skeletal muscle electrical stimulation assessed by lower-limb muscle oxygenation

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Introduction: In patients with sarcopenia or cachexia, muscle atrophy and functional decline often limit the ability to perform adequate voluntary exercise. Neuromuscular electrical stimulation has been investigated as an alternative intervention; however, its capacity to induce aerobic metabolic responses is not well established. This study aimed to examine the physiological effects of belt electrode skeletal muscle electrical stimulation (B-SES), which enables simultaneous stimulation of extensive regions of the lower-limb muscles, as a localized aerobic exercise in the supine position.
Methods: Twelve healthy male adults participated in this study. Belt electrodes were placed around the waist, distal thighs, and distal lower legs. After 10 minutes of rest, B-SES was applied at 4 Hz for 20 minutes. Stimulation intensity was adjusted to elicit maximal visible contractions without exceeding a Wong-Baker FACES pain score of 2. Blood pressure and heart rate changes from baseline were recorded, subjective lower-limb fatigue was assessed using the Borg scale, and tissue oxygenation of the rectus femoris (StO_2, oxy-Hb, deoxy-Hb, and total-Hb) was measured using near-infrared spectroscopy.
Results: No significant changes in blood pressure were observed, whereas heart rate increased and Borg scores increased to 13–14 ("somewhat hard") during B-SES. Tissue oxygen saturation (StO_2) of the rectus femoris significantly decreased during stimulation. Oxy-Hb transiently declined immediately after the onset of B-SES and subsequently recovered, while both deoxy-Hb and total-Hb progressively increased.
Conclusions: B-SES elicited circulatory and metabolic responses characterized by increased oxygen demand and aerobic energy metabolism in the lower-limb muscles, even in the supine position. These findings support the feasibility of B-SES as a novel adjunctive exercise modality for patients with sarcopenia or cachexia who are unable to perform sufficient voluntary exercise.

6-04

Progressive Resistance Exercises in Older Adults with Sarcopenia

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Introduction: Aging leads to a reduction in muscle mass, strength, and functionality, worsening sarcopenia, especially in stabilizing muscles and lower limbs. This study evaluated the impact of progressive resistance training in older adults with sarcopenia.
Methods: This quasi-experimental study involved participants (≥65 years) with sarcopenia who underwent fourteen sessions of progressive resistance training, performed twice a week, each lasting 40 minutes. Balance, gait speed, functional performance, and muscle strength were assessed before and after the intervention. Exercises included partial squats, knee extension and flexion, active bridge with isometric adduction, hip abduction with elastic bands, and sit-to-stand, all with gradual load progression. Statistical analysis included normality tests, paired t-test, and chi-square, with $p<0.05$ considered significant.
Results: Of the 50 participants, 20 completed the study. At baseline, 25% showed signs of sarcopenia (SARC-F+CC), reduced to 10% after the intervention. Regarding handgrip strength, before training, 50% were classified as normal, 20% intermediate, and 30% weak; after the program, proportions shifted to 65%, 30%, and 5%, respectively. Improvements were observed in gait speed and the Timed Up and Go (TUG) test, with the proportion of participants within normal parameters increasing from 15% to 40%, though not statistically significant. Significant improvements were found in quadriceps strength (right: from 15±7 to 18±8 kg; left: from 16±8 to 19±9 kg), hamstrings (right: from 9±4 to 11±4 kg; left: from 8±4 to 10±4 kg), and gluteal muscles (right: from 7±3 to 9±4 kg; left: from 8±3 to 10±4 kg) when comparing pre- and post-training values ($p<0.05$).
Conclusion: Progressive resistance training reduced signs of sarcopenia and significantly improved lower limb strength and handgrip strength, proving effective in enhancing strength and functionality in older adults with sarcopenia.

6-05

Resistance exercise intervention restores functional capacity and reverses frailty biomarkers in centenarians

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Introduction: Centenarians comprise an age group characterized by exceptional longevity and low age-associated pathologies. However, they still experience physiological decline, and different studies have linked frailty to this population. Exercise interventions reverse frailty and improve functional capacity. No studies addressed the effect of an intervention in centenarians. In this study, we assessed the impact of a 12-week resistance exercise intervention in a group of centenarians, examining their functional capacity and the expression of molecular frailty-associated biomarkers.
Methods: 19 centenarians were enrolled but 7 of them did not complete the study. The remaining 12 centenarians were randomly assigned to control or intervention group, which was a 12-week resistance exercise intervention. Molecular biomarkers were measured by qRT-PCR and ELISA.
Results: The intervention group improved their functional capacity measured by Short Physical Performance Battery (SPPB) (post 5.0 vs 2.3 in pre) and Physical Performance and Mobility Examination (PPME) (6.5 vs 3.8), as well as in frailty status studied by Fried Frailty Phenotype (FP) (3.0 vs 3.8), and Frailty Trait Scale 5 (FTS5) (30.7 vs 34.0) scales. ANCOVA revealed that the training led to significant improvements in SPPB ($p=0.01$) and PPME ($p<0.001$) scores, FP ($p=0.001$), and FTS5 ($p=0.05$). Frailty-related biomarkers (EGR1, miR194-5p, miR125b-5p, miR454-3p) and inflammation (IL-6, IL-1β) showed different expression patterns in centenarians (n=19) compared to both old (n=44, average of 79-year-old) and young adult (n=34, average of 29-year-old) groups. Notably, the intervention was associated with improvements in frailty and inflammation biomarkers expression. Finally, Correlation analyses showed significant associations between all functional and frailty variables, with SPPB correlating with miR454-3p ($p=0.73$ *), and FTS5 correlating with miR454-3p ($p=-0.83$ **), IL-6 ($p=0.60$ ≠), and miR125b-5p ($p=-0.55$ ≠).
Conclusions: Our results revealed that resistance exercise intervention enhances functional status and reduces frailty in centenarians and this is associated with improvements in frailty and inflammation biomarkers.

6-06

Association between cardiovascular health metrics and self-reported walking difficulty in community-dwelling middle-aged and older adults: results from the Longevity Check-up 8+

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Introduction: Mobility is a cornerstone of functional independence and healthy aging. Evidence suggests that self-reported walking difficulty may precede measurable functional decline, serving as a pragmatic early indicator when direct assessments are not feasible. Maintaining optimal cardiovascular health may also yield benefits beyond the cardiovascular system, supporting overall health and autonomy. This cross-sectional study explored the association between cardiovascular health, assessed through an 8-factor cardiovascular health (8F–CVH) score inspired by Life's Essential 8, and self-reported walking difficulty in community-dwelling middle-aged (40–64 years) and older adults (≥65 years).
Methods: Cardiovascular health was quantified through a composite score (range 0–100) comprising diet, physical activity, body mass index, blood pressure, total cholesterol, blood glucose, smoking, and sleep quality. Walking difficulty was evaluated using a single-item question: "Do you have any difficulty walking 400 meters?", and categorized dichotomously.
Results: Of 7372 participants (mean age 60.2 ± 11.3 years; 53.3% women), 15.8% reported walking difficulty, with prevalence rising from 10.5% in middle-aged adults to 26.1% in older adults (p for trend <0.001). Walking difficulty was reported by 31.4% of participants with low 8F–CVH scores, compared to 14.1% with moderate and 4.8% with high scores (p <0.001). Receiver operating curve analysis showed modest discrimination for the total score [area under the curve (AUC) 0.68; 95% CI 0.66–0.70], with physical activity yielding the highest AUC (0.71; 95% CI 0.69–0.72). In multivariable models adjusted for age, sex, low muscle mass, and dynapenia, moderate and high CVH scores were associated with 60% [odds ratio (OR) 0.40, 95% CI 0.33–0.47] and 84% (OR 0.16, 95% CI 0.11–0.22) lower odds of walking difficulty, respectively.
Conclusions: Higher cardiovascular health is independently associated with lower odds of self-reported walking difficulty. Supporting cardiovascular health may represent a valuable strategy to preserve mobility and delay functional decline.

