16th INTERNATIONAL CONFERENCE ON CACHEXIA, SARCOPENIA & MUSCLE WASTING

HOSTED BY KAROLINSKA UNIVERSITETSSJUKHUSET

Stockholm

FINAL PROGRAMME & ABSTRACTS

17-19 June 2023

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SCWD
SOCIETY ON SARCOPENIA, CACHEXIA & WASTING DISORDERS

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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

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General Information 4

Program Overview 5

Abstracts of Oral Presentations, Saturday, June 17, 2023 22

Abstracts of Oral Presentations, Sunday, June 18, 2023 44

Abstracts of Oral Presentations, Monday, June 19, 2023 82

Poster Sessions 96

Poster Abstracts 124

Faculty 188

GENERAL INFORMATION

Organization

Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD)
Vers-chez-les-Blanc, route du Jorat 67
c/o Intercomptas fiduciaire Sàrl,
1000 Lausanne 26
Switzerland

Congress Organizer

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Gianluigi Savarese, Sweden

International Scientific Committee

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John E. Morley, USA
Maurizio Muscaritoli, Italy
Florian Strasser, Switzerland
Stephan von Haehling, Germany
Hidetaka Wakabayashi, Japan

Conference Location

Karolinska Universitetssjukhuset
Eugeniavägen 3, Solna
Stockholm, Sweden

Opening Hours of the On-site Registration Desk

Saturday, 17 June 2023
10:00-18:30 hrs

Sunday, 18 June 2023
8:00-18:30 hrs

Monday, 19 June 2023
8:00-15:00 hrs

Poster Exhibition

Saturday,17 June 2023
11:00-19:30 hrs

Sunday, 18 June 2023
8:00-19:00 hrs

Monday, 19 June 2023
8:00-13:00

Poster Sessions

Saturday, 17 June 2023
16:20-17:10 hrs

Sunday, 18 June 2023
10:20-11:10 hrs
14:50-15:40 hrs

Monday, 19 June 2023
10:20-11:10 hrs

Coffee Breaks

Saturday, 17 June 2023
16:15-17:15 hrs

Sunday, 18 June 2023
10:15-11:15 hrs
14:45-15:45 hrs

Monday, 19 June 2023
10:15-11:15 hrs

Lunch Breaks

Sunday, 18 June 2023
12:30-13:30 hrs

Monday, 19 June 2023
12:30-13:30 hrs

A
12:30–13:45 **HALL A**

Opening session

(talk 1 and 2: 20 minutes + 5 minutes discussion, talk 3: 12 minutes + 3 minutes discussion)

Chairs: Stefan Anker (Germany)
Vickie Baracos (Canada)
Gianluigi Savarese (Sweden)

12:30 – 12:35
Welcome
Stefan Anker (Germany)

1. 12:35 – 12:55
"Prometheus" basic science key note lecture
Central mechanisms in cachexia: bench to bedside
Daniel Marks (USA)

2. 13:00 – 13:20
"Hippocrates" clinical science key note lecture
Small non-coding RNA profiling and cachexia in patients with cancer
Maurizio Muscaritoli (Italy)

3. 13:25 – 13:37
JCSM & SCWD – update 2023
Stephan von Haehling (Germany)
Stefan Anker (Germany)

B1
14:00–15:00 **HALL A**

GENERAL SARCOPENIA

Sarcopenia as a multisystem disorder

(each talk 15 minutes)

Chair: Ivan Aprahamian (Brazil)

1. 14:00-14:15
Sarcopenia and diabetes
Gustavo Duque (Canada)

2. 14:15-14:30
Sarcopenia and stroke / dysphagia
Hidetaka Wakabayashi (Japan)

3. 14:30-14:45
Sarcopenia and heart failure
Gianluigi Savarese (Sweden)

14:45 – 15:00
Discussion

B2
15:00–16:15 **HALL A**

GENERAL SARCOPENIA

The fat story of sarcopenia – the fat in muscle

(each talk 15 minutes)

Chairs: Ivan Aprahamian (Brazil)
Marianne Hjermstad (Norway)

1. 15:00 – 15:15
Intermuscular fat infiltration in sarcopenia
Gustavo Duque (Canada)
2. 15:15 – 15:30
Clinical implications of fat infiltration in sarcopenia
Reshma Merchant (Singapore)
3. 15:30 – 15:45
Metabolic role of fat in muscle
James Carson (USA)
4. 15:45 – 16:00
Targeting ACTIVIN receptors and the effect on muscle and fat tissue
David Glass (USA)

16:00 – 16:15
Discussion

C
15:00–16:15 **HALL B**

GENERAL CACHEXIA

Novel cancer cachexia biomarkers

(each talk 15 minutes)

Chairs: Nick Hoogenraad (Australia)
Stephan von Haehling (Germany)

1. 15:00 – 15:15
The MIC-1/GDF15 story – biomarker and therapeutic target
Samuel Breit (Australia)
2. 15:15 – 15:30
Targeted therapy relapse models to study cachexia development in lung cancer
Swarnali Acharyya (USA)
3. 15.30 – 15:45
Tumor genetic mutations and cancer cachexia – clinical findings
Puneeth Iyengar (USA)
4. 15:45 – 16:00
A geroscience approach to frailty biomarker discovery in cancer patients
Emanuele Marzetti (Italy)
16:00 – 16:15
Discussion

16:15-17:15

Coffee Break

16:20 – 17:10 **POSTER AREA**

Poster Viewing 1

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 1.1
Cachexia - mechanisms, animal models I (posters 1-01 to 1-08)
Chairs: Denis Guttridge, Jochen Springer

Poster session 1.2
Cancer cachexia I (posters 2-01 to 2-09)
Chairs: Joanne Reid, Florian Strasser

Poster session 1.3
Physical activity & training; Nutrition & appetite (posters 5-01 to 5-05 and 6-01 to 6-07)
Chairs: Stuart Phillips, Adrian Slee

Poster session 1.4
Diagnosis of cachexia / sarcopenia I (posters 3-01 to 3-12)
Chairs: Swarnali Acharyya, Philip Atherton

16:20 – 17:00 **HALL B**

Rapid Fire Abstracts Session 1

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Elke Dworatzek (Germany)
Maria Rohm (Germany)
Erin Talbert (USA)

16:20 – 16:25
Tumor organoid-derived factors from cachectic pancreatic cancer patients induce a pro-inflammatory macrophage phenotype – role of macrophage migration inhibitory factor (1-15)
Valerie d´Antonio (The Netherlands)

16:25 – 16:30
Elevated epicardial adipose tissue and aortic calcification, quantified from volumetric regional CT scans, are associated with postoperative complications in complex rectal cancer (3-23)
Dinh Mai (UK)

16:30 – 16:35
Validation of a deep learning model for automatic segmentation of skeletal muscle and adipose tissue on L3 abdominal CT images (3-30)
David van Dijk (The Netherlands)

16:35 – 16:40
The Rho GTPase inhibitor, RhoGDIα is a negative regulator of muscle mass and upregulated in sarcopenic human muscle (4-04)
Lisbeth Møller (Denmark)

16:40 – 16:45
Extracellular vesicles are possible mediators of the liver-muscle axis in sarcopenia associated to liver disease (4-13)
Manuela Merli (Italy)

16:45 – 16:50
Enhanced glutamine availability exerts different effects on protein and amino acid metabolism in muscles of healthy and septic rats (7-02)
Milan Holecek (Czech Republic)

16:50 – 16:55
A novel first-in-class USP19 inhibitor for the treatment of cancer-induced muscle atrophy (7-05)
Richard Wilkinson (UK)

16:55 – 17:00
Developing an evidence and theory based multimodal integrative intervention for the management of renal cachexia: a theory of change (7-08)
Carolyn Blair (UK)

D
17:15–18:30 **HALL A**

GENERAL SARCOPENIA

Sarcopenia in lung disease: interplay with chronic conditions

(each talk 15 minutes)

Chairs: Abigail Mackey (Denmark)
Hidetaka Wakabayashi (Japan)

1. 17:15 – 17:30
Definition, diagnostic criteria and treatment of respiratory sarcopenia
Akira Tamaki (Japan)
2. 17:30 – 17:45
Cytokine signaling in adipose tissue browning and muscle wasting in CKD
Robert Mak (USA)
3. 17:45 – 18:00
COPD and other chronic diseases
Marielle Engelen (USA)
4. 18:00 – 18:15
Sarcopenia in cardio-respiratory illnesses
Stephan von Haehling (Germany)

18:15 – 18:30
Discussion

E
17:15–18:30 **HALL B**

GENERAL CACHEXIA

Liver metabolism in cancer and cachexia

(each talk 15 minutes)

Chairs: Maria Rohm (Germany)
Jochen Springer (Germany)

1. 17:15 – 17:30
Cancer-induced rewiring of metabolism and zonation in the liver
Shinpei Kawaoka (Japan)
2. 17:30 – 17:45
Targeting bile acid metabolism to counteract cancer cachexia
Laure Bindels (Belgium)
3. 17:45 – 18:00
Liver mitochondrial function in cancer cachexia
Marilia Seelaender (Brazil)
4. 18:00 – 18:15
Liver NAD+ metabolism in cancer- and chemotherapy-induced cachexia
Fabio Penna (Italy)

18:15 – 18:30
Discussion

18:30–19:00 **POSTER AREA**

Meet & Greet at Poster Area

08:00 – 08:50 **FOYER**

Ken Fearon Career Café – Meet the Mentor

F
09:00 – 10:15 **HALL A**

NUTRITION

Nutritional issues in cachexia

(each talk 15 minutes)

Chairs: Joanne Reid (UK)
Florian Strasser (Switzerland)

1. 09:00 – 09:15
Appetite, food quantity and quality in cancer cachexia
Alessio Molfino (Italy)

2. 09:15 – 09:30
Gut barrier, nutrient absorption and cachexia
Laure Bindels (Belgium)

3. 09:30 – 09:45
Exercise, nutrition and omega-3 PUFA interventions for kidney cachexia
Adrian Slee (UK)

4. 09:45 – 10:00
Examining biological sex variability in cancer-induced cachexia
Nicholas P. Greene (USA)

10:00 – 10:15
Discussion

G
09:00 – 10:15 **HALL B**

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

New mechanisms of cancer cachexia

(each talk 15 minutes)

Chairs: Andrea Bonetto (USA)
Paola Costelli (Italy)

1. 09:00 – 09:15
Tissue crosstalk during cancer cachexia: consequences of altered metabolic networks
Selma Masri (USA)

2. 09:15 – 09:30
Inflammation as target in cancer cachexia
Erin E Talbert (USA)

3. 09:30 – 09:45
Examining the relationship between mitochondrial function and muscle force in cancer cachexia
Luca Delfinis (Canada)

4. 09:45 – 10:00
Deletion of FNDC5/Irisin protects against cancer induced cachexia syndrome
Fabrizio Pin (USA)

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
Cachexia – mechanisms, animal models II (posters 1-09 to 1-17)
Chairs: Denis Guttridge, Jochen Springer

Poster session 2.2
Cancer cachexia II (posters 2-17 + 2-19 to 2-26)
Chairs: Joanne Reid, Florian Strasser

Poster session 2.3
Muscle wasting & sarcopenia I (posters 4-01 to 4-11)
Chairs: Marielle Engelen, Olav Rooyackers

10:20 – 10:50 **HALL B**

Rapid Fire Abstracts Session 2

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Laurence Genton (Switzerland)
Marianne Hjermstad (Norway)

10:20 – 10:25
The association between protein intake and skeletal muscle parameters in patients with localized renal cell cancer (5-01)
Alina Vrieling (The Netherlands)

10:25 – 10:30
Preoperative supportive nutrition at major cancer surgery in weight-losing patients (5-03)
Britt-Marie Iresjö (Sweden)

10:30 – 10:35
Cancer-associated anorexia: DNA methylation signatures in patients with lung cancer (5-04)
Giovanni Imbimbo (Italy)

10:35 – 10:40
Higher fibroblast growth factor 23 levels are associated with low exercise capacity in patients with chronic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) (6-04)
Ryosuke Sato (Germany)

10:40 – 10:45
Anti-RANKL treatment attenuates mitochondria deterioration and suppresses macrophage infiltration during sarcopenia (7-01)
Can Cui (China)

10:45 – 10:50
Muscle protein synthesis with a hybrid dairy and plant-based protein blend (P4) is equal to whey protein in a murine aging model after fasting (7-04)
Francina Dijk (The Netherlands)

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H
11:15 – 12:30 **HALL A**

GENERAL SARCOPENIA

Update on aging & immobilisation related sarcopenia

(each talk 15 minutes)

Chairs: Philip Atherton (UK)
Robert Mankowski (USA)

1. 11:15 – 11:30
Effects of aging on human muscle atrophy with immobilization
Stuart Phillips (Canada)

2. 11:30 – 11:45
The human neuromuscular junction in aging and exercise
Abigail Mackey (Denmark)

3. 11:45 – 12:00
The role of nutrition in aging: appetite loss
Ivan Aprahamian (Brazil)

4. 12:00 – 12:15
Brain muscle cross talk
Reshma Merchant (Singapore)

12:15 – 12:30
Discussion

I
11:15 – 12:30 **HALL B**

GENERAL CACHEXIA

The role of extracellular vesicles in wasting

(each talk 15 minutes)

Chairs: Samuel Breit (Australia)
Adrian Slee (UK)

1. 11:15 – 11:30
Tumour-derived exosomes
Joanna Lima (UK)

2. 11:30 – 11:45
Intracellular peptides: potential biomarkers and therapeutic targets
Patrícia Reckziegel (Brazil)

3. 11:45 – 12:00
Extracellular vesicles and inflammation: from cachexia to COVID-19
Marilia Seelaender (Brazil)

4. 12:00 – 12:15
Tumor-host cross-talk: focus on the extracellular vesicles
Paola Costelli (Italy)

12:15 – 12:30
Discussion

12:30 – 13:30

Lunch Break

J
13:30 – 14:45 **HALL A**

CANCER CACHEXIA THERAPEUTICS

Endpoints in cancer cachexia clinical trials

(each talk 15 minutes)

Panel: Jeffrey Crawford (USA)
Jose Garcia (USA)
Frank Misselwitz (Germany)
Maurizio Muscaritoli (Italy)
Richard Skipworth (UK)

1. 13:30 – 13:45
Physical function endpoints
Barry Laird (UK)

2. 13:45 – 14:00
Appetite and dietary intake endpoints in cancer cachexia trials
Tora Solheim (Norway)

3. 14:00 – 14:15
Quality of life endpoints
Marianne Hjermstad (Norway)

4. 14:15 – 14:30
Approvable endpoints for cancer cachexia – an evolving field
Stefan Anker (Germany)

14:30 – 14:45
Discussion

K
13:30 – 14:45 **HALL B**

CANCER CACHEXIA THERAPEUTICS

New cachexia treatment approaches on the horizon

(each talk 15 minutes)

Chairs: Mauricio Berriel Diaz (Germany)
Nicolaas Deutz (USA)

1. 13:30 – 13:45
Anti-Fn14 therapy for cancer cachexia
Nick Hoogenraad (Australia)

2. 13:45 – 14:00
Peptide-based therapeutic approaches in cancer cachexia
Stephan Herzig (Germany)

3. 14:00 – 14:15
Targeting the TGFbeta pathway
Marcus D. Goncalves (USA)

4. 14:15 – 14:30
Modulating metabolic pathways – impact on cachexia and malnutrition
Bei B. Zhang (USA)

14:30 – 14:45
Discussion

14:45 – 15:45

Coffee Break

14:50 – 15:40 **POSTER AREA**

Poster Viewing 3

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 3.1
Muscle wasting & sarcopenia II (posters 4-12 to 4-22)
Chairs: Nick Hoogenraad, Robert Mak

Poster session 3.2
Therapeutic development pre-clinical / clinical (posters 7-01 to 7-13)
Chairs: Paola Costelli, Sander Rensen

Poster session 3.3
Diagnosis of cachexia / sarcopenia II (posters 3-14 to 3-22**)**
Chairs: Swarnali Acharyya, Philip Atherton

14:50 – 15:30 **HALL B**

Rapid Fire Abstracts Session 3

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Elke Dworatzek (Germany)
Sarah Judge (USA)
Lykke Sylow (Denmark)

14:50 – 14:55
Growth of GL261 glioblastoma tumors induced delayed body weight gain and stunted skeletal muscle growth in pediatric mice (1-01)
Nicholas Jamnick (USA)