6-07

Body composition abnormalities and their association with physical function in patients with idiopathic pulmonary fibrosis

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Introduction: A comprehensive evaluation of the full spectrum of body composition abnormalities (including lean soft tissue and bone mineral density) in patients with idiopathic pulmonary fibrosis (IPF), a relatively rare pulmonary disease, is lacking, particularly in relation to their impact on physical function and their overlap with obesity. We aimed to investigate the frequency of body composition abnormalities in patients with IPF and their impact on exercise capacity and muscle strength.
Methods: Patients with IPF underwent lung function testing, dual-energy X-ray absorptiometry for body composition assessment, six-minute walk testing (6MWT) for exercise capacity, and isokinetic dynamometry for quadriceps peak torque (PT). Overweight or obesity was defined by body mass index (BMI) >25kg/m^2. Body composition abnormalities included: osteopenia or osteoporosis classified by vertebral fractures or low T-scores and low lean soft tissue index (LSTI) defined as <10th percentile of sex-age-BMI-specific reference values.
Results: 224 patients were included (137 males, age: 67 [59–73] years, FVC: 80±23 %predicted, DLCO: 40[31-53] %predicted). Sixty-two patients (28%) had overweight/obesity, 7 (3%) had low LSTI, and 35 (16%) had osteopenia/osteoporosis. The overlap between low LSTI and overweight/obesity was observed in 14 (6%) patients, between low LSTI and osteopenia/osteoporosis in 13 (6%) patients, and between osteopenia/osteoporosis and overweight/obesity in 49 (22%) patients. Twenty-eight patients (13%) presented a triple overlap, while the remaining 16 (7%) had no abnormalities. Patients with low LSTI (-80 m; 95%CI: -147 to -12) and low LSTI associated with overweight/obesity (-65 m; 95%CI: -118 to -12) had lower 6MWD vs. patients with normal BMI and normal LSTI. Patients with low LSTI and osteopenia/osteoporosis had lower quadriceps PT (-26 Nm; 95%CI: -44 to -6) vs normal LSTI and no osteopenia/osteoporosis.
Conclusion: Body composition abnormalities were common in IPF and frequently overlapped. Low LSTI was consistently associated with reduced exercise capacity and muscle strength in this population.

6-08

Resistance training and protein supplementation during first-line chemotherapy in patients with incurable gastroesophageal cancer: a randomized feasibility trial

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Introduction: Cancer cachexia is associated with reduced physical performance, quality of life, and survival in patients with incurable gastroesophageal cancer. Resistance training and protein supplementation have the potential to improve these outcomes. Whether an intervention comprising resistance training and protein supplementation is feasible during treatment for incurable gastroesophageal cancer is not known.
Methods: Patients with incurable gastroesophageal cancer scheduled to undergo first-line chemotherapy were randomized 2:1 to resistance training three times per week and daily protein supplementation or to control. The primary outcome was feasibility assessed by recruitment, retention, adherence, and harms.

Secondary outcomes included body composition, physical performance, quality of life, and treatment tolerability.
Results: Out of 106 potentially eligible patients, 20 participants (5 women and 15 men, mean age 65) were randomized yielding a recruitment rate of 19%. 18 participants completed the trial with a retention rate of 90%. Median adherence to the resistance training sessions and to the protein supplements was 63% and 39%, respectively. Five participants (38%) met the minimum feasibility criteria of both interventions. No serious adverse events related to the intervention occurred. We found no between-group differences in body composition, physical performance, quality of life, or treatment tolerability.
Conclusions: Resistance training with protein supplementation was not feasible during first-line chemotherapy in patients with incurable gastroesophageal cancer due to low accrual.

6-09

Associations of long-term physical activity levels with sarcopenia in older adults: the HUNT study

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Background: Previous research has shown a protective effect of physical activity (PA) on sarcopenia; however, most studies have been cross-sectional. How long-term PA levels affect the likelihood of sarcopenia in old age remains unknown. Thus, this study aimed to investigate the association between PA levels measured over 20+ years and the odds of sarcopenia.
Methods: This longitudinal cohort study included 4702 individuals (76.4 ± 5.0 years, 53% females) participating in the 70+ sub-study of the fourth wave of the Trøndelag Health Study (HUNT4 70+), with PA data from the three earlier waves (HUNT1-3). Participants were classified as active or inactive for each respective timepoint (HUNT1-3) according to current PA guidelines. Sarcopenia at HUNT4 was defined as probable (low strength) or confirmed (low strength and muscle mass) based on European Working Group on Sarcopenia (EWGSOP2) criteria. We conducted a logistic regression analysis to examine the association of the number of active timepoints with the odds of sarcopenia.
Results: We observed a significant inverse dose-response relationship between the number of active timepoints and sarcopenia. The association was stronger for confirmed versus probable sarcopenia. Compared with persistently inactive participants, those active at all three timepoints had a 78% reduction in the odds of confirmed sarcopenia (OR 0.22, 95% CI: 0.08-0.65). Being active at two timepoints was associated with 36% lower odds (OR 0.64, 0.42-0.99) and being active at one timepoint with a 30% reduction (OR 0.70, 0.52-0.94).
Conclusion: This study demonstrates a clear inverse dose-response relationship between the number of active timepoints and the odds of sarcopenia, with stronger associations for confirmed versus probable sarcopenia. Our findings underscore the importance of sustained long-term PA to reduce the odds of sarcopenia after age 70.

6-10

Low-density lipoprotein cholesterol levels and exercise capacity in patients with chronic heart failure: Findings from the BIOSTAT-CHF study

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Introduction: Lipid-lowering strategies are well-established in atherosclerotic cardiovascular disease. However, their clinical implications in heart failure (HF) remain unclear. Moreover, cholesterol is an integral component of skeletal muscle and serves as a surrogate of nutritional, inflammatory, and immune status. This study aimed to investigate the association between low-density lipoprotein cholesterol (LDL-C) levels and exercise capacity in patients with chronic HF.
Methods: We included 746 patients with chronic HF (67±12 years, 77% male) from the BIOSTAT-CHF index cohort who had available lipid profiles and 6-minute walk distance (6MWD) data. Low exercise capacity was defined as the lowest tertile of 6MWD (<255 m). To examine the dose-response relationship between LDL-C and exercise capacity, LDL-C levels were stratified into septiles (<60, 60-76, 77-91, 92-106, 107-121, 122–142, ≥143 mg/dL).
Results: Patients with low exercise capacity had worse clinical profiles and lower LDL-C levels compared to those with high exercise capacity (85 vs. 105 mg/dL, p<0.0001). In multivariable analysis adjusted for clinically relevant factors including inflammation and albumin, lower LDL-C was independently associated with low exercise capacity (adjusted odds ratio (aOR) 1.28 per 1 SD decrease, p=0.02). 6MWD differed significantly across septile groups (p<0.0001), being lowest in the 1st septile group (240 m) and highest in the 7th septile group (349 m). The risk of low exercise capacity reached its minimum in the 5th septile group, whereas the 1st and 2nd septiles showed significantly higher ORs (aOR 3.46, p=0.002; aOR 2.65, p=0.01), suggesting a potential threshold effect between LDL-C levels and exercise capacity.
Conclusions: In patients with chronic HF, lower LDL-C levels were significantly associated with reduced exercise capacity. LDL-C may reflect pathophysiological mechanisms contributing to impaired exercise capacity beyond its role as a surrogate of nutrition or inflammation.
models can support clinical decision-making and guide early interventions to reduce HAD.

6-11

Effects of 4 weeks of multimodal prehabilitation on physical performance in head and neck cancer patients: preliminary results from a multicenter prospective trial

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Introduction: Oncological prehabilitation, positioned between cancer diagnosis and start of treatments, optimizes physical,

nutritional, and psychological status to reduce complications, improve tolerance to therapy, and enhance quality of life. While evidence in some surgical settings is strong, data in head and neck cancer (HNC) remain limited. The primary aim of the study is to assess the feasibility of multimodal prehabilitation. The efficacy of the intervention on physical performance is a secondary outcome.
Methods: The study is a prospective, multicenter, non-randomized clinical trial. Patients with stage III and IV (AJCC VII ed) HNC and candidated to multimodal treatment are recruited. After baseline assessment, patients engage in 4-week prehabilitation program, composed of both supervised (3/week, 1hour each) and unsupervised (3/week, 30min each) training sessions. Handgrip test (HG), and isometric knee extension torque (MVIT) are used to evaluate muscle strength. Aerobic fitness level is estimated by Ekblom-Bak test (EB). Exercise performance is tested by sit-to-stand (STS), timed up-and-go (TUG), and 6-minute walk test (6MWT). All tests are performed before and after prehabilitation, at the end of treatments and at 6-month follow-up. Statistical analyses were performed using repeated measures ANOVA.
Results: Among the 60 participants planned, preliminary data refer to eight male patients who completed the treatments (age=64.75±9.15years; height=1.72±0.06m; weight=72.3±7.0kg; BMI=24.56±2.87kg*m^{-2}). Attendance rate of the scheduled sessions was 73%. No adverse events were reported. At baseline, HG was 387.0±49.5N, MVIT was 123.8±13.7Nm, $\dot{V}O_2$peak from EB was 24.1±5.9ml*(kg*min)$^{-1}$. STS resulted in 13.9±1.8reps. TUG was 5.88±0.52s. During 6MWT patients covered 470.1±37.6m. A significant effect of time was observed for STS and TUG tests, with the latter worsening after treatments compared both with baseline and post-prehabilitation values.
Conclusion: Preliminary data show that oncological prehabilitation is safe and feasible. Despite the decline in exercise performance after treatments, four-week prehabilitation seems effective in maintaining strength and aerobic fitness.