14:55 – 15:00
Sexual dimorphism in the development of cancer cachexia in ApcMin/+ mice (1-02**)**
Benedicte Guegan (France)

15:00 – 15:05
Hepatic metabolism alterations and effects of niacin supplementation in experimental cancer- and chemotherapy-induced cachexia (1-05)
Natalia E Cortez (Italy)

15:05 – 15:10
Role of fibroadipogenic progenitors in pancreatic cancer cachexia (1-11)
Ashok Narasimhan (Canada)

15:10 – 15:15
Regulation of pancreatic cancer-induced muscle wasting through the obestatin/GPR39 system (1-14)
Icia Santos-Zas (Spain)

15:15 – 15:20
Microbiota-derived secondary bile acids to tackle cancer cachexia (2-04)
Morgane Thibaut (Belgium)

15:20 – 15:25
First-in-patient (Phase 1b) study of the GDF-15 inhibitor ponsegromab in patients with cancer and cachexia: safety, tolerability, and exploratory measures of efficacy (2-07)
Jeffrey Crawford (USA)

15:25 – 15:30
Scalable and privacy-preserving AI can characterise and discover more cachectic cancer patients compared to ICD codes and NLP based approaches (2-09)
Judith Sayers (UK)

L
15:45 – 17:00 **HALL A**

CANCER CACHEXIA THERAPEUTICS

Emerging trials in cancer cachexia

(each talk 15 minutes)

Chairs & Panelists:
Stefan Anker (Germany)
Vickie Baracos (Canda)
Frank Misselwitz (Germany)
Maurizio Muscaritoli (Italy)
Stephan von Haehling (Germany)

1. 15:45 – 16:00
Update on ponsegromab early clinical trial
Jeffrey Crawford (USA)

2. 16:00 – 16:15
Multimodal intervention for cancer cachexia - MENAC study
Barry Laird (UK)

3. 16:15 – 16:30
Pilot study of macimorelin for cancer cachexia
Jose Garcia (USA)

16:30 – 17:00
Discussion

M
15:45 – 17:00 **HALL B**

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

Tissue crosstalk in cancer cachexia

(each talk 15 minutes)

Chairs: Stephan Herzig (Germany)
Fabrizio Pin (USA)

1. 15:45 – 16:00
Adipocytokines in patients with cancer cachexia
Richard Skipworth (UK)

2. 16:00 – 16:15
Crosstalk of lipid metabolism and inflammation drives cachexia
Maria Rohm (Germany)

3. 16:15 – 16:30
Liver-derived factors contributing to cancer cachexia
Mauricio Berriel Diaz (Germany)

4. 16:30 – 16:45
Mechanisms of bioamplification in cancer cachexia
Daniel Marks (USA)

16:45 – 17:00
Discussion

17:00 – 17:15

Break

N
17:15 – 18:30 **HALL A**

CANCER CACHEXIA THERAPEUTICS

Therapy of sarcopenia and cachexia: emerging trials and late breaking results

(each talk 15 minutes)

Chairs & Panelists:
Stefan Anker (Germany)
Jose Garcia (USA)
Barry Laird (UK)
Maurizio Muscaritoli (Italy)
Richard Skipworth (UK)

1. 17:15 – 17:30
Treating the malignancy associated weight loss and anorexia with the ghrelin receptor agonist Anamorelin when administered in adult patients with non-small cell lung cancer (NSCLC) and cachexia
Daniela Domnica Rotaru (Switzerland)

2. 17:30 – 17:45
Non-clinical and clinical development of S-pindolol benzoate in cancer cachexia in patients with advanced non-small cell lung and colo-rectal cancer
Frank Misselwitz (Germany)

3. 17:45 – 18:00
Update on ponsegromab early clinical trial
Jeffrey Crawford (USA)

4. 18:00 – 18:15
BIOPHYTIS BIO101: a candidate treatment for muscle diseases
Cendrine Tourette (France)

18:15 – 18:30
Discussion

O
17:15 – 18:30 **HALL B**

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

New insights into the mechanisms of cancer-associated muscle wasting

(each talk 15 minutes)

Chairs: James Carson (USA)
Julien Gondin (France)

1. 17:15 – 17:30
Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: role of activin
Teresa Zimmers (USA)

2. 17:30 – 17:45
FoxP1 is a transcriptional repressor associated with cancer cachexia that induces skeletal muscle wasting and weakness
Andrew Judge (USA)

3. 17:45 – 18:00
Liver metastases enhance the pro-cachectic signaling in colorectal cancer hosts
Andrea Bonetto (USA)

4. 18:00 – 18:15
UBR2 targets myosin heavy chain IIb and IIx for degradation: molecular mechanism essential for cancer-induced muscle wasting
Yi-Ping Li (USA)

18:15 – 18:30
Discussion

P
08:00 – 08:50 **HALL A**

Young investigators award session

(each presentation: 5 minutes + 3 minutes discussion)

Chairs / Judges:
James Carson (USA)
Paola Costelli (Italy)
Daniel Marks (USA)
Maurizio Muscaritoli (Italy)
Maria Rohm (Germany)
Jochen Springer (Germany)
Teresa Zimmers (USA)

08:00 – 08:08
Mechanisms of skeletal muscle atrophy in patients with early breast cancer treated with chemotherapy: insights from acute and chronic measurements (1-12)
Joris Mallard (France)

08:08 – 08:16
Neutrophil-derived S100a8/a9 as a mediator of adverse cardiac remodeling in cancer-associated cachexia (2-01)
Parham Diba (USA)

08:16 – 08:24
Cachexia, sarcopenia and bone markers in patients with heart failure and hyperkalemia: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) (4-15)
Guglielmo Fibbi (Germany)

08:24 – 08:32
Exercise decreases catabolic protein signaling in rat skeletal muscle 40 days post-burn (6-01)
Dorien Dombrecht (Belgium)

08:32 – 08:40
Loss of hypoxia signalling-mediated PGC-1a expression underlies age-related loss of muscular adaptation to exercise (6-06)
Yori Endo (USA)

08:40 – 08:48
Assessing the effect of intra-abdominal malignancy on the impact of a short-term homebased unsupervised exercise on skeletal muscle mitochondrial OXPHOS function (7-12)
Thomas Smart (UK)

Q
09:00 – 10:15 **HALL A**

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

Current limitations in preserving muscle in cancer

(each talk 15 minutes)

Chairs: Andrea Bonetto (USA)
Erin Talbert (USA)

1. 09:00 –09:15
Pathological remodeling of respiratory muscles during cancer: mechanisms and therapeutic targets
Sarah Judge (USA)

2. 09:15 – 09:30
Molecular basis and clinical relevance of insulin resistance in cancer cachexia
Lykke Sylow (Denmark)

3. 09:30 – 09:45
Neuromuscular electrical stimulation training promotes muscle stem cell fusion, modulates inflammation and improves muscle function in a mouse model of cancer cachexia
Julien Gondin (France)

4. 09:45 – 10:00
Chemotherapy-specific effects on cardiorespiratory status and body composition
Ashley Smuder (USA)

10:00 – 10:15
Discussion

10:15 – 11:15

Coffee Break

10:20 – 11:10 **POSTER AREA**

Poster Viewing 4

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 4.1
Diagnosis of cachexia / sarcopenia III (posters 3-23 to 3-30)
Chairs: Nicholas Greene, Yi-Ping Li

Poster session 4.2
Muscle wasting & sarcopenia III (posters 4-23 to 4-34)
Chairs: Nick Hoogenraad, Hidetaka Wakabayashi

Poster session 4.3
Cancer cachexia III (posters 2-10 to 2-18)
Chairs: Mauricio Berriel-Diaz, Marcus Goncalves

R
11:15 – 12:30 **HALL A**

NUTRITION

New concepts in preventing muscle wasting in critically ill patients

(each talk 15 minutes)

Chairs: Maurizio Muscaritoli (Italy)
Joanne Reid (UK)

1. 11:15 – 11:30
Anabolic resistance in critically ill patients
Olav Rooyakers (Sweden)

2. 11:30 – 11:45
Ketogenic feeding in the critically ill patients
Zudin Puthucheary (UK)

3. 11:45 – 12:00
Persistent inflammation, immunosuppression and catabolism syndrome and the role nutrition in the surgical ICU
Robert Mankowski (USA)

4. 12:00 – 12:15
The metabolic response to critical illness – a therapeutic target?
Nicolaas Deutz (USA)

12:15 – 12:30
Discussion

12:30 – 13:30

Lunch Break

S
13:30 – 14:45 **HALL A**

CANCER CACHEXIA THERAPEUTICS

The microbiome and other novel therapeutic targets in cancer cachexia

(each talk 15 minutes)

Chairs: Laure Bindels (Belgium)
Denis Guttridge (USA)

1. 13:30 – 13:45
Gut microbiota alterations in patients with cancer cachexia
Sander Rensen (The Netherlands)

2. 13:45 – 14:00
Gut microbiota and muscle: from proof-of-concept to molecular mechanisms
Camille Lefevre (Belgium)

3. 14:00 – 14:15
Fecal microbiota transplantation (FMT) in cancer cachexia
Laurence Genton (Switzerland)

4. 14:15 – 14:30
Targeting CXCR2 signaling counteracts cancer cachexia
Andrew Judge (USA)

14:30 – 14:45
Discussion

T
14:45–15:45 **HALL A**

Highlights Session

Chair: Stephan von Haehling (Germany)

Basic Science
Jochen Springer (Germany)

Nutrition
Ivan Aprahamian (Brazil)

Sarcopenia
Vickie Baracos (Canada)

Cancer Cachexia
Teresa Zimmers (USA)

Poster Award
Young Investigator Award
Farewell

ABSTRACTS OF ORAL PRESENTATIONS

A - Opening Session *(20 minutes + 5 minutes discussion)*

"Prometheus" basic science key note lecture:
Central mechanisms in cachexia: bench to bedside

Daniel Marks
Oregon Health & Science University, Portland, Oregon, USA

A - Opening Session *(20 minutes + 5 minutes discussion)*

"Hippocrates" clinical science key note lecture:
Small non-coding RNA profiling and cachexia in patients with cancer

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

B1-1 *(15 minutes)*

Sarcopenia and diabetes

Gustavo Duque
McGill University, Montreal, Quebec, Canada

Diabetes and sarcopenia are highly prevalent and frequently occur together in older adults. The skeletal muscle is the most essential tissue for insulin-stimulated glucose disposal and the primary driver of whole-body glycemic control. Alterations in muscle biology, such as sarcopenia, could affect the muscle response to insulin, inducing glucose disposal alterations and increasing localized inflammation caused via inter- and intramuscular adipose tissue accumulation. At the same time, diabetes predisposes to sarcopenia via insulin resistance, inflammation, advanced glycation end-product accumulation and increased oxidative stress. These two-way interactions and shared biological mechanisms determine that patients with diabetes are at higher risk of developing sarcopenia and vice versa. In addition, alterations in target organs induced by diabetes, such as kidney disease or peripheral neuropathy, are also involved in the pathogenesis of sarcopenia. Therefore, a combined diagnostic and therapeutic approach should be implemented in these patients. This session will review the shared biological mechanisms between sarcopenia and diabetes and the most optimal diagnostic and therapeutic approach for patients with both conditions. In addition, research gaps will be discussed.

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B1-2 *(15 minutes)*

Sarcopenia and stroke / dysphagia

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Sarcopenia is common in stroke patients. A systematic review showed that the estimated prevalence of sarcopenia before stroke, within 10 days of stroke, and from 10 days to 1 month after stroke was 15.8%, 29.5%, and 51.6%, respectively. The higher rate of sarcopenia from 10 days to 1 month may be because only patients with moderate to severe stroke are still admitted and studied. Our study showed that sarcopenia was detected in 53.6% (125/233) of stroke patients (59.8%, 50.0%, and 34.6% of patients with cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage, respectively) in the convalescent rehabilitation unit. In addition, ADL and swallowing function were independently associated with loss of skeletal muscle mass and decreased muscle strength. Furthermore, improvement in sarcopenia is positively associated with improvement in ADL in stroke patients. Therefore, diagnosis and treatment of sarcopenia are very important in stroke rehabilitation.
Sarcopenic dysphagia is defined as difficulty swallowing due to sarcopenia of the general skeletal and swallowing muscles and is a common disorder in older people. The prevalence of sarcopenic dysphagia in hospitalized patients requiring dysphagia rehabilitation, hospitalized patients with pneumonia, and institutionalized elderly patients was 32%, 81%, and 45%, respectively. Skeletal muscle loss is common in stroke patients for many reasons, including denervation, impaired efferent neurovegetative control, and dysphagia. Furthermore, our study showed that sarcopenia was negatively associated with recovery of swallowing function in stroke patients without interaction by energy intake and rehabilitation duration in the convalescent rehabilitation unit. Therefore, both sarcopenia and stroke affect swallowing function in some stroke patients. Rehabilitation nutrition for sarcopenic dysphagia may improve swallowing function more.

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B1-3 *(15 minutes)*

Sarcopenia and heart failure

Gianluigi Savarese
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B2-1 *(15 minutes)*

Intermuscular fat infiltration in sarcopenia: the bad

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Intermuscular adipose tissue (IMAT) is defined as fatty infiltration that involves the storage of lipids in adipocytes underneath the deep fascia of muscle. This storage of lipids includes adipocytes located between the muscle fibers (also termed intramuscular fat) and between muscle groups. This infiltration also consists of a smaller group of lipids stored within the muscle cells, known as intramyocellular lipids. The origin and specific biological and metabolic characteristics of these lipid deposits in muscle and their association with sarcopenia are the subject of intense research. Whereas in healthy conditions it is considered a source of energy for the muscle, it is also known that high levels of IMAT are associated with insulin resistance and loss of muscle strength and function, particularly in the context of sarcopenia. Growing evidence suggests that these deleterious effects of IMAT on muscle are associated with the development of a lipotoxic profile that includes the secretion of inflammatory adipokines and fatty acids, which affect the function of the myocytes and other cells in their vicinity. Metabolically, IMAT is also a strong predictor of fasting glucose and insulin levels in both younger and older adults, suggesting that IMAT-induced metabolic impairments are associated with its role as a regulator of insulin sensitivity. Regarding interventions to reduce lipotoxic IMAT volumes or induce a healthier profile of this fat, like other ectopic fat depots such as those found in the liver, pharmacological interventions combined with exercise may be a treatment option worth exploring. This session will discuss the lipotoxic profile of IMAT and its impact on muscle biology, function, and insulin metabolism. In addition, current and future therapeutic interventions targeting IMAT to treat sarcopenia will be presented.

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B2-2 *(15 minutes)*

Clinical implications of fat infiltration in sarcopenia

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Sarcopenia is defined as age related changes in muscle quantity and quality resulting in poor physical function or low muscle strength. The current diagnosis of sarcopenia is focused on measurement of muscle mass. Aging is associated with low grade inflammation, visceral fat and ectopic fat deposition in muscle, liver, pancreas, and heart. Fat infiltration in the skeletal muscle or myosteatosis may disrupt muscle architecture causing reduced muscle contractility and quality, dysfunctional myokines secretion resulting in increased morbidity and mortality. Muscle releases various signaling myokines which can influence the onset and progression of various chronic diseases such as diabetes, osteosarcopenia, osteoarthritis, cancer, cardiovascular disease, fatty liver and other age-related diseases (1-4). Pro-inflammatory cytokines released from intramuscular fat further exacerbates the systemic inflammation cascade causing muscle atrophy, and myofibrosis. Myosteatosis is currently not addressed in the workup of sarcopenia. Most interventions on sarcopenia are centered upon improving muscle mass, strength and physical performance. Future intervention studies including pharmacological drug trials targeting fat infiltration within the muscle with downstream impact on function, non-communicable diseases and mortality are needed.

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B2-3 *(15 minutes)*

Metabolic role of fat in muscle

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Improving our understanding of how disease, inflammation, inactivity, and aging alter systemic and tissue metabolism is critical for developing therapies to improve human health and quality of life. The endocrine function of adipose tissue for regulating metabolism is widely examined in the context of obesity and various wasting conditions. Importantly, adipose tissue is a mediator of systemic inflammation and a source of regulatory adipokines. Therefore, adipose tissue's role in accelerating disease progression, decreasing functional capacity, and reducing muscle mass is being investigated. Regarding sarcopenia, frailty, and cachexia, the cellular consequences of metabolic, cytokine, and growth factor crosstalk between adipose tissue and skeletal muscle are being examined to identify novel therapies that improve muscle mass and function. Recent investigations into the role and regulation of adipose tissue lipolysis as a driver of muscle wasting in some conditions have elevated the interest in understanding the role of lipid metabolism in muscle. Furthermore, skeletal muscle mitochondrial dysfunction is being investigated as a significant driver of muscle mass loss with cancer and other wasting conditions. So, there is a critical need to understand better the metabolic role and regulation of fat in skeletal muscle. Skeletal muscle's metabolic flexibility to use lipids for energy is a crucial response to physiological stimuli that can be impacted by feeding and fasting, hormonal signaling, and physical activity and exercise. Unfortunately, there are significant gaps in our mechanistic understanding of how muscle metabolic flexibility is altered by systemic changes accompanying wasting conditions such as cancer. Furthermore, how muscle mitochondria dysfunction and aberrant metabolic signaling caused by the cachectic environment disrupt the muscle's metabolic use of lipids is unclear. Understanding these responses is critical for treating cachectic muscle mass, metabolic, and contractile function and will directly impact the patient's health and quality of life. A fundamental question is whether cachectic muscle maintains the metabolic flexibility to use lipids as fuel and can respond to physiological stimuli involving physical activity, feeding, and hormonal stimuli. This presentation will highlight the importance of skeletal muscle metabolic flexibility and muscle's use of lipids as fuel. First, lipids' critical importance and regulation as a fuel source in skeletal muscle will be examined. Then, the role of intramuscular triglycerides in muscle metabolism will be explored. The impact of the cachectic environment on metabolic flexibility in these conditions will be emphasized, including the effects of cancer, cancer treatment, and inflammatory signaling on these processes. Data from preclinical cancer models, cancer treatment, and cultured myotubes will be presented. Overall, the presentation will point to the need to better understand the role of lipids in regulating muscle metabolic flexibility and the potential for muscle contraction and dietary interventions to treat cachectic muscle successfully.

B2-4 *(15 minutes)*

Targeting ACTIVIN receptors and the effect on muscle and fat tissue

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C1 (15 minutes)

The MIC-1/GDF15 story – biomarker and therapeutic target

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GDF15, is a cell stress cytokine, that is overproduced in many disease states especially cancers and chronic renal, pulmonary and cardiac failure, and can be induced by some treatments including some cancer chemotherapy agents and radiotherapy. Increased GDF15 expression often leads to a rise in its serum levels which can increase by as much as 10-100 fold. GDF15 acts on its hindbrain neuron localised receptor, glial-derived neurotrophic factor receptor alpha like (GFRAL), to induce anorexia. When markedly overproduced in some disease states such as advanced cancer, it can cause an anorexia/cachexia syndrome. Antibodies to GDF15 or its receptor, are currently being trialled by several companies as therapeutics for patients with anorexia cachexia syndromes.

The link between GDF15 serum levels and anorexia/cachexia syndromes is advantagous as it provides a means for selecting patients who may be suitable for therapy directed at inhibiting the GDF15-GFRAL pathway. This selection is however made more complex by the recent discovery that some commercial assays for GDF15 underestimate its correct serum levels, because the antibodies used are directed to polymorphic epitopes which are not present on GDF15 protein from all subjects.

In this presentation, the mechanism of action of GDF15 and the strengths, uses and limitations of measurements of its serum levels for disease diagnosis and identifying patients with anorexia/cachexia syndromes will be discussed.

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C2 *(15 minutes)*

Targeted therapy relapse models to study cachexia development in lung cancer

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Somatic activating mutations in the epidermal growth factor receptor (EGFR) gene are detected globally in 50% of lung cancer patients. Targeted therapies using EGFR-tyrosine kinase inhibitors (TKIs), such as osimertinib, have transformed the treatment landscape for patients with EGFR-mutation and prolonged their progression-free survival (PFS). Despite striking initial responses, acquired resistance to osimertinib ultimately develops, which results in metastatic relapse and subsequent death. Importantly, weight loss and features of cachexia are often observed in patients who relapse on osimertinib, although this has not been systematically studied. To gain insights into cachexia development after osimertinib-targeted therapy, we have generated osimertinib-response-and-relapse models (Biswas et al.; Cancer Discovery, 2022) that develop cachexia. To this end, we generated long-term in-vivo treatment models using osimertinib-sensitive EGFR-mutant human lung cancer cell lines (PC9 and H1650) that metastasize to distant organs, such as the bone and brain. These mice show remarkable initial responses to osimertinib that are analogous to human patients, with a long window of progression-free survival, followed by metastatic relapse, cachexia, and death. After a striking response period (excellent tumor control and weight loss stabilization), 100% of the osimertinib-treated mice developed brain relapse and cachexia. Brain metastasis is associated with the loss of cognitive ability, cachexia, morbidity, and accelerated mortality. Interestingly, the brain is a frequent site of metastasis in over 50% of EGFR-mutant lung cancer patients and a common site of relapse after osimertinib. These targeted therapy response-and-relapse models could be used for studying molecular mediators of cachexia development in the context of EGFR-mutant lung cancer.

C3 *(15 minutes)*

Tumor genetic mutations and cancer cachexia – clinical findings

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Introduction: Cancer cachexia (CC), a wasting syndrome of muscle and adipose tissue resulting in weight loss, is identified in 30-40% of all non-small cell lung cancer (NSCLC) patients and associated with a 50% decrease in median overall survival. Management of CC is limited by the absence of biomarkers and knowledge of molecules that drive its phenotype. The evolving landscape of increased genomic testing of human tumors and derived cell lines has further given us an opportunity to leverage these findings to discover genetic biomarkers that regulate CC development through a novel in vivo human NSCLC cachexia screen.

Methods: To identify cachexia-associated molecules, we injected 54 human NSCLC lines into immunodeficient mice to form tumors, 17 of which produced an unambiguous phenotype of cachexia (n=10) or non-cachexia (n=7) in the murine hosts. Whole exome sequencing of these lines and tumors was conducted to evaluate for gene variants that segregated with cachexia potential. CRISPR/Cas9 targeted gene silencing in human NSCLC and mouse cancer lines verified if target genes conferred the cachexia phenotype. Circulating tumor DNA analysis of a 246 NSCLC patient cohort was used to confirm candidate gene variant association with cancer-related weight loss.

Results: Whole exome sequencing revealed that 8 of 10 cachexia lines, but none of the non-cachexia lines, possessed mutations in STK11/LKB1 (p= 2x10-12), a regulator of nutrient sensor AMP kinase. Silencing of STK11/LKB1 in human NSCLC lines conferred a cachexia phenotype after cell transplantation into immunodeficient and immunocompetent models, respectively. This host wasting was associated with an alteration in the immune cell repertoire of the tumor microenvironments that led to increases in local mRNA expression and serum levels of CC-associated cytokines resulting in adipose and muscle tissue wasting. Mutational analysis of circulating tumor DNA from 246 NSCLC patients identified 89% concordance between STK11/LKB1 loss of function variants and weight loss at cancer diagnosis (OR=17 ± 1, p=0.004).

Conclusions: The current data provides evidence that tumor STK11/LKB1 loss of function is a driver of CC in NSCLC, simultaneously serving as a genetic biomarker for this wasting syndrome.

C4 *(15 minutes)*

A geroscience approach to frailty biomarker discovery in cancer patients

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The process of carcinogenesis involves several mechanisms that, according to the geroscience hypothesis, also contribute to biological ageing. These processes, known as hallmarks of ageing, include genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, decreased nutrient sensing, cellular senescence, and stem cell exhaustion (1). The Targeting Aging with Metformin (TAME) Biomarkers Workgroup proposed a conceptual framework for biomarker selection in next-generation clinical trials in the geroscience field (2). The application of this theoretical framework has enabled the identification of dysregulation in energy production and metabolism, hypothalamic–pituitary–adrenal (HPA) stress response, and inflammation as relevant processes underlying frailty (3). Multi-biomarker analyses may therefore represent a suitable approach for tracking the multifaceted and dynamic nature of frailty in cancer patients. Based on this conceptual framework and taking advantage of the availability of well-characterised longitudinal cohorts of cancer patients, we are currently testing several panels of blood-borne biomarkers to obtain a deeper characterisation of frail patients, identify responders vs. non responders to cancer treatments, and provide prognostic information. These data will subsequenly be used to prescribe individualised treatments to cancer patients living with frailty, monitor treatment efficacy, and timely identify frailty progression.

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D1 *(15 minutes)*

Definition, diagnostic criteria and treatment of respiratory sarcopenia

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Although respiratory muscle function is indispensable for life support, its evaluation has not been included in the regular assessment of respiratory function or adequately evaluated in clinical practice. Considering this situation, we prepared a position paper outlining basic knowledge, diagnostic and assessment methods, mechanisms, involvement in respiratory diseases, intervention and treatment methods, and future perspectives on respiratory sarcopenia, and summarized the current consensus on respiratory sarcopenia. Respiratory sarcopenia is defined as a condition with low respiratory muscle strength and low respiratory muscle mass. We chose this definition because low respiratory muscle strength is essential in respiratory sarcopenia, just as muscle strength is becoming more critical in whole-body sarcopenia such as the EWGSOP2 and the SDOC, and because respiratory dysfunction is often observed in lung diseases other than respiratory sarcopenia. If respiratory muscle mass is difficult to measure, we can use appendicular skeletal muscle mass as a surrogate. Probable respiratory sarcopenia is defined when respiratory muscle weakness and decreased appendicular skeletal muscle mass are observed. If only respiratory muscle strength is decreased without a decrease in respiratory function, the patient is diagnosed with possible respiratory sarcopenia. Respiratory muscle strength is assessed using maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). MEP is performed at the maximum expiratory effort at the total lung capacity level, and MIP is usually performed at the maximum inspiratory effort at the residual volume level. The maximum value is recorded when the difference is less than 10% in the three measurements. Cut-off values for MIP and MEP are currently under consideration. Ultrasonography and computed tomography are commonly used to assess respiratory muscle mass such as diaphragm; however, there are insufficient data to propose the cutoff values for defining decreased respiratory muscle mass. Therefore, concerning respiratory muscle mass, standardization of measurement methods and the development of cutoff values, and minimal clinically important differences are required.

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D2 *(15 minutes)*

Cytokine signaling in adipose tissue browning and muscle wasting in chronic kidney disease-associated cachexia

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Pro-inflammatory cytokines, such as IL-6, trigger inflammatory cascades which may play an important role in the pathogenesis of chronic kidney disease (CKD)-associated cachexia. IL-6 elicits its function via classic signaling via binding to IL-6 receptor(R) and trans-signaling via binding to gp130. Recent studies suggest that trans-signaling of IL-6 has more diverse effects than classic signaling in inflammatory responses. Blockade of IL-6 trans-signaling by gp130 can affect cellular functions related to cytokines (such as IL-11, IL-27, CNTF, CLC, CT-1, LIF, OSM) other than IL-6.
Previously, we showed that cachexia phenotype (food intake, weight change, lean and fat mass content) was only partially rescued in Il6−/−/CKD mice. We now investigate the role of classic signaling of IL-6 (via anti-IL-6R mAb) versus trans-signaling of IL-6 (via sgp130Fc) in a mouse model of CKD-associated cachexia, induced by 5/6 nephrectomy. We compare energy homeostasis in CKD+anti-IL-6R, CKD+sgp130Fc, CKD+vehicle mice versus Sham+anti-IL-6R, Sham+sgp130Fc and Sham+Vehicle mice respectively. Sgp130Fc normalizes appetite and weight gain and increased lean mass content and skeletal muscle (gastrocnemius) in CKD mice and was superior to anti-IL-6R in CKD mice. Sgp130Fc ameliorates perturbations of energy homeostasis in adipose tissue and skeletal muscle whereas anti-IL-6R did not. Sgp130Fc normalizes lipolysis of adipose tissue by attenuating expression and protein content of adipose triglyceride lipase and protein content of phosphorylated hormone-sensitive lipase in CKD mice. Sgp130Fc normalizes the increased expression of beige adipocyte markers (UCP-1, CD137, Tbx1, Tmem26) and molecules implicated in adipose tissue browning (Cox2, Pgf2□, Tlr2, Traf6) in CKD mice. Additionally, sgp130Fc normalizes the molecular markers of processes implicated in CKD-associated muscle wasting such as myogenesis and muscle regeneration. Previously, we profiled gastrocnemius muscle expression of 84 key genes involved in tissue fibrosis in CKD mice. We found that 10 pro-fibrotic genes were upregulated while two anti-fibrotic genes were downregulated in CKD mice. In this study, sgp130Fc normalizes 10 of these 12 muscle fibrotic genes in CKD mice. By using RNAseq, we previously identified the top 12 skeletal muscle gene differentially expressed between mice with CKD versus control mice. These 12 genes' aberrant expression has been linked to increased muscle thermogenesis, fibrosis, and poor muscle and neuron regeneration. Sgp130Fc normalizes 10 of these top 12 differentially expressed muscle genes in CKD mice in this current study.
Our findings provide evidence that sgp130Fc may exert therapeutic advantage over anti-IL-6R in reversing adipose tissue browning and muscle wasting in CKD.

D3 *(15 minutes)*

Chronic obstructive pulmonary disease: a multi-organ disease

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Impaired muscle health (wasting, weakness, fatigue) is a major systemic comorbidity in Chronic Obstructive Pulmonary Disease (COPD) which enhances the impact of disease, and is associated with cognitive decline, impaired daily functional performance, and physical inactivity. Presence of muscle and cognitive dysfunction has also been observed in COPD patients with increased visceral adipose tissue and preserved lean mass 1. In the past years, the gut has become an increased area of research interest in COPD as 85% of the COPD population has one of more gastrointestinal symptoms. Using a comprehensive gut function panel, we recently found in COPD patients compromised small intestinal permeability and active carrier mediated transport (reflective of intestinal stress and enterocyte damage) and impaired protein digestion and absorption 2. Optimal gut function is needed to preserve amino acid availability to the periphery which is important for this population at high risk for muscle dysfunction and cognitive decline. In addition, impaired protein digestion influences the gut microbiome and production of microbial products (i.e., short-chain fatty acids (SCFA), acetate (C2), propionate (C3), and butyrate (C4), and branched-chain fatty acids (BCFA)) via increasing the colonic load of undigested proteins. Our recent data in COPD showed reduced plasma C2, increased fecal BCFA concentrations, and alterations in gut microbiome composition. Using a novel stable isotope approach to measure intestinal SCFA approach, we showed lower intestinal acetate, propionate, and butyrate productions in older than in young adults without further deterioration in COPD 3. In recent years, intestinal function has been linked to muscle and cognitive functionality in older persons and chronic diseases including COPD, heart failure and cancer 4, suggestive of a gut-muscle and gut-brain axis. The mechanisms underlying the gut-muscle–brain crosstalk need to be further explored in COPD to better understand the systematic features of these patients.

Factors known to affect function and metabolism are age and biological sex. A recent study examining 460 older adults > 50y stratified in young-older adults (50-70y) and middle old adults (70-85y) found that age independently affects protein and amino acid kinetics and muscle health in COPD. Whereas myofibrillar protein breakdown goes up with age, postabsorptive whole body protein balance decreases, and even more when a chronic morbidity such as COPD is present. The lower postabsorptive protein balance with age was associated with reduced muscle strength and physical performance and life expectancy in COPD 5. Sex-related differences exist in many lung diseases throughout the lifespan. For many years, COPD was considered a disease of older men but in the past 2 decades, its prevalence and rates of hospitalization have increased among women, closing this prevalence gap. There is an increased recognition that the clinical presentation of COPD is different in women than in men. Women with COPD have different disease burden, symptoms, and clinical trajectory than men and that women tend to develop COPD earlier in life. We recently observed that COPD males have a different nutritional and metabolic phenotype than the females despite similar levels of muscle wasting and weakness. COPD males were characterized by higher visceral adipose tissue, plasma CRP, metabolic syndrome characteristics (e.g., hypertension, dyslipidemia, obstructive sleep apnea), and upregulated protein and amino acid kinetics, whereas COPD females had lower BMI, fat mass, suppressed protein and amino acid turnover, and a severe reduction in net protein balance.

In conclusion, COPD is a multiorgan disease negatively affecting gut, muscle, and cognitive function. Age and sex have major effects on protein and amino acid metabolism in COPD which need to be considered when evaluating the systemic health features of these patients. Therefore, further research is necessary in COPD to assess when, how, and in whom certain systemic features develop to guide advances in future treatment approaches and personalized medicine.