6-12

Enhancing adherence and affective response to resistance training in females: a scoping review of strategies and protocols with implications for sarcopenia prevention

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Introduction: Resistance training (RT) confers significant health benefits, yet global female participation (14–25%) remains lower than male participation (18–34%). Barriers include confidence, access, and perceptions of RT as a masculine domain. This is particularly concerning given the role of RT in mitigating sarcopenia, muscle wasting, and age-related functional decline. This scoping review synthesised protocols and strategies designed to improve adherence and affective response to RT in adult and older females.
Methods: Following PRISMA-ScR guidelines, a protocol was registered on the Open Science Framework. PubMed, Scopus, and EBSCO databases were searched to August 2025. Eighty-five eligible studies were included. Data on adherence, affective response, supervision, intensity, and motivational strategies were charted and synthesised thematically.
Results: Over 75% of fully supervised interventions reported high adherence (>71%), typically in programmes lasting 2-3 months. Mixed supervision models sustained moderate adherence (51–70%) in longer interventions (>12 months). Unsupervised formats showed variable adherence but improved when combined with app-based support, reminders, follow-ups, or transtheoretical model (TTM)-based strategies. Moderate-to-high intensity RT (55–85% 1RM) was generally associated with higher adherence and more positive emotional responses, across age groups and populations. Non-conventional RT formats (functional, circuit, dyadic, Pilates, Tabata) yielded comparable adherence and affective outcomes to traditional protocols, supporting flexible, preference-based design. Considerable heterogeneity in how adherence and affect were defined highlighted the lack of standardised measures.
Conclusions: Supervision, behavioural support, and moderate-to-high intensity protocols appear central to sustaining adherence and enjoyment of RT in females. Flexible and non-conventional formats provide viable, personalised alternatives. Future research must prioritise standardised, theory-informed frameworks to evaluate adherence and affective response. These insights are directly relevant for designing interventions to prevent or manage sarcopenia and muscle wasting in females across the lifespan. To aid translation, a practitioner decision-support tool was developed from the findings.

6-13

Iron Deficiency and Impaired Skeletal Muscle Functional Capacity in Patients with ME/CFS

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Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is characterized by profound fatigue, post-exertional malaise, and muscular weakness. Cellular iron metabolism plays a crucial role in oxygen transport and mitochondrial energy production. Disturbances in iron homeostasis may therefore contribute to the impaired skeletal muscle metabolism observed in ME/CFS.
Patients and Methods: In this observational study, 79 patients with ME/CFS (74% female, mean age 43 ± 12 years, BMI 22.8 ± 4.4 kg/m², mean disease duration 7 years) were included at Charité – Universitätsmedizin Berlin. Iron deficiency (ID) was defined as ferritin < 100 µg/l, or ferritin 100–299 µg/l with TSAT < 20%. Clinical parameters and fatigue severity (Beel score) were assessed in all participants. In a sub-cohort (N = 12), quadriceps femoris muscle strength and fatigability was evaluated using a standardized fatigue protocol and compared with healthy controls (N = 8).
Results: Of the patients with ME/CFS, 73% demonstrated evidence of ID. Patients with ID presented more frequently with postural orthostatic tachycardia syndrome (POTS) compared to those without ID (16 % vs. 5 %, n.s.). Patients with ID had a shorter disease duration compared with non-deficient patients (median 4 vs. 9.5 years, $p < 0.05$). In the quadriceps muscle fatigue protocol, a significant advanced fatigability was observed in ME/CFS patients compared with controls (Fig. 1).
Discussion: Our findings indicate that iron deficiency is very common in ME/CFS and may be associated with impaired muscle function. Identifying and correcting iron deficiency could represent a targeted therapeutic approach to improve skeletal muscle energy metabolism and clinical outcomes in affected patients.

7-01

Low-magnitude high-frequency vibration combined with β-hydroxy-β-methylbutyrate treatment prevents neuromuscular junction degeneration in age-related sarcopenia

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Introduction: Sarcopenia is a progressive age-related condition marked by loss of muscle mass and strength. Degeneration of the neuromuscular junction (NMJ) plays a central role in its progression. This study aims to evaluate the combined effect of low-magnitude high-frequency vibration (LMHFV) and β-hydroxy-β-methylbutyrate (HMB) treatment in attenuating sarcopenia.
Methods: Sixty male senescence accelerated (SAMP8) mice (6 months old) were randomly assigned to four groups: control (CTL), LMHFV (35 Hz, 0.3 g, 20 min/day, 5 days/week), HMB (500 mg/kg/day), and combined treatment (COM). After 2 and 4 months of intervention, assessments included grip strength, *ex vivo* muscle force, and body composition. Histological analyses evaluated muscle fiber-typing and lipid infiltration. NMJ morphology was examined by whole-mount immunostaining. Mitochondrial ultrastructure was examined via transmission electron microscopy. Expression of NMJ-associated genes and Wnt signaling components was evaluated by qPCR and Western blot. Mechanistic studies included intramuscular injection of AAV9-siRNA-Wnt10b and rescue with recombinant Wnt10b protein.
Results: COM treatment significantly improved muscle mass and contractile force compared to control group. Fast-twitch fiber proportion increased, while lipid accumulation decreased in treatment groups. More importantly, the combination treatment preserved NMJ with reduced structural fragmentation and improved synaptic integrity. Mitochondrial morphology was maintained, and ATP production was elevated in treatment groups. Molecularly, the combination treatment upregulated Dok7 and Rapsyn expression, enhanced MuSK phosphorylation, and activated Wnt10b signaling while suppressing its inhibitors. Wnt10b knockdown impaired NMJ structure and muscle function, whereas recombinant Wnt10b recured these degenerations.
Conclusions: The LMHFV and HMB combination offers a synergistic, non-invasive strategy to combat sarcopenia by preserving NMJ function through Wnt10b-mediated signaling. This intervention enhances muscle quality, bioenergetics, and neuromuscular transmission. These findings support its translational potential for clinical management of sarcopenia.
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7-04

Deciphering the role of vasculature in cancer cachexia

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Introduction: Cancer cachexia is characterized by weight loss, muscle atrophy and inflammation. While anabolic approaches such as the ActRII antibody bimagrumab have shown promise in promoting muscle growth, recent findings highlight the vasculature as a key regulator of cachexia. Endothelial dysfunction was recently demonstrated to precede and promote muscle wasting in tumor-bearing mouse models, while our work demonstrates that combined gene therapy enhancing both angiogenesis and hypertrophy synergistically restores vascular integrity, muscle mass and function of skeletal muscle in healthy and diabetic mice. Here, we further investigate the role of vascular system in cachexia and potential therapies.
Methods: Self-produced bimagrumab and mAb27 (FLT1-blocking antibody that increases angiogenesis via VEGFR2) antibodies were first tested in healthy C57BL/6J female mice. To study their effects in cancer cachexia, we used KPC pancreatic adenocarcinoma (PDAC) xenograft mouse model. Adult C57BL/6J female mice (n=30) were divided into control, PDAC, PDAC + bimagrumab and PDAC + mAb27 groups. KPC cells (10^6) were injected intraperitoneally. Body weights and food intake were monitored regularly. Three-dimensional analyses of whole muscle vasculature and investigation of tumor-secreted cachexia-inducing factors are currently ongoing.
Results: In healthy mice, bimagrumab increased muscle fiber size, whereas mAb27 did not have significant effect on either vasculature or fiber size. In KPC mice, weight loss began rapidly after 7 days in all PDAC groups, but bimagrumab modestly slowed this loss. Bimagrumab improved overall survival and preserved muscle mass in the tibialis anterior and quadriceps muscles, while mAb27 treatment was associated with reduced survival. Findings from ongoing histological and molecular analyses will be presented at the meeting.
Conclusion: Bimagrumab shows therapeutic potential in cachexia, whereas mAb27 seems to impair survival without significant effect on skeletal muscle vasculature. To improve muscle vascularization for enhanced muscle growth and inhibition of muscle wasting, we need to identify more efficient treatment options.