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D4 *(15 minutes)*

Sarcopenia in cardio-respiratory illnesses

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E1 *(15 minutes)*

Cancer-induced rewiring of metabolism and zonation in the liver

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The liver plays a central role in metabolism. This role is closely related to a spatially organized tissue structure known as zonation, formed by repetitive hexagonal units called liver lobules. The lobules are associated with portal veins and central veins. Portal veins are at the junction of neighboring lobules, supplying nutrient- and oxygen-rich blood to nearby hepatocytes. Those hepatocytes are active for energy metabolism, consuming nutrients and oxygen. The consequently exhausted blood is then drained by central veins. In contrast to portal vein-associated hepatocytes, hepatocytes nearby central veins highly express xenobiotic metabolism genes.

Using spatial transcriptome analysis, we recently found that murine breast cancers remotely disrupt liver zonation in various distinct manners depending on biological pathways. For example, aspartate metabolism and triglyceride catabolic processes retain relatively intact zonation patterns, but the zonation of xenobiotic catabolic process genes exhibits a strong disruption. Such complexly rewired zonation might account for cancer-dependent pathophysiology in the liver. We recently revealed that nicotinamide-N-methyltransferase (NNMT), a portal vein-associated gene, mediates cancer-dependent disruption in liver metabolism, including urea cycle dysfunction. NNMT is an enzyme that methylates nicotinamide using S-adenosyl-methionine to produce 1-methylnicotinamide. We found that remote cancers rewire the NNMT pathway in hepatocytes, resulting in dysfunction in the urea cycle and pyrimidine metabolism.

In the presentation, I will summarize those recent discoveries on cancer-induced pathophysiology in the host livers and share our ongoing projects.

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E2 *(15 minutes)*

Targeting bile acid metabolism to counteract cancer cachexia

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Cancer cachexia is a multifactorial syndrome characterized by multiple metabolic dysfunctions. Besides the muscle, other organs such as the liver may also contribute to this syndrome. Using untargeted transcriptomics analyses, we identified a major downregulation of the bile acid pathway in the liver of cachexia mice. Bile acids can act as powerful signaling molecules and exert diverse actions on host metabolism, inflammation and energy homeostasis, which are key features of cancer cachexia.
In this talk, I will present our data indicating that cancer cachectic mice and patients display altered bile acid profile, with the demonstration in mice of the contribution of the bile acid to hepatic inflammation. We also found that alterations in the bile acid pathways and profile were intrinsically associated to cachexia and could not be attributed only to the tumoral presence. As cachectic mice exhibit a reduced bile flow, they were treated with ursodeoxycholic acid (UDCA), a choleretic compound commonly used in the treatment of chronic cholestatic diseases. We observed that UDCA did not improve hepatic inflammation and worsened muscle atrophy in cachectic mice.
Interestingly, the gut microbiota, an emerging player in the field of cancer cachexia, contribute to the bile acid diversification profile. The two main steps involved in the microbial metabolism of bile acids are the hydrolysis of conjugated bile acids into free bile acids, catalyzed by bile salt hydrolases (BSH), and the 7α-dehydroxylation (7αDH) to generate secondary bile acids. Therefore, our current investigation of the gut microbiota-bile acid crosstalk in cancer cachexia will be evoked.

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E3 *(15 minutes)*

Liver mitochondrial function in cancer cachexia

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Cancer cachexia is characterised by chronic systemic inflammation and major metabolic alterations, leading to lean and fat mass wasting. Cachexia compromises the success of cancer treatment and remains an unsolved problem in the clinical setting. While the liver plays a most prominent role in the control of intermediary metabolism, few studies have targeted the organ, and fewer still, in human cachexia. We therefore sought to address hepatic metabolic and inflammatory changes both in rodent models of cachexia (Walker 256 carcinosarcoma and Yoshida AH-130), and in patients (cachectic or weigh-stable colorectal cancer patients). The findings to be discussed point out to the presence of widespread CD68+ Myeloid cell infiltration in the organ, and decreased long-chain fatty acid oxidation capacity in hepatocytes. We shall describe disruption of metabolic zonation in the organ, commenting on results provided by models. In cachexia, the liver was found to actively secrete inflammatory factors, in particular, IL-1B, in concord with activation of the inflammasome pathway. Increased inflammation and the ATP deficit imposed by the Cori cycle (tumour-liver) both contribute to the aggravation of disease. The postulated mechanisms include inflammation-driven impairment of long-chain fatty acid transport in the cytoplasm (L-FABP) and to the mitochondrial matrix (carnitine palmitoyltransferase system) compromising hepatocyte energy balance, hence impairing liver function.

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E4 *(15 minutes)*

Liver NAD+ metabolism in cancer- and chemotherapy-induced cachexia

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Both tumor growth and chemotherapy contribute to the complex and the multi-systemic pathogenesis of cachexia (CC). The mechanisms underlying anorexia and muscle wasting have been quite well characterized, showing a marked energy depletion and wasting in cancer hosts. We have recently demonstrated that muscle NAD+ deficiency is a common trait of CC, likely resulting from impaired biosynthesis, as observed in both preclinical CC models and cancer patients1. Beyond the peripheral muscle impairments of energy production, also the liver control of systemic energy and glucose metabolism may be affected by both the tumor and chemotherapy exposure, making the liver a neglected, although with high potential, target for anti-cachexia interventions. Indeed, the administration of the cardiolipin-binding mitochondria-targeted compound SS-31 to mice bearing the C26 tumor and receiving Folfox chemotherapy (C26-F) determines a robust metabolome normalization in the liver, with little effects on the skeletal muscle2. In light of the several energetically demanding processes occurring in the liver of cancer hosts, NAD metabolite loss occurs in both severe (C26-F mice) and mild (conditional MSH2 KO mice) experimental cachexia1. Targeting NAD+ metabolism with vitamin B3 niacin effectively cures such deficiency and counteracts mitochondrial dysfunction in both the liver and the skeletal muscle. Our results highlight that NAD+ metabolism aberrations in CC are rather of systemic nature than specifically distinctive for the skeletal muscle. This presentation will summarize the available evidence on liver NAD+ metabolism in CC and will show a deeper molecular characterization of the impact of NAD+ repletion in the above-mentioned preclinical CC models.

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F1 *(15 minutes)*

Appetite, food quantity and quality in cancer cachexia

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Anorexia is one of the main domains of cancer cachexia occurring frequently and early during cancer journey. Different metabolic changes have been described in cancer-associated anorexia with multiple and often unclear mechanisms. In this scenario, anorexia represents a clinically relevant problem in cancer and is associated with negative outcomes and, in particular, with increased mortality [1]. Many factors were indicated to play a role in the development of cancer-associated poor appetite, such as high circulating levels of proinflammatory cytokines, tumor-derived anorexigenic factors, chemotherapy and altered gut microbiota. More recently, we found that GDF-15, a member of the transforming growth factor beta family, was higher in cancer patients and in particular in those presenting with low appetite [2]. However, research is still ongoing to clarify the complex pathophysiology of poor appetite in cancer.
From a more clinically point of view, physicians during cancer often diagnose anorexia in association with reduced food intake (i.e., hypophagia). In fact, tumor per se or anticancer treatments may determine the development of nausea, vomiting or specific nutrients malabsorption. Different type of tumors can determine anorexia and more frequently lung cancer and gastrointestinal tumors. These latter ones are associated with dysphagia, stomatitis, bowel obstruction and hormonal changes. Also, pain, anxiety and depression can be present and impact on appetite loss.
Our recent data showed a high prevalence of anorexia and hypophagia in gastrointestinal cancer patients newly diagnosed with the disease and naïve to any anticancer treatments [3]. These patients presented with malnutrition and an increased risk for it [3]. Also, a high prevalence of cachexia was present associated with low consumption of calories and protein that were significantly lower than ESMO/ESPEN recommended values.
These observations highlight the need for nutritional and metabolic interventions to be performed in the early phases of cancer journey.

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F2 *(15 minutes)*

Gut barrier, nutrient absorption and cachexia

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Cancer cachexia is a multifactorial syndrome characterized by multiple metabolic dysfunctions. Besides the muscle, other organs such as the gut and its inhabitants may also contribute to this syndrome. Indeed, intestinal disorders often occur in cancer patients, in association with body weight loss, and this alteration is commonly attributed to the chemotherapy. Whether alterations in the gut barrier function occurs before any chemotherapeutic treatment has been much less investigated.
During this talk, I will discuss the current evidence of alterations in the gut barrier function in cancer cachexia and how these phenomena may be related. How the gut microbiota may be a triggering factor or a biomarker of such alterations of the gut barrier function will also be evoked. Finally, potential consequences on nutrient absorption will be discussed.

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F3 *(15 minutes)*

Exercise, nutrition and omega-3 PUFA interventions for kidney cachexia

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Chronic kidney disease (CKD) hemodialysis patients have been shown to be at greater risk of developing conditions such as malnutrition, protein-energy wasting, cachexia, sarcopenia and frailty, and these conditions overlap, with some confusion in definitions and terminologies. Our group has investigated the presence of cachexia in hemodialysis patients from a cohort in Northern Ireland, UK (1). In particular, we detected a high prevalence of muscle weakness/dynapenia (up to 79% for males) (2). This is a key component for disability risk and poor quality of life in patients and needs to be addressed alongside overall body wasting.
Our current work has been focused on the development of a potential multimodal intervention to combat renal cachexia. We have recently published a framework for an intervention using a theory of change (TOC) approach, which is based upon expert consensus with critical review of the current evidence base (3). The ToC approach provides a theoretical framework which allows the effective elements of an intervention for patients with CKD who have cachexia to be better understood.
Within the proposed intervention, resistance training (RT) is deemed to be a key feature which is aimed to promote improvements in muscle strength, mass and potentially function. RT has a good level of evidence base on reducing sarcopenia and frailty in a range of studies and population groups, with some evidence in CKD (4). Nutritional counselling is also suggested with focus on providing adequate protein intake and dietary energy to promote systemic protein anabolic effects required to treat severe muscle wasting. However, improving the nutritional status and body composition in individuals who have cachexia is much more complex due to additional, profound metabolic alterations (e.g. due to heightened inflammatory burden). Therefore, we also have considered an anti-inflammatory component essential due to the pro-inflammatory and catabolic nature of the stage of disease. There is good evidence that Omega-3 fatty acids have potent anti-inflammatory effects in different groups, with some evidence in the hemodialysis population (5). This programme of work will be supplemented by a Cochrane review on multimodal interventions for cachexia management, the protocol for which is accepted and currently in press (6).

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F4 *(15 minutes)*

Examining biological sex variability in cancer-induced cachexia

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The heterogeneity of mechanisms involved in a variety of complex-trait diseases has become increasingly appreciated, leading to a greater understanding of the need for personalized medicine. Cancer cachexia is no different from other diseases, with the frequency and severity varying by tumor type, while known mechanisms of the condition vary in a similar manner. In recent years sexual dimorphisms in mechanisms of cachexia, and muscle atrophy overall1, have become ever more appreciated. We2 and others3 have provided evidence that the phenotype of cachexia may differ between sexes wherein, at least within preclinical studies, females appear to exhibit delayed impact on cancer-induced muscle wasting despite loss in fat mass and hepatosplenomegaly. Our laboratory has sought to better understand the intrinsic differences within the cachectic skeletal muscle from functional and -omics based approaches between biologic sexes across preclinical models of cachexia2. Further works in our laboratory are examining the efficacy of similar interventional approaches on muscle wasting during cachexia, suggesting a biologic sex-based dichotomy in response to mitochondria-targeted therapeutic approaches. Here I will discuss heterogeneity of muscle alterations during the early stages of cancer cachexia between biological sexes across models of lung and colorectal cancer-induced cachexia.

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G1 *(15 minutes)*

Tissue crosstalk during cancer cachexia: consequences of altered metabolic networks

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The circadian clock is the biological mechanism that dictates an array of physiological processes, including sleep/wake cycles, feeding rhythms, metabolic and endocrine functions. The circadian clock consists of a tightly controlled transcriptional-translational feedback loop that governs precise rhythms which maintain biological synchrony in all peripheral tissues. Importantly, disruption of the circadian clock results in altered timekeeping, and this rewiring of rhythms is detrimental to normal physiology and homeostasis. Recent advances from our group and other labs have connected disruption of the circadian clock with multiple signaling networks controlling tumor progression and metabolism. Our studies have identified that the circadian clock impinges on carbohydrate metabolism, and specifically de novo glucose production in the liver, in a genetically engineered mouse model of lung cancer cachexia. Specifically, we found that Rev-Erb□, a component of the circadian system, governs hepatic production of glucose from lactate/pyruvate sources, which are likely tumor-derived metabolites. Using metabolic fate mapping, our work now sheds light on the defined substrates that are preferentially utilized during cachexia-associated activation of gluconeogenesis. Our stable isotope tracing and metabolomics data indicate that activated lipolysis in adipose tissue provides key substrates to drive hepatic gluconeogenesis during lung cancer cachexia. Our molecular findings now implicate an intricate inter-tissue crosstalk between adipose tissue and liver as an important driver of de novo glucose production during lung cancer cachexia. A critical hallmark of cancer cachexia is the profound systemic alteration of metabolism, and our studies now suggest that these altered metabolic programs can be leveraged to further drive tumor metabolism.

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G2 *(15 minutes)*

Inflammation as target in cancer cachexia

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Cachexia is a multi-factorial syndrome accompanying cancer, with the most notable symptom being unintentional weight loss. Cachexia affects approximately 50% of all cancer patients, and nearly all patients with advanced disease. Increased morbidity and mortality in cachectic patients are due at least in part to decreased tolerance of chemo- and radiotherapy and worse surgical outcomes.

Patients with gastrointestinal cancers are disproportionally affected by cachexia. Patients with pancreatic ductal adenocarcinoma (PDAC) have amongst the highest incidence and greatest severity of weight loss. Importantly, although the incidence of cachexia is higher in patients with more advanced disease, approximately 70% of patients are considered cachectic at the time of PDAC diagnosis.

Increased circulating inflammatory cytokines have long been believed to drive wasting in cancer patients. In particular, elevated circulating levels of tumor necrosis factor, interleukin-6, and interleukin-1beta are often associated with weight loss in cancer patients. However, clinical trials targeting individual inflammatory factors have not been successful in mitigating cancer cachexia. Our work has revealed that significant heterogeneity exists in the levels of circulating inflammatory factors in cachectic PDAC patients, which is a potential explanation of why clinical trials targeting a single inflammatory factor in all patients have not been successful.(1) Further, in our dataset, the circulating inflammatory profile differs between male and female PDAC patients with cachexia. Other work in gastrointestinal cancers has suggested that age impacts circulating inflammatory profiles, with older individuals lacking significant correlations between weight loss and canonical inflammatory cytokines present in younger individuals.(2)

In summary, increasing evidence suggests significant heterogeneity of circulating factors in cachectic PDAC patients. Much like the targeting of a patient's tumor mutation profile, cachectic patients are likely to benefit from consideration of the complex factors that may contribute to their cachexia risk.

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G3 *(15 minutes)*

Examining the relationship between mitochondrial function and muscle force in cancer cachexia

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Cancer-induced cachexia is a multifactorial syndrome characterized, in part, by a loss of skeletal muscle mass and leads to progressive reductions in functional independence1,2. Such declines in muscle mass also reduce tolerance to anticancer therapies and overall survivability3 and is associated with increased hospitalization time4. Recent literature suggests skeletal muscle mitochondria are subject to damage during cancer cachexia5–7 and may be direct contributors to either muscle weakness or atrophy. Oxidative phosphorylation is impaired in the soleus, gastrocnemius and plantaris muscle of tumour-bearing mice, while reactive oxygen species (ROS) - in the form of mitochondrial H_2O_2 emission (mH_2O_2) - can be increased or decreased depending on the muscle and duration of cancer5,6,8. However, the time-dependent relationship between muscle atrophy, weakness and mitochondrial function remains unclear, as does the degree to which this relationship may vary between muscle types. Exploring the natural divergence of muscle responses to cancer may be an opportunistic approach to identify distinct mechanisms underlying muscle weakness and wasting during cancer cachexia. In order to investigate this, we used the Colon-26 (C26) carcinoma mouse model. C26 cells or phosphate-buffered saline (PBS) were injected in the hind flank of 8-week-old CD2F1 male mice. Tumours developed for 2 and 4 weeks. At 2 weeks, small tumours had no effect on body or muscle mass, while specific force production was lower in both quadriceps and diaphragm vs control. Pyruvate-supported ADP-stimulated mitochondrial respiration was lower in quadriceps, while mitochondrial H_2O_2 emission was elevated in diaphragm without changes in ETC protein contents in both muscles. At 4 weeks, the presence of large tumours corresponded to lower tumour-free body mass, muscle mass, and cross-sectional area of quadriceps and diaphragm fibres. Specific force production was the same as control in the quadriceps but remained lower in diaphragm. Mitochondrial respiration was increased in both muscles vs control across a range of [ADP] despite lower ETC protein content in quadriceps and unchanged contents in diaphragm. Using the C26 tumour-bearing mouse model, we reveal muscle weakness precedes atrophy in quadriceps and diaphragm. Energetic insufficiencies were more pronounced in quadriceps whereas mitochondrial redox stress was more evident in diaphragm, yet both muscles showed a delayed correction, if not super-compensation, as cancer progressed. In quadriceps, increased mitochondrial respiratory control was related to a surprising increase in specific force production at 4 weeks that likely mitigated the magnitude of reduction in absolute force due to atrophy. These findings demonstrate the effects of cancer on one muscle do not necessarily predict the response in another muscle type. Moreover, the heterogeneous muscle-specific and time-dependent mitochondrial relationships to cancer may provide an opportunity for informing a more targeted approach to developing mitochondrial therapies to improve muscle health in this debilitating disorder.

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G4 *(15 minutes)*

Deletion of FNDC5/Irisin protects against cancer induced cachexia syndrome

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Cancer cachexia (CC) is characterized by severe skeletal muscle wasting and white adipose tissue (WAT) metabolic abnormalities. As the browning of WAT is a feature of CC and as the hormone irisin has been shown to promote thermogenic energy conversion in adipocytes, we sought to determine if deletion of the precursor for irisin, Fibronectin type III domain-containing protein 5 (FNDC5), could improve CC. Irisin is a circulating hormone cleaved from FNDC5 in response to exercise.
Global FNDC5 knock-out, KO, animals were implanted with Lewis Lung Carcinoma (LLC) or metastatic MC38 colorectal cancer (mMC38). Our data show that male FNDC5 KO mice are protected against CC induced by both tumors. In contrast, no significant protective effects were observed in the female KO mice. Tumor growth had no effect on male FNDC5 KO tumor hosts body weight not skeletal muscle mass in contrast to wildtype (WT) control mice carrying the same tumor mass. More importantly, the deletion of FNDC5/irisin prevented muscle weakness and increased total locomotor activity. Increased expression of UCP1 characterized the WAT of both male and female WT LLC bearers, however, only in the male FNDC5 KO was there no increase in UCP1. To verify that irisin, the cleaved product of FNDC5, is directly contributing to the pathogenesis of CC, irisin was reintroduced by means of AAV8-Irisin into male KO mice bearing the LLC tumor. The introduction of irisin into the circulation reversed the protective effect of irisin global deletion on muscle wasting. The cachectic phenotype returned to the KO animals carrying the LLC tumor. Although reintroduction of normal levels of irisin reversed the positive effects of irisin deletion, the hyperexpression of irisin could have negative effects in healthy, non-tumor bearing wildtype mice. Healthy wild-type mice were infected with the AAV8-Irisin to express pathological levels of irisin. At the time of the sacrifice, the elevated levels of Irisin were associated with reduced WAT mass with increased levels of UCP1. More importantly, we observed reduced skeletal muscle mass with increased expression of UCP2 and UCP3.
Our findings suggest that presence of FNDC5/Irisin is a regulator WAT and skeletal muscle metabolism in cancer and could represent a novel target for the treatment and prevention of cancer cachexia and potentially other conditions associated with muscle loss.

H1 *(15 minutes)*

Effects of aging on human muscle atrophy with immobilization

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Muscle disuse-induced atrophy is a rapid process, whether induced by disease, inactivity, or hospitalization (Nunes et al., 2022). For older individuals who may already be experiencing sarcopenia, episodic disuse represents a threshold event from which they may not recover lost muscle mass or function (Bell et al., 2016). Older adults are more prone to periods of disuse, which can be as innocuous as a period of reduced physical activity (McGlory et al., 2018), resulting in the rapid onset of insulin resistance and accelerating mitochondrial dysfunction. As such, muscle disuse profoundly affects the trajectory of various metabolic diseases and can affect mobility. A critical question central to mitigating disuse is what process predominates to bring about disuse. This question is not completely settled (Phillips & McGlory, 2014), and this is pivotal as the process most affected by disuse – muscle protein synthesis (MPS) or muscle protein breakdown (MPB) – would be the best candidate to aim at therapeutically. The balance of evidence from humans points towards a decline in MPS as a key event in disuse (Atherton et al., 2016), and thus therapies to augment MPS have been attempted. Several nutraceutical therapies show promise, including protein with high leucine content, n-3 fatty acids, and possibly creatine; however, critical trial data are still unavailable to make definitive recommendations. The impact of any reloading or even contraction of the muscle in the form of physical therapy or electrical stimulation is likely to offer some anti-atrophy therapeutic benefit. The best strategies may be a combination of this with nutraceutical support.

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H2 *(15 minutes)*

The human neuromuscular junction in ageing and exercise

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Ageing is associated with a loss in skeletal muscle mass and function. While there are many contributing factors to this decline, the loss of muscle fibres is one of the most striking and prominent. Importantly, once muscle fibres are lost, they cannot be replaced, so the loss of muscle fibres is permanent and irreversible. How muscle fibres are lost is debated but there are at least two possibilities: 1) lumbar motoneurones are reported to decrease in number with age; and 2) the loss of muscle fibres one by one through deterioration of the neuromuscular junction. The loss of a single motoneurone innervating muscle fibres in the human thigh muscle will orphan thousands of muscle fibres at once. While some fibres will be rescued by sprouting of a neighbouring motoneurone axon, some fibres will begin to atrophy and inevitably die in the absence of action potential delivery. On the other hand, the loss of innervation at the level of the neuromuscular junction only affects one fibre at a time and is potentially reversible. At least it has been shown in animal models that exercise can reverse age-related synaptic alterations. Studying this in humans is more challenging but measures of innervation and denervation can be detected in muscle biopsy tissue samples (Soendenbroe et al. 2021). For example, denervated fibres express neural cell adhesion molecule and acetylcholine receptors throughout the fibre rather than solely at the neuromuscular junction. The muscle of older healthy individuals contains a higher proportion of denervation muscle fibres, and it appears that remodelling of the neuromuscular junction is evident after a single bout, or several weeks, of resistance exercise, as well as lifelong exercisers (Soendenbroe et al. 2022a; Soendenbroe et al. 2022b). The positive impact of exercise on muscle innervation may explain the superior muscle mass and function observed in lifelong exercisers when they reach advanced age, potentially by promoting motoneurone survival.

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H3 *(15 minutes)*

The role of nutrition in aging: appetite loss

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Appetite loss is a common occurrence among older adults, cancer patients, those using polypharmacy, and those with chronic organ failure such as heart failure, renal failure or COPD. Anorexia of aging turns out a common term to identify this condition in older adults irrespectively if occurring primarily or secondarily. Weeks to months after appetite is lost, some degree of weight loss is observed. Weight loss has several adverse outcomes and is associated with sarcopenia, frailty and mortality. Thus, the identification of appetite loss among older patients is crucial to implement preventive measures of weight loss and to rapidly identify diseases that can begin altering appetite as a tip of the iceberg phenomenon. Good clinical examples are depression and dementia. Among various instruments, the Simplified Nutritional Appetite Questionnaire (SNAQ) is an easy and fast alternative to identify appetite loss and to add monitoring clinical response. In this lecture we will speak on how to identify appetite loss or anorexia of aging and update the evidence on therapeutic approaches. Besides oral nutritional supplementation, evidence of treatment options are low to very low, including among oncologic patients.

H4 *(15 minutes)*

Brain muscle cross talk

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Skeletal muscle is an endocrine organ and secretes myokines in response to exercise which plays a biological role in glucose and lipid metabolism, immune function, cognition, endothelial cell function and cancer (1). Physical exercise has been shown to reduce anxiety, depression, and has positive effects on memory, attention, executive function, processing speed, language, motor skills, visuospatial skills, and brain volume (2). Declining handgrip strength or gait speed are known to be associated with cognitive decline. Brain-muscle crosstalk is mediated through cytokines, hormonal responses and myokines such as irisin which may stimulate the release of brain-derived neurotrophic factor and neurogenesis. In addition, physical exercise improves insulin sensitivity, overall metabolic profile and endothelial function which reduces overall stroke risk which is a known risk factor for future cognitive decline (3). Both sarcopenia and neurodegenerative disorders share a bidirectional relationship where sarcopenia can lead to decline in cognition, and physical inactivity can accelerate decline in muscle mass and muscle quality.

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I1 *(15 minutes)*
Tumor-derived exosomes in cachexia

Joanna Lima
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Colorectal cancer (CRC) is the third most common cancer worldwide and represents the second cause of cancer death. In up to 60% of CRC cases, the most severe complication is the unintentional loss of muscle mass, with or without loss of adipose tissue and increased inflammatory state, which is broadly defined by cachexia. Furthermore, cachexia research is still understudied and unfortunately, was recently described as a direct cause of death of approximately 20%-30% of cancer patients.
Exosomes are extracellular vesicles that originate from multivesicular bodies that carry with them lipids, proteins, DNAs, RNAs, mitochondrial components, and microRNAs, delivery to some target cell, constituting a new type of cell-cell communication. It is well known that exosomal content can be altered in response to different stimuli, and exosomes are potentially transferred to nearby cells altering the signalling of other cells. Tumour cells release a higher number of extracellular vesicles than normal cells and they can contribute to tumour growth, inflammation, hypoxia-related signalling, and angiogenesis. This has led to an interest in characterizing the effects of tumour cell-derived exosomes in cancer cachexia. We performed a quantitative proteomic in colorectal tumour biopsies of patients diagnosed with and without cachexia and we identified HSP70 and HSP90 as key markers in tumors of cachectic patients. High levels of chaperones are known to modulate proliferation, immune escape, tumor aggressiveness and it has been demonstrated that the Hsp70 expressed in extracellular vesicles can activate inflammatory signalling pathways. Thus, we identified high levels of HSP70 in exosomes derived from tumours of cachectic patients are associated with cachexia biomarkers, such as c-reactive protein and BMI. Furthermore, we characterized TNF-α and IL8 as cytokines mediated by tumour-derived exosomes from cachectic patients.

I2 *(15 minutes)*

Intracellular peptides: potential biomarkers and therapeutic targets

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Introduction: Peptides are important signaling molecules involved in a wide range of biological processes. Intracellular peptides (InPeps) are specific peptides produced within cells by proteasome-mediated protein degradation, and they have been found to exhibit biological activities. The presence of InPeps in biological samples such as plasma and liquor raises the question of whether these peptides can participate in cell signaling beyond their production site, potentially affecting physiological processes far away from their origin. In this context, the study of InPeps is of significant importance in understanding cell communication. Objective: This presentation aims to explore the potential role of InPeps in cell communication, focusing on their identification and biological activities. Recent advances in peptidomics and the identification of novel InPeps will be discussed, highlighting the potential for these molecules as biomarkers and therapeutic targets. Methods: A literature review shall be conducted to present relevant studies on InPeps, and their potential role in cell communication. Results: Recent advances in electrospray ionization mass spectrometry have enabled the identification of thousands of InPeps in diverse biological models. The relative levels of InPeps were shown to change during cell cycle, obesity, thermogenesis, among others. As examples of InPeps, hemopressin (PVNFKFLSH) and Pep19 (DIIADDEPLT) have been identified as inverse agonists of CB1 cannabinoid receptors and have been shown to affect blood pressure, food intake, and browning of white adipose tissue. In addition, InPeps profile were modulated in liquor of patients with cerebral aneurism, and in plasma of patients with COVID-19. Conclusion: The identification of InPeps in biological samples and their biological activities provide new insights into the mechanisms of cell communication. Furthermore, it raises the possibility of using these peptides as biomarkers and therapeutic targets to various diseases. Further research is still required to understand the specific roles of ECV-associated peptides and their potential effects on pathophysiological processes.

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I3 *(15 minutes)*

Extracellular vesicles and inflammation: from cachexia to COVID-19

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Cachexia, a comorbidity of cancer, is a complex inflammatory/metabolic syndrome, in which organ crosstalk contributes to body mass wasting, with negative impact on the success of anti-cancer therapy. Circulating extracellular vesicles, secreted by the different organs of the host and by the tumour, may be of relevance in the scenario, as our findings point out to a 2-fold increase in the number of circulating vesicles in cachectic patients (colorectal cancer, $p<0.0001$), as compared to the weight stable controls. The acute phase proteins HSP70 ($p<0.02$) and HSP90 ($p<0.04$) were enriched in the circulating exosomes of cachectic patients, in relation to weight stable cancer patients, as also was the content of TNF-a ($p<0.039$) and of IL-8 (<0.02). Exosome-associated HSP-70 was found to bear a positive correlation with both decreasing BMI and increased circulating C-Reactive protein concentration. Bearing in mind the marked inflammatory status of patients with the severe form of COVID-19, we postulated that, in a similar manner to cachexia, the organs of the patient would very likely, contribute to the systemic nature of the disease, by actively releasing exosomes loaded with inflammation controlling factors. Having examined hospitalised COVID-19 patients (n-=31), we found that disease severity was related with progressive decrease of IL2 and IL6 content of isolated exosomes. We intend to discuss and contrast the role of exosome-associated inflammatory factors in both diseases, and briefly comment on new findings in patients with long COVID syndrome.

I4 *15 minutes)*

Tumor-host cross-talk: focus on the extracellular vesicles

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The tumor-host interaction is becoming the most complex challenge to be faced in the management of cancer patients, in terms of both treatment effectiveness and quality of life. Indeed, this cross-talk is crucial for cancer onset and progression, impacting on tumor clonal expansion, enlargement, invasiveness and metastasis, immune escape and drug resistance. The other way around, a developing tumor markedly impinges on the host organism draining substrates and oxygen, shaping the tumor microenvironment and the host organism to its own needs, progressively interfering with metabolism and function of distant tissues. Humoral mediators produced by cancer as well as by the host in response to the presence of the tumor, are the main actors in such cross talk. In this regard, pro-inflammatory cytokines, neuroendocrine mediators, hormones, but also epigenetic modulators such as microRNAs (miRNAs) have been proposed to play a role.
In the last few years, extracellular vesicles (EVs) have been shown to contribute to the cross-talk occurring among distant tissues, including the tumor, as well as among cells within the same tissue, through the exchange of canonical signaling factors, proteins, nucleic acids and lipids (1).
EVs released by cancer cells impinge on both cells and extracellular matrix in the tumor microenvironment (1). EVs derived from lung or pancreatic cancer cells have also been proposed to contribute to cancer-induced muscle wasting. Such an effect would be achieved through the release of miRNA-21 (2). Along this line, cultured myotubes exposed to EVs released by the C26 colon carcinoma cells showed changes in oxidative metabolism and mitophagy (3). Consistently, EVs circulating in the blood of tumor-bearing animals were able to transiently mimic cancer-induced muscle wasting when infused into healthy animals (3). Finally, EVs have been proposed to be used as tools to vehicle drugs/siRNAs/miRNAs aiming to target specific molecules involved in the pathogenesis of cachexia (4).
According to these observations, EVs are an additional tool by which cancer cells convey signals to both the tumor microenvironment and distant tissues, where they can contribute to pathological events such as, inflammation, metabolic derangements, and loss of proteostasis.