7-05

Myostatin/activin A neutralization improves muscle quality and function during GLP-1 receptor agonism-induced weight loss in obese mice.

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Introduction: Myostatin and activin-A, proteins from the TGFb superfamily, are ActRII ligands that regulate muscle catabolism. Recent clinical trial data report that inhibiting this pathway in combination with the GLP-1 receptor agonist semaglutide (GLP-1RA) attenuates muscle loss while potentiating adipose reduction in patients with obesity. Currently, there is little mechanistic insight regarding the effects of GLP-1 monotherapy or combination with inhibitors of the ActRII pathway on skeletal muscle structure/composition and function, including metabolism, strength, and endurance.
Methods and Results: This study examined the effects of a combination of monoclonal antibodies against myostatin (anti-MSTN) and activin A (Anti-Act-A) on muscle metabolism and function during semaglutide-induced weight loss in diet-induced obese (DIO) mice. Co-administration of semaglutide (30 nmol/kg, daily) and Anti-MSTN/Act-A (20 mg/kg, bi-weekly) resulted in a greater reduction of fat mass compared to semaglutide alone after 34 days of treatment. Combining semaglutide with Anti-MSTN/Act-A prevented lean body mass loss (measured by echo MRI) and maintained gastrocnemius tissue weight, counteracting the decline seen with semaglutide monotherapy. Both semaglutide alone and in combination with Anti-MSTN/Act-A reduced myosteatosis assessed by micro-CT and decreased pro-inflammatory and fibrotic gene expression. Muscle lipidomic analysis revealed that semaglutide reduces diacylglycerol content, consistent with improvements in glucose clearance. Semaglutide did not change muscle strength assessed by *in vivo* maximum force generation, however the combination group showed increased muscle strength. Semaglutide and Anti-ActRIIa/b combination therapy also increased basal metabolic rate and exercise capacity during treadmill running, an effect not observed with semaglutide monotherapy.
Conclusion: Overall, semaglutide does not improve muscle strength despite reducing muscle lipid content and inflammation. However, blocking MSTN and Act-A in conjunction with semaglutide improves both muscle metabolism and strength, supporting this combination as a sustainable candidate for the preservation of musculoskeletal function during weight loss.

7-06

Nicotinamide Riboside Mitigates Adipose Tissue Wasting and Systemic Metabolic Dysregulation in Ritonavir-Induced Lipodystrophy

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Introduction: Ritonavir, a protease inhibitor initially developed for HIV/AIDS therapy and recently repurposed in COVID-19 management, is clinically limited by adverse metabolic sequelae, including lipid redistribution, hyperlipidemia, and insulin resistance. Nicotinamide riboside (NR), a vitamin B3 derivative and NAD^+ precursor, plays a central role in cellular energy metabolism and mitochondrial function. This study investigates the advanced efficacy of NR in alleviating Ritonavir-induced lipid metabolism disorders.
Methods: Murine models were treated with Ritonavir alone or in combination with NR, followed by comprehensive assessments of lipid metabolism, adipose tissue morphology, systemic energy balance, and organ integrity. Complementary *in vitro* studies were performed to evaluate adipocyte differentiation, maturation, and mitochondrial function under Ritonavir stress with or without NR. Transcriptomic profiling was employed to delineate molecular pathways impacted by NR intervention.
Results: Ritonavir administration induced marked hyperlipidemia, adipocyte atrophy, and abnormal fat redistribution, which were significantly ameliorated by NR supplementation. In cell-based assays, Ritonavir impaired adipocyte differentiation and disrupted mature adipocyte homeostasis, while NR restored differentiation capacity and preserved adipocyte integrity. Transcriptomic analyses revealed that NR reprogrammed gene expression networks linked to energy metabolism, mitochondrial respiration, and oxidative phosphorylation. Beyond adipose tissue, NR

conferred protection against Ritonavir-induced cardiac and hepatic injury, underscoring systemic benefits.
Conclusions: NR supplementation effectively mitigates Ritonavir-induced lipid metabolic derangements and safeguards systemic organ function through restoration of mitochondrial and metabolic homeostasis. These findings highlight NR as a promising therapeutic adjunct to attenuate the metabolic complications of Ritonavir and broaden its safe clinical applicability.

7-07

Platelet Releasate partially rescues C2C12 myoblasts from chemotherapeutic drug-induced impairments

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Introduction: The use of anthracycline drugs, such as Doxorubicin and Cisplatin, is essential in cancer treatment but is often accompanied by skeletal muscle impairments, including atrophy and cachexia. Dexamethasone, commonly used as a supportive corticosteroid, can also induce muscle atrophy**.** These effects contribute to reduced physical function and a decline in patients' quality of life. Identifying strategies to protect skeletal muscle during chemotherapy is therefore critical. Platelet releasate, a platelet-derived product containing growth factors and cytokines, is known to promote cell proliferation and tissue regeneration. This study investigated the effects of Doxorubicin, Cisplatin, and Dexamethasone on C2C12 myoblast proliferation, senescence, and cytotoxicity, and whether platelet releasate can mitigate these effects *in vitro.*
Methods: Platelet releasate was prepared from blood using a serial centrifugation and aggregation protocol. C2C12 myoblasts were treated with Doxorubicin, Cisplatin, or Dexamethasone, with or without platelet releasate. Proliferation was assessed via EdU incorporation, senescence through beta-galactosidase staining, and cytotoxicity with Toxilight assays. Additionally, qRT-PCR and migration assays were also performed.
Results: Doxorubicin and Cisplatin significantly reduced myoblast proliferation, increased senescence, and cytotoxicity. Co-treatment with platelet releasate partially restored proliferation and migration, reduced cytotoxicity, but did not significantly decrease senescence. Dexamethasone caused minor cytotoxicity compared to both drugs but displayed similar senescence. Platelet releasate also enhanced myoblast migration across all treatments.
Conclusion: Platelet releasate partially rescues proliferation and migration and protects against cytotoxicity in myoblasts treated with Doxorubicin or Cisplatin, although it does not significantly prevent senescence, including in Dexamethasone-treated cells. These findings suggest that platelet releasate may serve as a potential therapeutic strategy to mitigate chemotherapy-induced skeletal muscle impairments.

7-08

UCN2 treatment enhanced fat mass loss while increasing muscle mass and function in preclinical models

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Introduction: Urocortin 2 (UCN2) is a member of the corticotropin-releasing hormone (CRH) family and an agonist of the G protein-coupled receptor CRH receptor type 2 (CRHR2). Data from our lab and others has shown that UCN2 overexpression or administration increases muscle mass while reducing fat mass in young lean and obese animals. The goal of this study is to determine how a modified long acting UCN2 affects both muscle mass and function.
Methods: Obesity model: Male 24-week-old diet-induced obese (DIO) mice were treated with a modified UCN2 peptide every 3 days for a total of 17 days.
Sarcopenic obesity model: Male 20-month-old mice were placed on a high-fat diet and housed at thermoneutrality (30°C) for 8 weeks prior to being treated with a modified UCN2 peptide twice a week for 4 weeks.
Results: In obese animals, UCN2 treatment resulted in fat mass loss with preservation of lean mass as measured by EchoMRI. UCN2 increased muscle mass measured by weighting isolated muscle tissues and protein synthesis measured with deuterated water. In addition, UCN2 treatment also increased muscle force production in vivo measured with the Aurora 3-in-1 system. UCN2 treatment also improved whole-body glucose homeostasis and insulin sensitivity. In a murine model of sarcopenic obesity, UCN2 resulted in fat mass loss with preservation of lean mass and increased muscle mass. Moreover, UCN2 treatment also improved muscle function measured with wire hang time and grip strength.
Conclusions: Overall, these results highlight the potential of UCN2 to reduce fat mass while preserving or increasing muscle mass and function in two different preclinical models of obesity.