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J1 *(15 minutes))*

Physical function endpoints in cancer cachexia clinical trials

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In cancer cachexia there is a lack of clarity on optimal endpoints for clinical trials. This has served to impede progress and led to the refusal of marketing authorisations of investigational medicinal products. Experience with the FDA, MHRA and EMA has highlighted that a detailed appraisal of cachexia trials and endpoints used, may help to inform clinical trial design. To address this the cachexia endpoints working group seeks to appraise trials done (including methodological quality) in an effort to elucidate which endpoints may be optimal.
Following registration in PROSPERO (CRD42022276710) an electronic search was conducted of Ovid Medline, Embase and Cochrane from 1stJanuary 1990 to 31st December 2021. Eligible trials met the following criteria: randomised design, intervention (drug or non-drug), sample size >40 participants, cancer and >14 days intervention. The search and outputs were managed using Covidence (AUS) and two independent reviewers carried out article selection. Following a pilot, an electronic data extraction template was used to summarise key data. The Downs and Black checklist evaluated the methodological quality of all eligible trials. The following objective clinical assessments of physical function were assessed: Hand grip strength (HGS), six minute walking test (6MWT), stair climb power, short physical performance battery (SPPB) and the timed 'up and go' test (TUG) as were functional assessments as part of other assessments (e.g. FAACT).
The literature search identified 5965 potential studies. After Review and appraisal, 71 studies were identified as eligible for this review. Trials varied considerably in terms of sample size, tumour sites studied and which physical function endpoints were used (40 – 929). Pharmacological interventions were assessed in 38 trials (53.52%) of these 11 (28.95% - n=1184) examined megestrol and 5 (13.15% - n=1928) examined anamorelin, nutritional interventions were assessed in 21 trials (29.57%), and exercise-based interventions were assessed in six trials (8.4%). The remaining six trials (8.4%) assessed multimodal interventions. Among the objective measures of physical function, hand grip strength (HGS) was most commonly examined (33 trials, n=5081), followed by the 6-minute walk test (12 trials, n=1074), and SCP, TUG and SPPB were each assessed in three trials. KPS was more commonly assessed than the newer ECOG-PS (16 vs 9 trials), and patient reported EORTC QLQ-C30-PF was reported in 25 trials. Twenty-nine studies assessed two or more measures of physical function.

This presentation will focus on measures of physical function as endpoints investigating cachexia therapies.

J2 *(15 minutes)*

Appetite and dietary intake endpoints in cancer cachexia trials: A systematic review

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Rationale: There is no consensus on the optimal endpoint for evaluating effect on appetite or dietary intake in cancer cachexia trials. The variety of endpoints used is an obstacle both when comparing interventions, and when trying to understand the clinical value of an intervention. It is of fundamental importance to agree on how to evaluate appetite and dietary intake in cancer cachexia trials. The optimal endpoint must be meaningful to the patient and health care personnel, reflect the mechanism of action of the intervention studied, be easy to measure, and measure what is intended precisely and consistently. The aim of this systematic review is to summarize and evaluate outcome measures previously used.
Method This systematic review is reported as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes Statement (PRISMA). A protocol was previously published in PROSPERO database under registration 2022 CRD42022276710.
A search for studies published from 1st January 1990 until June 2nd, 2021, was conducted using the databases MEDLINE (Ovid), EMBASE (Ovid) and Cochrane Cochrane Central Register of Controlled Trials. Eligibility criterions were controlled trials aiming to treat or attenuate cachexia in adult patients with cancer, sample size >40, and >14 days intervention. Studies using pharmacological, nutritional, exercise, and/or behavioral interventions were included. There were no restrictions concerning type of comparator.
All articles identified were transferred to Covidence software (AU), and two independent reviewers carried out article selection. A data extraction table was developed, pilot-tested and refined within the review group. Data was extracted by two independent review authors. The methodological quality of each study was assessed by modified Downs and Black Checklist.
Results The literature search resulted in 5975 articles, of which 369 were fully read, and 80 articles included in the final qualitative synthesis.
The retrieved trials included 40 to 628 patients, A wide range of cancer diagnoses were studied, most frequently gastrointestinal and lung cancer. To investigate effects on appetite, pharmacological interventions were primarily used, while nutritional interventions were mainly used when investigating effects on dietary intake. Intervention periods varied between 4 and 16 weeks (range 2 weeks - 2 years).
Sixty-four of the 80 trials included outcome measures on appetite, and 22 included outcome measures assessing dietary intake. Six studies evaluated/assessed both appetite and dietary intake. Appetite was the primary outcome for fifteen studies, and dietary intake for four.
The most frequent outcome used in studies assessing appetite was VAS (visual analog scale) or NRS (numeric rating scale) (26 of 64 studies). Also, the appetite question from EORTC QLQ -C30 or PAL-15 (24 studies) and the appetite question from NCCTG (11 studies) were frequently applied. Study specific or health care reported assessments were seldom used, particularly not in recent years. Of the studies assessing dietary intake, 14 used food records (prospective registrations) and 10 used retrospective methods (24-hour recall or dietary history).
The focus in this presentation is use of nutritional endpoints in cancer cachexia studies.

Ref: Endpoints in clinical trials in cancer cachexia: where to start? Laird BJA, Balstad TR, Solheim TS.Curr Opin Support Palliat Care. 2018 Dec;12(4):445-452

J3 *(15 minutes)*

Quality of life endpoints

Marianne Hjermstad
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Background. The use of patient-reported outcome measures (PROMs) of Quality of Life (QOL) is common in cachexia trials. Besides being a regulatory requirement in pharmaceutical trials, the patient's self-report on health, functioning, well-being, and their own perceptions of life and care is an important information source. The main objective is to describe the frequency, diversity, and reporting of QOL endpoints used in cachexia clinical trials.
Methods. Electronic literature searches were performed in Medline, Embase, and Cochrane (1990 to 2021). After the removal of duplicates, 5,975 articles were retained for evaluation. Eligibility criteria included QOL being a study endpoint using a validated measure, controlled design, adults (>18 years), >40 participants randomized, and an intervention exceeding two weeks. The review procedures and data extractions were conducted using the Covidence software. Two or more independent authors screened all records to reach a consensus. The review process followed the PRISMA guidance for systematic reviews was followed. The protocol can be found on PROSPERO (CRD42022276710).
Results. After review and appraisal, 46 papers were deemed eligible for evaluations of QOL. Sample sizes varied considerably (n=42 to n=469). Thirty-five trials (76%) included multiple diagnostic groups. Twenty-seven trials (58%) were multi-component with various drugs and dietary supplements, while seven (15%) used a nutritional intervention alone. The median duration of the interventions was 12 weeks (4-96). The most frequent QOL measure was the EORTC QLQ-C30 (57%), relative to different FACIT questionnaires (30%).
QOL was a primary, secondary, or exploratory endpoint in 15 (33%), 26 (56%), and five (1%)trials, respectively. Statistically significant results on one or more QOL items favoring the intervention group were found in 15 trials. Eight of these used a complete multidimensional measure, while a summary QOL measure was the most common overall. Nine trials (20%) had defined a statistically or clinically significant difference for evaluation of effect, five of these using QOL as a primary outcome. None of the trials presented effect size as a magnitude of change. Correlation statistics with other study outcomes were rarely performed.
Conclusions. QOL is an important endpoint in cachexia trials, but the assessment and reporting vary considerably. We recommend using well-validated QOL measures, including cachexia-specific items such as X, Y, and Z. We also encourage a more strategic and scientific-based approach to PROM research in cachexia rather than looking at QOL as an add-on metric. This focused approach will improve the research base in this field.

J4 *(15 minutes)*

Endpoints for cancer cachexia clinical trials

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Clinical trials serve several different purposes, including for regulatory approval processes, to support reimbursement decision making as well as to informing the medical community and international guidelines in their efforts to recommend optimized therapeutic strategies. Hence, clinical trials need appropriate and valid endpoints. The presentation will review available options for cachexia and sarcopenia trials and comment on strengths and weakness of the different approaches that can be taken for morbidity/mortality endpoints, functional outcomes, strength and quality of life asessment as well as PROs in general.

K1 *(15 minutes)*

Anti-Fn14 therapy for cancer cachexia

Nick Hoogenraad
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Cancer cachexia is an underestimated condition with huge impact on survival and quality of life for many cancer patients. Currently, there is no reliable diagnosis for this condition and developing therapies for cancer cachexia has not been successful to date, in part due to the challenges of achieving robust quantitative measures as a readout of patient treatment. Hence, identifying biomarkers to assess the outcomes of treatments for cancer cachexia is of great interest and important for accelerating future clinical trials. Developing a sensitive method able to distinguish other conditions that often occur with cancer such as sarcopenia and anorexia and which can objectively monitor and quantify the outcome of specific treatments for cancer cachexia is urgently required.
We have previously reported that tumoral Fn14 induces cancer cachexia in several preclinical models, with an antagonistic anti-Fn14 antibody treatment able to reverse this condition, making Fn14 a potential target for treating cancer cachexia [1]. We also showed that the signal for cachexia originated in the tumour as Fn14-/- mice developed cachexia, dependent on tumoral Fn14 and that this activity of Fn14 was independent of its ligand, TWEAK.
To assist us in finding biomarkers that are specific for cachexia, we established a novel xenograft model for cancer cachexia with a cachectic human prostate cancer cell line, which was responsive to anti-Fn14 mAb treatment. Using RNA-seq and secretomic analysis, genes differentially expressed in cachectic and non-cachectic tumors were identified and validated by digital droplet PCR. Correlation analysis was performed to investigate their impact on survival in cancer patients. This led to the discovery of a total of 46 genes which were highly expressed in cachectic tumors and which were downregulated by anti-Fn14 mAb treatment [2]. High expression of the top 10 candidates was correlated with low survival and high cachexia risk in different cancer types. Elevated levels of LCN2 were observed in serum samples from cachectic patients compared with non-cachectic cancer patients. The top 10 candidates identified could serve as potential biomarkers for cancer cachexia. The diagnostic value of LCN2 in detecting cancer cachexia was confirmed in patient samples.

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K2 *(15 minutes)*

Peptide-based therapies for cancer cachexia

Stephan Herzig
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Cancer cachexia is a severe systemic wasting disease in cancer patients that negatively affects quality of life and survival. Despite the severity of the condition, no FDA-approved drug is available. We recently discovered the destabilization of the AMPK complex in adipose tissue as a key event in cachexia-related adipose tissue dysfunction and developed an AAV-based approach to prevent AMPK degradation and prolong cachexia-free survival. Here, we discuss the development and optimization of a prototypic peptide, which is efficiently taken up by adipocytes, inhibits lipolysis and restores AMPK signaling. Systemic delivery of this peptide into tumor-bearing animals prevents the progression of cancer cachexia and preserves body weight and adipose tissue mass with no discernable side effects in other peripheral organs, thereby achieving proof-of-concept.
This peptide approach now provides a promising platform for further (pre)clinical development towards a novel, first-in-class approach against cancer cachexia.

K3 *(15 minutes)*

Targeting the TGFbeta pathway

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Cancer cachexia is a debilitating condition characterized by muscle wasting, weight loss, and weakness. It affects up to 80% of advanced cancer patients and contributes to increased morbidity and mortality. The pathophysiology of cancer cachexia is multifactorial, but it is believed to involve the activation of inflammatory cytokines and growth factors, including the transforming growth factor beta (TGF-β) pathway. The TGF-β family are key regulators of muscle growth and differentiation, and dysregulation has been implicated in the development of cachexia. Inhibition of the TGF-β pathway has been shown to prevent muscle wasting in preclinical models of cancer cachexia, and early clinical trials have shown promising results. In this presentation, we will discuss the current understanding of the TGF-β pathway in cancer cachexia and the preclinical and clinical evidence for targeting this pathway for the treatment of cachexia. We will also discuss the challenges and opportunities in developing TGF-β inhibitors as therapeutics for cancer cachexia. Finally, we will highlight the potential of combination therapies targeting both TGF-β and other pathways in improving the efficacy of cachexia treatments.

K4 *(15 minutes)*

Modulating metabolic pathways – impact on cachexia and malnutrition

Bei B. Zhang
Pfizer, USA

Cachexia associated with cancer and other chronic illnesses is a complex multi-system syndrome driven by the composite effects of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism, and altered inflammation. Cachexia is characterized by involuntary weight loss, including skeletal muscle mass, that progresses to functional impairment over time. The impairment of muscle function can cause a significant decline in physical performance, which leads to worse clinical outcomes and poor quality of life in patients with cachexia. Meanwhile, there are significant unmet needs in malnutrition and anorexia in older adults and there is a breadth of adverse outcomes associated with anorexia/appetite loss in older populations. Growth differentiation factor 15 (GDF15) is a stress-responsive cytokine secreted by damaged/stressed cells, immune cells and tumor cells. Neutralization of GDF15 represents a effective therapy with the potential to be transformative in the management of cachexia, including body mass restoration and improvement in muscle function and physical performance as demonstrated in preclinical models. In addition, data from human genetics and aged rat studies imply that MC4R antagonism affords the novel opportunity for appetite and body weight regulation.

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L1 *(15 minutes)*

GDF-15 inhibition with ponsegromab for treating cachexia in patients with advanced cancer

Jeffrey Crawford
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Patients with advanced cancer often experience cachexia, a debilitating metabolic syndrome causing unintended weight loss, anorexia, fatigue, muscle atrophy, impaired physical function, and increased risk of death.1,2
A cytokine associated with cachexia, growth differentiation factor 15 (GDF-15), is elevated in certain types of cancer, especially advanced cancers.1-3 GDF-15 inhibition may improve cachexia-related symptom burden and is being investigated as a potential therapeutic target.
Ponsegromab, a humanized monoclonal antibody, is a highly selective and potent GDF-15 inhibitor that showed promise in a mouse tumor model of cachexia3 and has progressed into clinical trials. In the first-in-patient, open-label, single-arm, Phase 1b trial (NCT04299048), 10 participants with advanced cancer, cachexia, and elevated serum GDF-15 concentrations received ponsegromab subcutaneously every 3 weeks plus standard of care anti-cancer treatment for 12 weeks. Ponsegromab demonstrated an acceptable safety profile with no treatment-related adverse events, injection site reactions, anti-drug antibodies, or adverse trends in clinical laboratory tests, vital signs, or electrocardiogram parameters. Ponsegromab serum levels, evident from the first dose and sustained through treatment, were associated with substantially reduced serum unbound GDF-15 levels. In exploratory analyses, body weight increased at all time points through 12 weeks of treatment and the subsequent 12 weeks of follow-up. Least square mean weight gain of 4.6 kg at week 12 represented a 6.6% increase from baseline. Signals for improved physical activity and quality of life, including appetite, were also observed.
The clinical development of ponsegromab for cancer-related cachexia continues with a Phase 2 trial (NCT05546476) currently enrolling ~168 participants with cancer, cachexia, and elevated serum GDF-15 concentrations. This trial has a Part A and a Part B. Part A consists of a 12-week randomized, double-blind, placebo-controlled period, during which patients receive 1 of 3 ponsegromab doses or placebo every 4 weeks. Body weight change from baseline at 12 weeks is the primary endpoint. Changes in physical activity, gait, anorexia/appetite, nausea, vomiting, fatigue, and safety are secondary endpoints. Upon completion of Part A, participants can opt to receive open-label ponsegromab every 4 weeks for up to 1 year in Part B.
Ponsegromab is showing early promise for cancer-related cachexia and the clinical development program is continuing.

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L2 *(15 minutes)*

Multimodal exercise nutrition and anti-inflammatories for cachexia (MENAC)

Barry Laird
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Barry Laird, Tora Solheim, Trude Balstad, Marie Fallon, Stein Kaasa
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It has been hypothesised that due to the multi-faceted genesis of cancer cachexia, interventions should target physical function, nutritional and systemic inflammation simultaneously in the context of systemic anti-cancer therapy (SACT).
The MENAC (Multimodal Exercise Nutrition and Anti-Inflammatories for Cachexia) aims to test this hypothesis through a large international randomised controlled trial. Adult patients with incurable pancreatic cancer or stage 3b/4 non small cell lung cancer were randomised to receive the MENAC intervention versus standard cancer care, alongside SACT. The MENAC intervention consisted of patient directed exercise (resistance and aerobic), nutritional interventions (dietary advice and omega 3 fatty acid containing Oral Nutritional Supplements) and ibuprofen. Assessments included body weight, lean mass and physical activity alongside assessments of quality of life.
The trial has now completed recruitment and analysis is underway. The rationale for the trial will be presented including the feasibility study. The challenges of designing and running such a complex intervention trial will be discussed, as will the potential implications for future work in this area.