7-09

Peripheral administration of long-acting Y5R agonist PEP-300 induces hyperphagia and shifts energy homeostasis in mice

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Introduction: Neuropeptide Y (NPY) is a key regulator of energy homeostasis, through its action on the Y1-5 receptors (Y1-5R) in the brain. This study aimed to characterize the pharmacology of PEP-300, the first long-acting Y5R agonist developed for subcutaneous administration.
Methods: The *in vitro* potency and selectivity of PEP-300 were evaluated towards mouse and human YRs. The half-life was assessed *in* vivo in mice and efficacy was assessed by daily subcutaneous injections (0.15, 0.5, and 1.5 mg/kg) of chow-fed C57BL/6Jrj mice over 14 days, measuring food intake, body weight, and post-treatment rebound. Metabolic effects were examined through a single injection of PEP-300 followed by 48 hours of indirect calorimetry to monitor substrate utilization (RER). Additionally, iDISCO cFOS immunostaining was employed to identify brain regions activated by PEP-300.
Results: PEP-300 exhibited high potency for the Y5R (EC_{50} of 5.15 nM in humans and 3.78 nM in mice) and high selectivity over other receptor isoforms. The half-life of PEP-300 in mice is 8.55 hours after a single subcutaneous administration. PEP-300 treated mice showed dose-dependent increases in food intake (~14%, ~35%, ~60%) and body weight (~15%, ~28%, ~40%) over 14 days which was normalized after 14 days off-treatment. A single PEP-300 injection caused an upward shift in RER (0.994 vs 0.899 in vehicle) which was sustained for >40 hours, indicating a long-lasting increase in carbohydrate utilization. cFOS staining revealed increased neuronal activation in appetite-related brain regions such as the lateral hypothalamus (LH) and tubular nucleus (TN).
Conclusions: PEP-300 is a novel long-acting NPY derived Y5R agonist that acts centrally, and with a high selectivity towards the Y5R. It significantly elevates food intake and body weight while

shifting metabolic fuel preference towards carbohydrates. These findings advance our understanding of the Y5R pharmacology and suggest potential therapeutic applications for conditions characterized by energy imbalance, such as cachexia.

7-10

AntimiR therapy improves muscle mass and function in in vivo models of muscle wasting

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Introduction: Muscle wasting is a multifactorial condition associated with chronic diseases and aging, leading to a progressive loss of skeletal muscle mass, weakness, and functional impairment. Dysregulated protein metabolism, characterized by increased protein degradation and decreased synthesis, underlies the atrophic phenotype observed in cancer cachexia or sarcopenia. MicroRNAs (miRNAs) play key roles in regulating protein turnover and muscle maintenance, and their dysregulation contributes to muscle atrophy. Antisense oligonucleotides (antimiRs) have emerged as a novel therapeutic approach to inhibit miRNAs and restore muscle homeostasis. In this study, we evaluated the therapeutic potential of an antimiR to preserve muscle mass as a treatment for muscle wasting disorders.
Methods: The antimir was administered intravenously in different in vivo models of muscle wasting to assess its ability to preserve muscle mass and improve muscle phenotypes. Delivery efficiency was confirmed by ELOSA (Enzyme-Linked OligoSorbent Assay) to detect the amount of compound in relevant tissues. Therapeutic potential was evaluated by measuring grip strength, skeletal muscle mass, and quantifying the expression of atrophic-related genes and the regulation of protein synthesis and breakdown.
Results: The treatment increased skeletal muscle mass and grip strength across in vivo models of muscle wasting, mitigating the progression of muscle loss. Efficient delivery to skeletal muscle was achieved, and the target-specific miRNA inhibition was confirmed, validating the accuracy of the approach. The antimir therapy restored the protein balance by downregulating atrophy-related genes, decreasing ubiquitin-proteasome-mediated protein degradation, and preserving protein synthesis.
Conclusions: Results from this study support the antimir therapy as a promising therapeutic strategy for muscle atrophy-related diseases such as cachexia or sarcopenia. Although further studies are required to optimize dosing and assess long-term efficacy, these findings validate the specificity of the antimiR targeting a dysregulated miRNA to improve muscle function.

7-11

Characterization of the Systemic Impact of Glucocorticoid-Treated Exacerbation of COPD in a Novel mouse model

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Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder with extra-pulmonary manifestations including muscle wasting. Muscle wasting contributes to disease burden and is accelerated by an exacerbation of COPD (ECOPD). Glucocorticoids (GCs) are widely used as treatment for ECOPDs due to their potent anti-inflammatory effects, though, GCs may aggravate muscle wasting through their catabolic actions, diminishing their overall therapeutic efficacy. We developed a mouse model of GC-treated-ECOPD for preclinical testing of compounds that target muscle wasting in this disease context.
Materials and Methods: Emphysema ('COPD') was induced in male C57BL/6J mice by intratracheal (IT) instillation of elastase, followed by VC or LPS to evoke pulmonary inflammation ('ECOPD'). Dexamethasone (DEX, a GC) was injected daily ('GC-ECOPD'). Weekly µCT scans were used to verify emphysema development, and pre/post-LPS to measure muscle volume (MV) using automated segmentation analysis of the right hind limb. Plasma and bronchoalveolar lavage fluid (BALf) TNF-α levels were determined by ELISA.
Excised hindlimb muscles were weighed (MW) and used for gene expression analyses.
Results: Body weight (BW) reductions were observed in ECOPD (-14%) and GC-ECOPD (-9%) mice. ECOPD mice showed reduced MW compared to COPD (-8.0%). µCT scans showed MV reductions in ECOPD (-10%) and GC-ECOPD mice (-5%). Plasma and BALf TNF-α levels increased in ECOPD (12 and 153-fold respectively) and GC-ECOPD (6 and 73-fold) compared to COPD, and both were reduced in GC-ECOPD vs ECOPD (0.5-fold and 0.5-fold). In muscle, Atrogene expression (Atrogin-1 [9-fold] and MuRF1 [4-fold]) was increased in ECOPD vs COPD, but only Atrogin-1 [2.5-fold] in GC-ECOPD.
Conclusion: To conclude, we established a mouse model of GC-treated ECOPD that impacts on skeletal muscle, shows significant body weight loss and incorporates the biological actions of GCs which can be utilized to test compounds aiming to improve the therapeutic index of GCs in this setting.

7-12

Activin Type II Receptor Blockade Impacts Muscle Wasting in Glucocorticoid-Treated Exacerbations of COPD

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Introduction: Chronic obstructive pulmonary disease (COPD) is often accompanied by muscle wasting. Muscle wasting intensifies during exacerbations of COPD (ECOPD), partially driven by glucocorticoids (GCs) given as standard-of-care treatment. As GC-driven wasting partially relies on myostatin signaling, we hypothesized that blocking its receptor (with CDD866) would attenuate muscle wasting in GC-treated ECOPD.
Materials and Methods: Emphysema ('COPD') was induced in male C57BL/6J mice by intratracheal elastase followed by vehicle or lipopolysaccharide (LPS) instillation to evoke pulmonary inflammation, mimicking ECOPD. Dexamethasone (GC) was injected daily ('GC-ECOPD') and CDD866 (CDD, provided by Versanis Bio) once with the first GC dose. µCT scans were made weekly to confirm development of emphysema, and before and 48h after LPS to measure muscle volume. Excised hindlimb muscles were weighed and used for gene expression analyses.
Results: Body weight change of GC-ECOPD differed from control (-6.4%, $p<0.001$) whereas body weight change of GC-ECOPD/CDD866 did not. GC-ECOPD was not different from GC-ECOPD/CDD866. Muscle wet weight at endpoint of GC-ECOPD differed from control (-6.7%, $p<0.01$), but GC-ECOPD/CDD866 did not. GC-ECOPD muscle weight was not different from GC-

ECOPD/CDD866. Preliminary analysis of right hindlimb muscle volume change (pre-post 48h VC/LPS) showed no significant difference of GC-ECOPD (-6.6%) or GC-ECOPD/CDD866 (+0.7%) compared to control (-1.8%), while GC-ECOPD associated muscle volume loss was prevented in GC-ECOPD/CDD866 (-6.6% vs +0.7%, p<0.05). While atrogene expression was not increased in GC-ECOPD compared to control, it tended to decrease in GC-ECOPD/CDD866 compared to GC-ECOPD (Atrogin-1: p=0.053; MuRF1: p=0.076).
Conclusion: In conclusion, in this model of GC-ECOPD, CDD866 significantly preserved hindlimb muscle volume and tended to reduce atrogene expression. These findings warrant further investigation of myostatin signaling blockade as an approach to prevent or restore GC-treated ECOPD-associated muscle wasting, thereby increasing the therapeutic efficacy of GCs.

8-01

Motor Unit Potential and Nerve Conduction Velocity as Novel Electrophysiological Correlates of Muscle Health in Sarcopenia

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Introduction: Sarcopenia is the age-related loss of muscle mass and strength and strongly influenced by the peripheral nervous system. Electromyography investigations, such as quantitative electromyography, conduction velocity study and single fiber electromyography (SFEMG), are crucial for evaluating neuromuscular function. The objective of this study is to conduct a case-control study utilizing EMG to identify neurophysiological predictor variables of high diagnostic value for sarcopenia status in older adults in Hong Kong.
Methods: This project is a case-control study of 78 community-dwelling, ambulatory older adults. Subjects will be screened for sarcopenia based on AWGS 2019 and divided into normal and sarcopenia groups. Each subject will receive SFEMG screening at tibialis anterior (TA) for NMJ-related parameters, including fiber density, jitter, block; Motor/sensory nerve conduction velocity on lower extremities will be tested bilaterally. Motor unit action potential (MUAP) recruitment including duration, amplitude and phase will be recorded on TA via needle EMG.
Results: Sarcopenic patients displayed impaired motor nerve function, particularly in conduction velocity. For the right and left motor peroneus recorded on fibular head, conduction velocity was reduced ($p < 0.05$), accompanied by a diminished area. For sensory conduction velocity, the right tibialis, left tibialis, and left peroneus demonstrated slower velocities (all $p < 0.05$) compared to non-sarcopenic participants. Sarcopenic patients exhibited altered neuromuscular activity, characterized by a reduced interference pattern in the right tibialis anterior ($p < 0.05$). SFEMG analysis revealed increased neuromuscular jitter ($p < 0.01$) and elevated fiber density ($p < 0.05$) in the right tibialis anterior, suggesting impaired neuromuscular transmission and possible compensatory reinnervation.
Conclusion: The present study provides comprehensive neurophysiological insights into sarcopenia, revealing significant differences in motor and sensory nerve function, neuromuscular transmission, and muscle activity. These findings underscore that sarcopenia extends beyond skeletal muscle atrophy, implicating peripheral nerve integrity and neuromuscular junction stability in its pathophysiology.

8-02

Bioimpedance analysis for the detection of intensive care unit acquired weakness: a prospective observational study

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Introduction: Intensive care unit (ICU) acquired weakness (ICUAW) affects up to 40% of critically ill patients and is associated with prolonged ICU stays and impaired recovery. Diagnosis typically requires manual muscle strength testing using the Medical Research Council (MRC) score, which is not feasible in sedated or unresponsive patients. Bioelectrical impedance analysis (BIA) is a non-invasive, bedside tool for estimating skeletal muscle mass (SMM), but its diagnostic role in ICUAW remains unclear.
Methods: We conducted a prospective observational study in 41 critically ill patients receiving ventilatory support across three surgical ICUs at Charité-Universitätsmedizin Berlin. The primary objective was to assess the agreement between BIA-derived SMM and the MRC score using Bland-Altman analysis. Secondary outcomes included associations between SMM and ultrasound-derived muscle cross sectional area of the rectus femoris, serum biomarkers, and clinical outcomes. Exploratory analyses examined the diagnostic performance of BIA in detecting ICUAW (MRC <48) using ROC curve.
Results: A total of 141 paired SMM–MRC measurements were analysed. Bland-Altman analysis showed a mean bias of 22.9 (95%CI: 18.9–26.9), with wide limits of agreement, indicating poor interchangeability. BIA-derived SMM demonstrated high discriminatory capacity to detect ICUAW at the same time point (area under the curve: 0.967 (95%CI: 0.936–0.990)), with an exploratory cut-off of 28.77kg. Patients with ICUAW (n = 17) had significantly lower ICU Mobility Scale scores (median [IQR]: 3.0 [3.0–6.0] vs. 5.0 [5.0–8.0]; p=0.036), longer mechanical ventilation (2.0 [1.0–14.0] vs. 0.0 [0.0–2.5] days; p=0.029), and prolonged ICU stays (13.0 [9.0–34.0] vs. 8.0 [5.8–12.2] days; p = 0.028). No significant associations were found between SMM and ultrasound or biomarkers.
Conclusion: BIA-derived skeletal muscle mass was not interchangeable with MRC strength testing but showed a strong ability to identify ICUAW. An exploratory cut-off identified in this study requires validation in future research.

8-03

Phase 1 Trial in Healthy Participants of KER-065, Modified Activin Receptor Ligand Trap, Supports Development in Sarcopenia and Neuromuscular Disorders

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Sarcopenia is a progressive and debilitating condition characterized by the pervasive loss of skeletal muscle mass, strength, and function. KER-065 is a modified investigational activin receptor ligand trap designed to inhibit muscle catabolism by blocking activins and myostatin. In preclinical models, KER-065 demonstrated significant anabolic effects on skeletal muscle and bone. Here, we report initial results from a first-in-human trial evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics (PD) of KER-065 in healthy male participants This double-blind, placebo-controlled trial was conducted in two parts: Part 1, where participants received a single dose (1, 3, or 5mg/kg), and Part 2, where three Q4W doses (1.25 or 2mg/kg) were administered. Beyond safety and PK, exploratory assessments specifically evaluated KER-065's impact on body composition through serum biomarkers, dual-energy X-ray absorptiometry (DXA), and magnetic resonance imaging (MRI).
A majority of the observed treatment-emergent adverse events were mild to moderate in severity, with no dose-limiting toxicities or serious adverse events. The PD analyses revealed anabolic and metabolic effects:

- **Increased Lean Body Mass:** KER-065 significantly increased total lean body mass as measured by DXA.
- **Increased Muscle Volume:** MRI analyses confirmed a direct increase in thigh muscle volume.
- **Improved Body Composition:** KER-065 reduced whole-body and visceral fat mass (via DXA), supported by favorable changes in adipokines (adiponectin and leptin).
- **Bone Anabolic Activity:** KER-065 increased bone mineral density and serum markers of bone formation, supporting overall musculoskeletal health.
- **Changes in structural remodeling proteins** were observed by serum-wide proteomic analysis using SomaScans.

KER-065 was generally well tolerated. The PD analyses provide compelling evidence of robust target engagement, resulting in a direct anabolic effect on skeletal muscle—increasing mass and volume while favorably altering overall body composition. These findings support the continued development of KER-065 as a potential therapy to counteract the core pathophysiology of sarcopenia.

8-04

Efficacy and safety of kyung-ok-ko for cancer-related fatigue in patients with lung cancer: a randomized, double-blind, placebo-controlled, parallel-group trial

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Introduction: Cancer-related fatigue (CRF) is a prevalent and debilitating symptom among patients with lung cancer, with limited effective therapeutic options. Kyung-Ok-Ko (KOK), a traditional herbal medicine, has been used to treat exhaustion, but its efficacy for CRF lacks rigorous clinical evidence.
Methods: A single-center, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at Kyung Hee University Korean Medicine Hospital, Seoul. Fifty adults with lung cancer who completed primary treatment and reported a Brief Fatigue Inventory (BFI) score of ≥4 were randomized to receive KOK or placebo twice daily for 6 weeks. The primary outcome was mean BFI score at week 6. Secondary outcomes included other fatigue scales, pulmonary function, 6-minute walk test, and serum inflammatory markers.
Results: All 50 participants completed the trial. At week 6, the KOK group showed a significantly lower mean BFI score (3.45 [SD 1.10]) compared to placebo (3.88 [SD 1.11]); mean difference -0.44 (95% CI, -0.80 to -0.07; p=0.021). Significant reductions in serum IL-1β (p=0.030) and IL-8 (p=0.029) were observed in the KOK group. No significant differences were found for other secondary outcomes. No serious adverse events were reported; adverse event incidence was similar between groups.
Conclusions: A 6-week course of KOK significantly improved cancer-related fatigue in lung cancer patients compared to placebo and was well-tolerated. KOK may be a potential therapeutic option for managing CRF, warranting confirmation in larger trials.
Acknowledgement: This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: RS-2022-KH127464).