L3 *(15 minutes)*

Pilot clinical trial of macimorelin to assess safety and efficacy in patients with cancer cachexia

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Background: Cancer cachexia is associated with reduced body weight, appetite, and quality of life (QOL) with no approved treatments (1). Growth hormone secretagogues like macimorelin have potential to mitigate these effects (2).
Methods: This pilot study assessed the safety and efficacy of macimorelin for one week. Efficacy was defined a priori as one-week change in body weight (≥0.8 kg), plasma insulin-like growth factor (IGF)-1 (≥50 ng/mL), or QOL (≥15%). Secondary outcomes included food intake, appetite, functional performance, energy expenditure, and safety laboratory parameters. Patients with cancer cachexia were randomized to 0.5 or 1.0 mg/kg macimorelin or placebo; outcomes were assessed non-parametrically.
Results: Participants receiving at least one of either macimorelin dose were combined (NN=10; 100% male; median age = 65.50 +/- 2.12) and compared to placebo (N=5; 80% male; median age = 68.00 +/- 6.19). Efficacy criteria achieved: body weight (macimorelin N=2; placebo N=0; p=0.92); IGF-1 (macimorelin N=0; placebo N=0); QOL by Anderson Symptom Assessment Scale (macimorelin N=4; placebo N=1; p=1.00) or Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; macimorelin N=3; placebo N=0; p=0.50). No related serious or non-serious adverse events were reported. In macimorelin recipients, change in FACIT-F was directly associated with change in body weight (r=0.92, p=0.001), IGF-1 (r=0.80, p=0.01), and caloric intake (r=0.83, p=0.005), and inversely associated with change in energy expenditure (r=-0.67, p=0.05).
Conclusions: Daily oral macimorelin for one week was safe and numerically improved body weight and QOL in patients with cancer cachexia compared to placebo. Longer-term administration should be evaluated for mitigation of cancer-induced reductions in body weight, appetite, and QOL in larger studies.

Conflict of Interest: Jose Garcia received research support from Aeterna Zentaris GmbH. and Novo Nordisk.

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M1 *(15 minutes))*

Adipocytokines in patients with cancer cachexia

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We have previously shown that visceral adipose tissue is metabolically active in cancer, and that the gene showing the largest difference in expression in this tissue was ITLN1, the gene that encodes for intelectin-1, a novel adipocytokine associated with weight loss in other contexts. In this talk, we will discuss further studies in intelectin-1 expression in humans, including a systematic review and a Bayesian meta-analysis. To investigate the role of intelectin-1 in fat-muscle crosstalk in cancer cachexia, we will present the results of administration of this adipokine (in varying concentrations) to human skeletal muscle myotubes.
It is well known that systemic inflammation plays a key role in the aetiology of cancer cachexia. However, the exact mechanisms and chief mediators are not fully understood in humans. Therefore, in a wider investigation of cytokines in general, we will discuss the evidence for an association between inflammatory mediator levels and the specific presence of cachexia or patient symptoms in cancer. We will present our own preliminary results of repeated circulating cytokine analyses during longitudinal phenotyping of patients with incurable cancer (REVOLUTION study), and the implications for human therapy.

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M2 *(15 minutes)*

Crosstalk of lipid metabolism and inflammation drives cachexia

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Cancer is frequently associated with cachexia, a systemic metabolic disease causing wasting. Cachexia represents a fatal energy-wasting syndrome that mostly results in a pathological loss of skeletal muscle and adipose tissue and an inflammatory phenotype. Disturbed adipocyte function and lipid metabolism are important contributors to wasting. We have identified AMPK dysfunction in cachectic white adipose tissue as common factor in various cachexia mouse models [1]. Further, and in line with disturbed lipid metabolism, we identified a lipid signature defining cachexia in mice and patients [2]. In particular ceramides are enriched in the circulation, and may contribute to impaired insulin sensitivity and inflammation as described in diabetes. Being located at a convergence point linking impaired lipid metabolism and inflammation, ceramides represent a promising molecule class for further investigation, and I will share the latest developments linking adipocyte dysfunction, dyslipidemia, and cachexia.
Cachexia leads to multiple metabolic alterations including insulin resistance, altered glucose metabolism, and inflammation, which are typical features of type 2 diabetes and metabolic syndrome. Metabolic alterations related to age or diabetes are not frequently considered in cachexia studies, despite obvious differences in the inflammatory response of these subpopulations, for instance in aged compared to young mice and patients [3]. Diabetes has been linked with increased mortality in patients with cancer, but it is currently unknown if and how pre-existing type 2 diabetes mellitus influences cachexia development and prognosis. I will share data to demonstrate that cancer patients with type 2 diabetes have a higher weight loss and increased inflammatory profile compared to patients without diabetes. This translates to overall higher cachexia incidence in patients with diabetes and cancer, and may explain the increased mortality.

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M3 *(15 minutes)*

Liver-derived factors contributing to cancer cachexia

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Cancer cachexia is a multifactorial wasting syndrome characterized by involuntary body weight loss and associated with reduced survival. Muscle atrophy and adipose tissue wasting, both established hallmarks of cancer cachexia, have been widely studied; however, the role of the liver in cachexia progression is less well understood. To investigate the effects of cachexia on the hepatocyte chromatin and gene landscape, we applied an approach involving transgenic labelling and affinity-based pulldown of nuclei1 from various murine models of weight-stable cancer and cancer cachexia. Our analyses uncovered a cachexia-associated hepatocyte transcriptional landscape, distinct from healthy or weight-stable cancer bearing mice. Further, we identified key transcriptional regulators of the cachexia-associated gene program. In particular, we found that downregulation of the core clock transcriptional regulator Rev-erbα was associated with cachexia progression. Intriguingly, hepatocyte-specific overexpression of Rev-erbα in mice attenuated loss of adipose tissue, muscle, and heart mass in cancer cachexia. We found that hepatocyte clock disruption during cancer cachexia induces the expression of secreted proteins, including specific hepatokines capable of inducing adipocyte lipolysis and myotube/cardiomyocyte atrophy in vitro. Notably, the circulating levels of these secreted proteins were associated with cachexia progression in human patients with cancer. Taken together, our work provides new insights into the role of the liver in tissue cross-talk mechanisms contributing to cachexia progression.

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M4 *(15 minutes)*

Mechanisms of bioamplification and central nervous system dysfunction in cancer cachexia

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Illness behaviors, metabolic disturbances, and cognitive decline are common in patients with chronic systemic diseases, and contribute substantially to quality of life and ultimate survival. Other illness-induced morbidities including anorexia and lethargy also compromise the ability of patients to recover from life-saving or extending interventions, and diminish the motivational drive to aggressively battle the underlying condition. Although cachexia in cancer patients was described more than two thousand years ago, the central mechanisms underlying this disorder are poorly understood. Furthermore, there is currently no effective pharmaceutical treatment. Cognitive decline is common in all chronic diseases, and can be a presenting complaint in cancer patients, even prior to initiation of therapy. Our laboratory is dedicated to unraveling the basic mechanisms whereby cancer triggers neuroinflammation, a key driver of cachexia and cognitive decline in patients with cancer. In this presentation, I will focus on understanding the scope and mechanism by which cancer or other systemic insults induces the production of molecules that provide an amplified signal to brain centers regulating appetite and metabolic output. This will include the induction of lipocalin-2, a molecule that acts on the brain to directly cause loss of appetite and cognitive decline. There will also be a focus on the induction of paracrine inflammatory signaling within the brain itself, both by stimulating local production of inflammatory cytokines, and by the recruitment of unique immune cells into the brain parenchyma. Finally, we will discuss efferent signaling from the brain to the periphery, including detrimental impacts on neuroendocrine outputs, as well as changes in autonomic tone that are ultimately detrimental to the host. This discussion will provide an overview of our historical focus on neuroendocrinology and neuroinflammation, with new collaborations and efforts directed at understanding the extent and mechanisms of anorexia and neurocognitive decline in patients with cancer. The discussion will conclude with a description of a novel therapeutic strategy that is derived from this body of work, and describe our ongoing clinical trials with a novel melanocortin-4 receptor antagonist.

N1 *(15 minutes)*

Treating the malignancy associated weight loss and anorexia with the ghrelin receptor agonist anamorelin when administered in adult patients with non-small cell lung cancer (NSCLC) and cachexia

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Cancer cachexia is a multifactorial condition, usually defined as >5% weight loss during the six months prior to screening, or >2% weight loss and body mass index (BMI) <20 kg/m2 in the presence of uncontrolled cancer, is not reversible by nutrition alone, is frequently observed in NSCLC patients and is characterized by decreased body weight, reduced food intake, and impaired quality of life, often leading to treatment delays, disease progression and decreased survival.
Cancer cachexia is a multi-layered syndrome consisting of the interaction between tumor cells and the host, modulated by the anti-cancer treatments provided, activating key cellular and soluble mediators which induce metabolic and nutritional alterations.
The focus in all our studies (12 Phase 1 studies, four Phase 2 studies, two Phase 3 programs (ROMANA and SCALA) was to target the 2 cardinal characteristics of the cancer cachexia - weight and appetite loss/anorexia - with the ghrelin analogue Anamorelin which has the advantage of stimulating appetite / food intake, as well as promoting anabolism and significant weight and muscle mass gain.
Two phase 3 programs with Anamorelin were conducted on NSCLC patients with cachexia: the ROMANA program, the largest clinical program for cancer cachexia research to date, consisting of two phase 3 studies followed by a 12-week safety double-blind extension study, and the SCALA program consisting of two phase 3 studies. The Japanese studies on Anamorelin, showing improvements in lean mass, weight, and anorexia over 12 weeks, have led to its approval in Japan on January 2021 for the treatment of cancer cachexia in patients with NSCLC, gastric cancer, pancreatic cancer, or colorectal cancer,
Also, the SCALA program introduced a new tool for evaluating appetite - the 5-IASS scale-, and, based on request from Regulatory Authority, established the clinical meaningful threshold based on within patient clinically meaningful change on body weight and appetite for determining the duration of treatment benefit on body weight and anorexia.

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N2 *(15 minutes)*

Non-clinical and clinical development of S-pindolol benzoate in cancer cachexia in patients with advanced non-small cell lung and colo-rectal cancer

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Actimed Therapeutics Ltd, London, UK

Misselwitz, Frank, MD, PhD; Morten, Elaine, PhD, Anker, Stefan, MD, PhD; Coats, Andrew, MD, PhD

Cancer cachexia affects up to 80 % of cancer patients and may lead to functional impairment, loss of quality of life and mortality in about 20 % of those patients[1].

Stereoisomers or enantiomers may have substantially different physico-chemical properties and pharmacological actions[2]. It was found that S-enantiomers of certain non-specific ß1- and ß2-receptor blockers exert potent anti-cachectic actions. S-pindolol has been characterized as an ACTA (anabolic-catabolic transforming agent) and was capable to improve survival in several cachexia models in rats[3]. S-pindolol has also been shown in a pilot proof-of-concept trial, the ACT-ONE trial, to significantly increase body weight, lean mass, and handgrip strength in patients with NSCLC and CRC[4].

We report here on the non-clinical and clinical development of S-pindolol benzoate, a new stable salt form of S-pindolol. Results of an *in vitro* Receptor-Binding Study demonstrate a higher potency of the S-enantiomer towards beta Adrenoceptors compared to the R-enantiomer. A Phase I PK/PD study of single doses and multiple doses of S-pindolol vs Pindolol in healthy subjects will be described. The Phase IIb/III clinical development programme in two studies in patients with NSCLC and CRC will be outlined.

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N3 *(15 minutes)*

GDF-15 inhibition with ponsegromab for treating cachexia in patients with advanced cancer

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Patients with advanced cancer often experience cachexia, a debilitating metabolic syndrome causing unintended weight loss, anorexia, fatigue, muscle atrophy, impaired physical function, and increased risk of death.1,2
A cytokine associated with cachexia, growth differentiation factor 15 (GDF-15), is elevated in certain types of cancer, especially advanced cancers.1-3 GDF-15 inhibition may improve cachexia-related symptom burden and is being investigated as a potential therapeutic target.
Ponsegromab, a humanized monoclonal antibody, is a highly selective and potent GDF-15 inhibitor that showed promise in a mouse tumor model of cachexia3 and has progressed into clinical trials. In the first-in-patient, open-label, single-arm, Phase 1b trial (NCT04299048), 10 participants with advanced cancer, cachexia, and elevated serum GDF-15 concentrations received ponsegromab subcutaneously every 3 weeks plus standard of care anti-cancer treatment for 12 weeks. Ponsegromab demonstrated an acceptable safety profile with no treatment-related adverse events, injection site reactions, anti-drug antibodies, or adverse trends in clinical laboratory tests, vital signs, or electrocardiogram parameters. Ponsegromab serum levels, evident from the first dose and sustained through treatment, were associated with substantially reduced serum unbound GDF-15 levels. In exploratory analyses, body weight increased at all time points through 12 weeks of treatment and the subsequent 12 weeks of follow-up. Least square mean weight gain of 4.6 kg at week 12 represented a 6.6% increase from baseline. Signals for improved physical activity and quality of life, including appetite, were also observed.
The clinical development of ponsegromab for cancer-related cachexia continues with a Phase 2 trial (NCT05546476) currently enrolling ~168 participants with cancer, cachexia, and elevated serum GDF-15 concentrations. This trial has a Part A and a Part B. Part A consists of a 12-week randomized, double-blind, placebo-controlled period, during which patients receive 1 of 3 ponsegromab doses or placebo every 4 weeks. Body weight change from baseline at 12 weeks is the primary endpoint. Changes in physical activity, gait, anorexia/appetite, nausea, vomiting, fatigue, and safety are secondary endpoints. Upon completion of Part A, participants can opt to receive open-label ponsegromab every 4 weeks for up to 1 year in Part B.
Ponsegromab is showing early promise for cancer-related cachexia and the clinical development program is continuing.

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N4 *(15 minutes)*

BIOPHYTIS BIO101: a candidate treatment for muscle diseases

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Background
BIO101 (20-hydroxyecdysone) is an oral investigational product that activates Mas receptor, part of the renin-angiotensin system, downstream of the SARS-CoV-2 virus receptor (ACE2) and involved in several protective pathways including muscle metabolism and structure.
Objectives
Assessment of safety and efficacy of BIO101 treatment in 2 vulnerable populations: sarcopenic seniors and hospitalized severe COVID-19 patients.
Methods
SARA-INT was a randomized three-arm interventional study (BIO101 175 mg or 350 mg bid / placebo) with planned treatment duration of 6 Months (up to 9 months for 50 subjects). Eligibility criteria for sarcopenia: meeting FNIH criteria and SPPB score ≤ 8/12 in community-dwelling seniors. Primary endpoint was the 400-meter walking test (400MWT).
COVA trial was a randomized, placebo-controlled phase 2/3 trial. Hospitalized adults ≥45 years with respiratory decompensation due to SARS-CoV-2 were randomized 1:1 to placebo or BIO101 350 mg bid, up to 28 days. Primary endpoint was proportion of patients dying or requiring high-flow oxygen, mechanical ventilation or ECMO (negative events).
Results
Besides the promising results of SARA-INT, COVA included 233 participants in the ITT population. Primary analysis at day 28 showed a statistically significant difference favouring BIO101 (BIO101: 15.8%, placebo: 26.0%), adjusted difference -11.4% (p=0.042), a relative risk (RR) reduction of negative events of 44.0%. Kaplan-Meier analysis of difference in proportion of patients with negative events over 28 days was nominally statistically significant favouring BIO101 at D28 (10.9%, p=0.023), a 45.0% RR reduction.
In both studies, safety of BIO101 was very good: less patients treated with BIO101 350mg bid experienced adverse events compared to placebo.
Conclusion
BIO101 is a candidate to treat vulnerable populations (sarcopenic seniors and severe hospitalized COVID-19 patients), with meaningful efficacy data and very good safety profile at the dose of 350 mg bid and may be a potential pharmacological strategy against muscle deterioration in these indications.

O1 *(15 minutes)*

Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: role of activin

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O2 *(15 minutes)*

FoxP1 is a transcriptional repressor associated with cancer cachexia that induces skeletal muscle wasting and weakness

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Cancer-induced skeletal muscle wasting affects up to 80% of cancer patients and is associated with reduced quality of life and survival [1, 2]. We previously identified the transcriptional repressor, protein Forkhead box P1 (FoxP1), as a novel downstream target gene of Forkhead box O1 whose skeletal muscle expression is elevated in several mouse models of cancer cachexia as well as in cachectic cancer patients. Our results showed that FoxP1 upregulation in muscle is sufficient to induce pathological features of cancer cachexia, such as muscle wasting and weakness [3]. In a follow-on study, using skeletal muscle specific FoxP1 knockout (FoxP1SkMKO) mice, we found that the absence of FoxP1 is protective against muscle tissue wasting and myofiber atrophy in an orthotopic model of pancreatic cancer. These findings identify that FoxP1 is necessary and sufficient for the induction of a cachexia phenotype in skeletal muscle.