8-05

Efficacy and safety of ponsegromab in patients with pancreatic cancer, cachexia, and elevated growth differentiation factor: insights from the Phase 2 PROACC-1 trial

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Background: Ponsegromab is a monoclonal antibody targeting growth differentiation factor 15 (GDF-15), a circulating cytokine implicated in cachexia. We report body weight and safety findings from participants with pancreatic cancer (PDAC) in a phase 2, randomized, double-blind trial of ponsegromab vs placebo in patients with cancer cachexia (PROACC-1; NCT05546476).
Methods: Patients with cancer, cachexia, and elevated serum GDF-15 (≥1500 pg/mL) were randomized 1:1:1:1 to receive subcutaneous ponsegromab (100, 200, 400 mg) or matching placebo every 4 weeks for 12 weeks. The primary endpoint was change from baseline (CFB) in body weight at 12 weeks. Safety and tolerability were key secondary endpoints.
Results: Overall, 59 (31.6%) of 187 participants randomized in this phase 2 study had PDAC (aged 64.4±9.9 years; 57.6% male). Baseline mean body weight was 57.1±11.9 kg; 47.5% and 50.8% had a body mass index <20 kg/m^2 and weight loss over the prior 6 months of ≥10%, respectively. There was an imbalance in the frequency of stage IV disease across treatment groups: placebo, 71.4%; 100 mg, 50.0%; 200 mg, 66.7%; and 400 mg, 92.9%. The observed mean (SD) CFB in body weight at Week 12 was −0.36 (1.94) kg for placebo compared to +0.65 (3.16), +1.72 (2.93), and +3.37 (5.54) kg for participants receiving ponsegromab 100, 200, and 400 mg, respectively. Placebo-adjusted LS mean weight gain with ponsegromab 400 mg was 3.29 kg (90% CI: 0.58, 6.00), *P*=0.02. All-causality and treatment-related adverse events occurred in 80.0% and 8.9% of ponsegromab-treated patients and 92.9% and 14.3% of placebo-treated patients, respectively. Nausea and diarrhea were reported less frequently among ponsegromab-treated than placebo participants: 8.9% vs 28.6% and 13.3% vs 21.4%, respectively.
Conclusion: Among patients with PDAC, cachexia, and elevated GDF-15 levels, GDF-15 inhibition with ponsegromab through 12

weeks was associated with body weight gain and was generally well tolerated.

8-06

RIVER-mPDAC: a phase 2b/3 study of ponsegromab for the treatment of cachexia in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving first-line (1L) chemotherapy

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Introduction: Ponsegromab, a growth differentiation factor 15–targeted antibody, significantly increased body weight and improved appetite and cachexia symptoms vs placebo, with tolerable safety, in patients with cachexia and non-small cell lung, colorectal, or pancreatic cancer (Groarke NEJM 2024).
Methods: RIVER-mPDAC (NCT06989437), a double-blind, placebo-controlled, randomized phase 2b/3 study, will evaluate ponsegromab with 1L chemotherapy in patients with cachexia and mPDAC. Approximately 1000 patients will be enrolled into the study with no interruption in enrollment between phase 2b and 3. The phase 2b/3 primary endpoints are percent change from baseline in body weight and change in appetite-related symptoms by Functional Assessment of Anorexia/Cachexia Therapy 5-item Anorexia Symptom Scale at Week [W]12. Secondary endpoints include change from baseline in physical activity at W12 and overall survival. Other secondary endpoints include safety/tolerability, tumor response endpoints (PFS, ORR, DOR, DCR), and change in body composition. Eligibility criteria include age ≥18 years, mPDAC with measurable disease, cachexia (Fearon criteria), ECOG PS ≤1, and receiving 1L chemotherapy (nab-paclitaxel+gemcitabine or FOLFIRINOX [modification allowed]). Exclusion criteria include active reversible causes of decreased food intake, tube feedings or parenteral nutrition, and mPDAC-unrelated cachexia. Phase 2b patients will be randomized 1:1:1 to subcutaneous ponsegromab (200 or 400mg Q4W) or placebo Q4W, stratified by ECOG PS and chemotherapy regimen. The phase 3 ponsegromab dose will be based on phase 2b results. Phase 3 patients enrolled before dose selection will be randomized 1:1:1 per phase 2b doses, stratified by ECOG PS, chemotherapy regimen, and BMI-adjusted weight loss. Those enrolled after the phase 3 dose decision will be randomized 1:1 to the selected ponsegromab dose or placebo Q4W. An optional open-label extension (≤1 year) is included.
Results: Recruitment is starting.
Conclusions: RIVER-mPDAC is evaluating a novel agent for the treatment of cachexia in patients with mPDAC receiving 1L chemotherapy.

8-07

Efficacy and safety of ponsegromab in patients with cancer-associated cachexia: results from the open-label extension of a randomized, placebo-controlled, phase 2 study

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Introduction: Ponsegromab, a growth differentiation factor 15 (GDF-15)–targeted antibody, improved body weight, symptoms, physical activity, and muscle mass in patients with cancer cachexia in a 12-week, double blind phase 2 trial (Part A; NCT05546476). We report findings from the 1-year, open-label extension (Part B).
Methods: Participants with cancer cachexia and serum GDF-15 ≥1500 pg/mL received subcutaneous (SC) ponsegromab (100, 200, 400 mg) or matching placebo Q4W during Part A. At 12 weeks, participants could pursue open-label treatment with ponsegromab 400 mg Q4W SC through Week 64 (Part B). Change in body weight and safety were assessed through Weeks 64 and 72, respectively.
Results: Of 137 participants completing Part A, 117 (85.4%) participants (44.4% non-small cell lung, 29.1% colorectal, and 26.5% pancreatic cancer; 70.9% stage 4) entered Part B. Median (IQR) age and weight at baseline were 68 (61–74) years and 54.7 (46.0–63.8) kg, respectively. Overall, progressive weight gains were observed with mean (SD) increases of 2.74 (4.89), 4.43 (5.95), and 5.18 (5.93) kg at Weeks 24, 52, and 64, respectively. Weight gains were lowest in Part A placebo participants (mean [SD] increases of 2.28 [3.41] kg versus 5.57 [4.48], 4.01 [6.78], and 7.61 [6.72] kg for the ponsegromab 100, 200, and 400 mg groups, respectively, at Week 64). All-cause and treatment-related adverse events were reported in 84.2% and 4.4% of participants from Weeks 12-72, respectively. None of the 23 deaths during Part B were related to treatment.
Conclusions: Improvements in body weight during 12-week Part A were maintained with ponsegromab through 64 weeks in Part B. Part A placebo participants showed weight stabilization during Part B, but weight gain was less than for Part A ponsegromab participants. Ponsegromab continued to be safe and well-tolerated through 72 weeks.
 Previously presented at ESMO 2025; Berlin, Germany.

8-08

Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-07258669, a small-molecule MC4R antagonist: Results from first-in-human Phase 1 studies

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Introduction: PF-07258669 is a highly potent and selective brain-penetrant, oral small-molecule melanocortin-4 receptor (MC4R) antagonist that is currently in development for loss of appetite and unintended weight loss related to ageing. Herein, we report the key findings of two Phase 1 studies of PF-07258669 in healthy adults.
Methods: The single ascending dose study was a randomized, placebo-controlled, first-in-human, crossover study (NCT04628793). The multiple ascending dose study was a randomized, placebo-controlled study (NCT05113940). The primary and secondary objectives were to evaluate safety/tolerability and pharmacokinetics of PF-07258669, respectively. Placebo-adjusted change from baseline in body weight after 14 days of treatment was an exploratory pharmacodynamic endpoint.
Results: Oral administration of PF-07258669 as single doses of 0.1–300 mg or multiple doses of 2–180 mg every 8 hours (q8h) to healthy adults aged ≤60 years was generally safe and well tolerated. Treatment-emergent adverse events were predominantly mild or moderate in intensity, and no treatment-related serious adverse events were reported. Following single or multiple doses, PF-07258669 was rapidly absorbed (median T_{max}, 0.58–1.50 hours), with plasma exposures increasing in an approximate dose-proportional manner. PF-07258669 at doses ≥60 mg q8h was associated with mean placebo-adjusted weight gains ≥0.77 kg after 14 days of treatment. Bayesian E_{max} analysis showed statistically significant, dose-responsive increases in body weight at all PF-07258669 dose levels compared with placebo on Day 14 reaching 0.83 (90% credible interval: 0.19-1.48) kg in the 180-mg q8h treatment group.
Conclusions: We report for the first time that MC4R antagonism with an oral small molecule was associated with increases in body weight and appeared to be safe and well tolerated through 14 days of dosing in healthy adults. These findings highlight MC4R antagonism as a potential therapeutic target for management of unintentional weight loss associated with ageing.

8-09

Biophytis: BIO101 (20E) as a drug candidate targeting the reduction of GLP1-RA-induced muscle mass or function loss in patients with obesity.

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Introduction: GLP-1 receptor agonists (GLP-1RAs) effectively reduce body weight. However, up to 40% of the total lost weight is lean body mass, including skeletal muscle mass. BIO101 (20-hydroxyecdysone; 20E), an oral MAS receptor activator, could be a promising treatment to prevent muscle mass or strength loss in patients with obesity or overweight treated with GLP-1RAs.
Methods: Preclinical studies of 20E-treated myoblasts and Diet-Induced Obese (DIO) mice (four weeks treatment of BIO101 in combination with a GLP-1RA) were completed to characterize muscular properties of 20E. In addition, a 12-week double-blind placebo-controlled study (6-week hypocaloric intervention phase + 6-week weight loss maintenance phase) with 37.5mg 20E was conducted in 58 participants with overweight or obesity (BMI ≥ 27 kg/m² and ≤ 38 kg/m²) aged 20-65 years.
Results: 20E has pro-differentiating effects *in vitro* in murine and human myoblasts, increasing myotube diameter. *In vivo*, BIO101, in combination with GLP-1RA, significantly improved animal mobility (endurance) and grip strength when compared to untreated group. Notably, the combination of drugs compensates for muscle contractility alterations induced by GLP-1RA.
In patients with overweight or obesity, 37.5mg 20E significantly decreased android fat mass (p=0.039). Biopsy analyses showed a statistically significant reduction in adipocyte diameter. Compared to placebo, a trend for improvement in handgrip strength occurred in the subpopulation with > 5% body weight loss *versus* baseline.
Biophytis designed an interventional, randomized, double-blind, placebo-controlled clinical phase 2 trial targeting obese (BMI≥30) and overweight (BMI≥27) adults treated with semaglutide. Planned primary endpoint is muscle strength. Secondary endpoints include physical performance, body composition parameters and questionnaires.
Conclusions: Supported by these data, a phase 2 trial combining BIO101 plus GLP-1 RA was approved by competent authorities in USA and Belgium and will be initiated shortly. Interactions are ongoing with ethics committees**.** Biophytis will expand the trial to Brazil.
Disclosures: RvM, CF, ML, RD, SC, SR, PJD, JM WD are employees of Biophytis S.A.

8-10

Trial-in-progress: A phase 1b dose escalation study of AV-380 (anti-GDF15 monoclonal antibody) in combination with standard-of-care therapy in cancer patients with cachexia

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Background: Cachexia is a complex and common cancer comorbidity associated with a high risk of death; however, no FDA-approved therapies exist. Current off-label treatments are limited and increase the risk of side effects. Circulating GDF-15, an inflammatory cytokine involved in the stress response and body weight regulation, has emerged as a main modulator of cachexia. AV-380 is a high-affinity anti-GDF-15 IgG1 monoclonal antibody that eliminates circulating GDF-15 and was well tolerated, without serious AEs, in a Phase I healthy volunteer study (in-house data). In animal cancer models, GDF-15 reversed weight loss and increased muscle recovery.
Methods: This is an open-label, dose-escalation, multicenter phase 1b study to assess the safety, tolerability, PK, and PD of AV-380. Eligible patients are ≥18 years of age, have cancer with cachexia (per international consensus criteria), receive standard-of-care antineoplastic therapy, have a prognosis of ≥3 months, and an ECOG PS ≤2. Patients with known brain metastases (unless treated and stable for ≥2 weeks), myocardial infarction or grade 3/4 heart failure (≤3 months), uncontrolled third-spacing of fluids (pleural effusion, pericardial effusion, and/or ascites), or non-cancer-related cachexia, are excluded. Primary endpoints evaluate the safety and tolerability per dose-limiting toxicities, adverse events (NCI CTCAE v5), and laboratory test results. Secondary endpoints include PK analysis, and exploratory endpoints include anti-drug antibodies, weight changes, patient-reported outcomes (Functional Assessment of Anorexia Cachexia Therapy, Patient Global Impression of Severity, Patient's Global Impression of Change, Patient-Reported Outcomes Measurement Information System) physical function (by digital measures), and body composition (Lumbar 3 Skeletal Muscle Index). Each escalating, 28-day course, dose cohort will have 3-6 patients following standard 3+3 design. Patients receive AV-380 by IV infusion until they have unacceptable toxicity, complete 4 courses, withdraw consent, or the sponsor terminates the study. Statistical analyses will be completed by cohort and summarized descriptively. (NCT05865535)

FACULTY

Volker **Adams,** Germany
E, Poster session 2.3

Simone **Agostini,** Italy
E4

Markus **Anker,** Germany
Symposium Thursday, J1

Stefan **Anker,** Germany
D, D1, Symposium Thursday, J, N, P1, R, U, W, Meet the Editor Saturday

Hidenori **Arai,** Japan
F

Paige **Arneson-Wissink,** USA
Poster session 3.4, V3

Philip **Atherton,** UK
Poster session 2.4, N2

Ken **Attie,** USA
N, U1, W6

Kamal **Awad,** USA
C3

Jürgen **Bauer,** Germany
F2

Faisal **Beg,** Canada
Rapid Fire 3, R1

Mauricio **Berriel Diaz**, Germany
B, Poster session 1.3, K2, Poster session 4.2

Bharatsinha **Bhosale,** India
COACH-ED Saturday

Gianni **Biolo,** Italy
G3

David **Blum,** Switzerland
X4

Andrea **Bonetto,** USA
A4, K, Poster session 4.3

John **Borg,** Malta
J, N, U, W

Anja **Bosy-Westphal,** Germany
Y

Samuel **Breit,** Australia
D2

Nenad **Bursac,** USA
T2

Riccardo **Calvani,** Italy
F3

James **Carson,** USA
Poster session 2.1, V4

Marco **Cintoni,** Italy
Y3

Andrew **Coats,** Australia
Symposium Thursday, J3, N, P4, R, S, U4, W

Paola **Costelli,** Italy
C2, Poster session 1.3, I, Poster session 4.2

Jeffrey **Crawford,** USA
J, COACH-ED Saturday, Highlights

Egidio **Del Fabbro**, USA
L4, Poster session 3.4

David **Dias,** Portugal
Y1

Waly **Dioh,** France
W4

Wolfram **Doehner,** Germany
L3, S

Fabio **Dorigotti,** Switzerland
N, R

Richard **Dunne,** USA
Lunch Symposium Friday

Gustavo **Duque,** Canada
C4, Poster session 2.2, Poster session 4.1, Meet the Editor Saturday

Elke **Dworatzek,** Germany
A, Rapid Fire 1

Bill **Evans,** USA
H3

Andreas **Fischer,** Germany
Poster session 2.2, V1, Poster session 4.1

Guilherme **Fonseca,** Brazil
Poster session 1.4, Highlights

Tim **Friede,** Germany
J4

Jose **Garcia,** USA
S, U2, COACH-ED Saturday

Katja **Gehmlich,** UK
E1, Rapid Fire 1

David **Glass,** USA
N4, P, R, U

John **Groarke,** USA
W2, W3

Denis **Guttridge,** USA
K, M1, Poster session 4.3

Pauline **Henrot,** France
T

Steve **Heymsfield,** USA
H2

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B1, Rapid Fire 2

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L, O3

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I2, Rapid Fire 3, S

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J2, R, COACH-ED Saturday

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C1, Poster session 3.1

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A, Poster session 1.2, Symposium Thursday, M

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I4, S

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D4, F1, Poster session 1.1, R3, Meet the Editor Saturday

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C, K1

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H, S, COACH-ED Saturday, Highlights

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