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O3 *(15 minutes)*

Liver metastases enhance the pro-cachectic signaling in colorectal cancer hosts

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Colorectal cancer (CRC) is a deadly disease that often metastasizes to the liver and is accompanied by cachexia, a wasting condition characterized by profound muscle and fat wasting, systemic inflammation, and reduced survival. Our preliminary and published findings suggest that formation of liver metastases (LMs) accelerates muscle and bone loss in tumor hosts1,2,3. However, the mechanisms responsible for the worsening of the muscle phenotype remain partially unclear. Here, we aimed to investigate the liver- and tumor-associated changes in gene expression that could explain the exacerbated cachectic phenotype following formation of LMs.
We employed 8-week-old male NSG mice injected subcutaneously (HCT116) with human HCT116 CRC cells, or intrasplenically (mHCT116) to model the dissemination of LMs. At time of euthanasia, livers and tumors from the subcutaneous and metastatic models, alongside their respective controls, were collected and RNA sequencing performed to identify differentially expressed genes, gene signatures and molecular pathways modified by CRC. Ingenuity Pathway Analysis (IPA) was used to identify molecular pathways with common and unique enrichment between datasets.
Livers from HCT116-bearing mice displayed 1,797 upregulated genes and 1,987 downregulated genes, while livers from mHCT116 hosts presented 3,727 upregulated and 3,456 downregulated genes when compared to the respective controls. Similarly, mHCT116 tumors displayed 2,425 upregulated and 1,809 downregulated genes compared to HCT116 tumors. By utilizing IPA and FDR<0.05, we found that the mHCT116 bearers demonstrated greater activation in cachexia-associated molecular processes, including the ones dependent on IL8, IL6, TGF□, IGF1, GM-CSF, and HIF1□. Interestingly, we also found increased expression of gap junction and adhesion-related genes in both tumor and liver from tumor hosts, as well as in co-cultures between AML12 hepatocytes and HCT116 cells.
Overall, our data suggests that formation of CRC LMs triggers cachexia-associated signaling pathways, thus likely contributing to the exacerbated cachexia phenotype observed in these animals. We also speculate that upregulation of gap junction and adhesion signaling molecules may underlie activation of cachexia-associated signaling.

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O4 *(15 minutes)*

UBR2 targets myosin heavy chain IIb and IIx for degradation: molecular mechanism essential for cancer-induced muscle wasting

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Cancer cachexia is a lethal metabolic syndrome features muscle wasting with preferential loss of fast-twitching muscle mass through undefined mechanism. Here we show that cancer induces muscle wasting by selectively degrading myosin heavy chain (MHC) subtypes IIb and IIx through E3 ligase UBR2-mediated ubiquitylation. Induction of MHC loss and atrophy in C2C12 myotubes and mouse tibialis anterior (TA) by murine cancer cells required UBR2 upregulation by cancer. Genetic gain or loss of UBR2 function inversely altered MHC level and muscle mass in TA of tumor-free mice. UBR2 selectively interacted with and ubiquitylated MHC-IIb and MHC-IIx through its substrate-recognition and catalytic domain, respectively. Elevation of UBR2 in muscle of tumor-bearing or free mice caused loss of MHC-IIb and MHC-IIx but not MHC-I and MHC-IIa or other myofibrillar proteins including α-actin, troponin, tropomyosin and tropomodulin. Muscle-specific knockout of UBR2 spared KPC tumor-bearing mice from losing MHC-IIb and MHC-IIx, fast-twitching muscle mass, cross-sectional area and contractile force. Rectus abdominis muscle of patients with cachexia-prone cancers displayed a selective reduction in MHC-IIx in correlation with higher UBR2 levels. These data suggest that UBR2 is a regulator of MHC-IIb/IIx essential for cancer-induced muscle wasting, and that therapeutic interventions can be designed by blocking UBR2 upregulation by cancer.

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Q1 *(15 minutes)*

Pathological remodeling of respiratory muscles during cancer: mechanisms and therapeutic targets

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Cancer cachexia is a multifactorial condition characterized by skeletal muscle atrophy and dysfunction that affects the vast majority of cancer patients, with pancreatic ductal adenocarcinoma (PDAC) and gastro-oesophageal cancers showing the highest prevalence of cachexia. Cachexia is estimated to contribute to ~30% of cancer-related deaths, with deterioration of respiratory muscles (1) suspected to be a major contributor to cachexia-associated morbidity and mortality. In recent studies we identified fibrotic remodeling of respiratory muscles as a key pathological feature associated with cachexia in patients with PDAC (rectus abdominis muscle) (2), and esophageal cancer (diaphragm and intercostals) which may contribute to respiratory muscle deterioration and dysfunction. Importantly, we are able to recapitulate these findings in the mouse diaphragm in pre-clinical models of PDAC that utilize either human (3) or murine tumors. Time course studies conducted in the orthotopic KPC model further demonstrate that immune cell infiltration and expansion of fibroadipogenic progenitors within the diaphragm are early events that precede myofiber atrophy and fibrotic remodeling, including ECM expansion and collagen deposition. Overlap of transcriptomic data from respiratory muscles of cachectic PDAC patients and mice with PDAC revealed connective tissue growth factor *(Ctgf*), a matricellular protein with pro-inflammatory and pro-fibrotic functions, as a commonly upregulated gene that could play a role in mediating these pathologies. To determine the role of CTGF activity in mediating diaphragm wasting and remodeling, we treated mice bearing human or murine PDAC tumors with a CTGF neutralizing antibody (FG-3019), which preserved diaphragm muscle fiber size, morphology and excursion. CTGF targeting also reduced systemic inflammation and deterred the loss of muscle, cardiac and fat mass, despite controlling for CTGF-dependent effects on tumor size, providing broader implications for CTGF as a regulator of PDAC cachexia. In summary, these finding collectively demonstrate the pathological progression towards fibrosis within respiratory muscles as a key feature of PDAC cachexia that can be mitigated through systemic blockade of CTGF activity.

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Q2 *(15 minutes)*

Molecular basis and clinical relevance of insulin resistance in cancer cachexia

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Insulin resistance is a critical cause of metabolic dysfunctions and might cause muscle wasting1,2. Metabolic dysfunction and cancer cachexia are associated with poor cancer prognosis3, yet the molecular mechanisms causing cancer-induced metabolic dysfunction and cachexia remain to be defined.
A key link between metabolic- and muscle mass-regulation is adenosine monophosphate-activated protein kinase (AMPK). As AMPK could be a potential treatment, we established AMPK's roles in cancer-associated metabolic dysfunction, insulin resistance, and cachexia.
In vastus lateralis muscle biopsies from N=26 patients with Non-Small-Cell Lung Carcinoma (NSCLC), AMPK signaling and protein content were examined by immunoblotting. To determine the role of muscle AMPK, male mice overexpressing a dominant-negative AMPKα2 (kinase-dead; mAMPK-KiDe) specifically in striated muscle were inoculated with Lewis Lung Carcinoma (LLC) cells.
Patients with NSCLC presented increased muscle protein content of AMPK subunits α1, α2, β2, γ1, and γ3; ranging from +27% to +79% compared to control subjects. In patients with NSCLC, AMPK subunit protein content correlated with weight loss, fat-free mass, and fat mass. Tumor-bearing mAMPK-KiDe mice presented increased fat loss and glucose and insulin intolerance. LLC in mAMPK-KiDe mice displayed lower insulin-stimulated 2-DG uptake in skeletal muscle (- 50%) and the heart (-29%) compared to non-tumor-bearing mice. In skeletal muscle, mAMPK-KiDe abrogated the tumor-induced increase in TBC1D4thr642 phosphorylation. Protein expression of TBC1D4 (+26%), pyruvate dehydrogenase (PDH, +94%), and PDH-kinases (PDKs, +45% to +100%), and glycogen synthase (+48%) were increased in skeletal muscle of tumor-bearing mice in an AMPK-dependent manner. Lastly, chronic AICAR treatment elevated hexokinase-II protein content and normalized phosphorylation of p70S6Kthr389 (mTORC1 substrate) and ACCser212 (AMPK substrate) and rescued cancer-induced insulin intolerance.
These observations highlight the potential for targeting AMPK to counter cancer-associated metabolic dysfunction and possibly cachexia.

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Q3 *(15 minutes)*

Neuromuscular electrical stimulation training promotes muscle stem cell fusion, modulates inflammation and improves muscle function in a mouse model of cancer cachexia

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Cancer cachexia (CC) is characterized by systemic inflammation resulting in drastic body weight loss, skeletal muscle wasting (i.e., reduced muscle size) and weakness (i.e., reduced force production). CC reduces patient survival and no curative treatments exist. Emerging studies reveal that CC may result from dysfunction of muscle stem cells (MuSCs). Indeed, tumor-derived circulating factors block both MuSC differentiation and fusion leading to muscle atrophy1. Skeletal muscle homeostasis is also influenced by the dynamic interactions between MuSCs, myofibers and immune cells (i.e., macrophages). We recently demonstrated that increased myofiber contractile activity by neuromuscular electrical stimulation (NMES) promotes MuSCs fusion in healthy muscles2. We aimed to determine whether NMES improves MuSC fate and reduces muscle weakness, wasting and inflammation in the mouse model of CC bearing the C26 carcinoma.
We showed that NMES training improves muscle force and mass in C26 mice. These functional and structural changes occur in association with MuSC fusion improvement and a transition toward an anti-inflammatory status of macrophages in muscle, validated by both in vivo and in vitro studies.
These findings demonstrate that stimulated myofibers positively regulate MuSC fate and tissue inflammation in the context of CC. NMES might be a promising therapeutic approach to minimize the deleterious effects of CC in patients.

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Q4 *(15 minutes)*

Chemotherapy-specific effects on cardiorespiratory status and body composition

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Advances in patient screening and treatment have reduced cancer mortality. However, the optimistic increase in survivorship has been limited by cardiorespiratory toxic chemotherapy. Due to its broad-spectrum anti-neoplastic properties, doxorubicin (DOX) remains a first-line therapy for cancer treatment. While DOX has facilitated reductions in relapse and mortality, its use is associated with cardiotoxicity. Efforts have been made to reduce the detrimental off-target effects through dose reduction and formulation changes; however, there is no standard of care to prevent cardiorespiratory muscle dysfunction. In this regard, preclinical models are fundamental to understanding the off-target effects of anthracycline chemotherapy treatment, with rodent models the most commonly utilized. Although there are cardiovascular differences between rodents and humans, primarily related to the large variation in heart rate across species, there are distinct advantages to utilizing small rodents to model human disease. In the case of DOX chemotoxicity, the ability to assess cardiac damage, cardiorespiratory capacity and body composition has allowed for improvements in the translatable potential of rodent models of acute and chronic DOX toxicity, while also allowing for investigation at the molecular level. Utilizing a novel rat model where DOX was administered every three weeks for a total of four cycles, we tested the effects of moderate intensity and high intensity interval training on cardiorespiratory and body composition outcomes. Our results echo reported patient outcomes and highlight the feasibility and efficacy of including exercise training as adjuvant therapy.

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R1 *(15 minutes)*

Anabolic resistance in critically ill patients

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Patients with critical illness treated in and intensive care unit (ICU) loose muscle mass with about 10% per week [1] and the question addressed in this presentation is whether this is due to an anabolic resistance.

Anabolic resistance is a diminished anabolic response of skeletal muscle to known anabolic stimuli like protein nutrition/supplement, exercise, and insulin. Anabolic resistance is well described in the progressive loss of muscle mass and strength during aging and during chronic disease such as COPD and diabetes. However, it is less well studied in acute wasting diseases.

The loss of muscle in the critically ill is mainly the result of a dramatically increased muscle protein breakdown and less due a decrease in protein synthesis [2]. Muscle protein synthesis is on average similar to normal subjects or sometime even higher. However, the variation is large and there are also patients with lower protein synthesis rates [3]. Several studies have indirectly indicated that this dramatic muscle wasting in the critically ill cannot be affected by protein nutrition, suggesting an anabolic resistance. There is only one study that directly measured the response of muscle protein synthesis to a protein feed and this study shows an anabolic resistance [4]. But the study is small and doesn't allow for studying subgroups.

In general, critically ill patients suffer from a dramatic insulin resistance. High amounts of insulin are needed to keep circulating glucose levels kind of normal. But it is less clear to what extend this insulin resistance affects muscle protein synthesis. One study directly studies this in patients after major surgery and shows that the insulin resistance extends to muscle protein metabolism but that this might be overcome by high amounts of insulin [5]. To what extend these patients are similar to critically ill patients is not clear.

Exercise or physical activity has been tested in the ICU and some studies show positive effects on muscle function, but no studies are directly studying the anabolic resistance of muscle activity in critically ill patients.

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R2 *(15 minutes)*

Ketogenic feeding in the critically ill patients

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Critical illness is a state of ill health with vital organ dysfunction and a high risk of imminent death if care (pharmacological or mechanical) is not provided and has the potential for reversibility. The physiological characteristics of critical illness have significant overlap across a wide range of presenting diseases, challenging commonly used disease-related taxonomies1. Multiple diverse stressors result in a unifying state of altered tissue metabolism and bioenergetics, compounding organ dysfunction and cell death in multiple tissues such as the brain, lung, kidney and skeletal muscle2. Specifically, substrate utilisation in the tri-carboxylic acid (TCA) cycle is impaired in critical illness, with tissue hypoxia and inflammation prevent glucose-derived pyruvate from being converted to acetyl-CoA, as a result of the Pasteur effect3. Amino acids may be recycled for pyruvate reconstitution in starvation, but such processes (e.g., the Cahill cycle) are affected by tissue hypoxia, inflammation, impaired Glucose Transporter Type 4 (GLUT-4) translocation, exogenous insulin therapy and other hallmarks of critical illness3. Finally, mitochondrial fatty acid oxidation is downregulated, and the resultant inability to use any of these three substrates efficiently leads to a bioenergetic crisis3.
Under conditions of physiological stress, ketone bodies provide a source of substrate for Adenosine Tri-Phosphate (ATP) generation. Ketone bodies may form an alternative substrate source, but the feasibility and safety of inducing a ketogenic state in physiologically unstable patients is not known.
Twenty-nine mechanically ventilated adults with multi-organ failure were randomised into a two-centre pilot trial of ketogenic versus standard enteral feeding. Ketogenic feeding was feasible, safe, well tolerated and resulted in ketosis. Patients receiving ketogenic feeding had fewer hypoglycaemic events (0% vs. 1.58%), required less exogenous insulin (0.0 IU (IQR 0-16) vs.78 IU (IQR 0-412) but had slightly more daily episodes of diarrhoea (53.5% vs. 42.9%) over the trial period. Untargeted metabophenotyping revealed altered Cahill cycle flux and bioenergetic states, suggesting an advantageous metabolic profile. Ketogenic feeding is feasible and may be a novel intervention for addressing bioenergetic failure in critically ill patients.
Clinical Trials.gov registration: NCT04101071; 19.09.2019.

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R3 *(15 minutes)*

Persistent inflammation, immunosuppression and catabolism syndrome and the role nutrition in the surgical ICU

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Background: Sepsis is caused by a dysregulated immune response to an infection. Hospital deaths after sepsis have decreased substantially but many survivors develop chronic critical illness (CCI) with poor long-term outcomes, including muscle wasting and physical dysfunction with greater age being an important contributing factor. The persistent inflammation, immunosuppression and catabolism syndrome (PICS) may be a driver of CCI, but the effect of age on in-hospital and long-term outcomes and PICS biomarker evidence is unknown. Additionally, early nutrition is essential for improving ICU outcomes but its role in alleviating PICS is unknown.
Methods: Patients were characterized by a) demographics and predisposing baseline factors, b) septic insult and its severity, c) hospital outcomes and discharge disposition, d) 12-month mortality and e) Zubrod Performance status and physical function (by Short Physical Performance Battery and handgrip strength) at three, six and 12-month follow-up. Serial blood samples over 14 days were analyzed for selected biomarkers reflecting PICS. We also identified patients who received early, adequate nutrition per an established surgical ICU protocol.
Results: Compared to the young and middle-aged patients, older patients had: 1) significantly more comorbidities at presentation, intra-abdominal infections (14% vs 25% vs 37%), septic shock (12% vs 25% vs 36%) and organ dysfunctions, 2) higher 30 day mortality (6% vs 4% vs 17%) and fewer ICU free days (median 25 vs 23 vs 20), 3) more progression into CCI (22%, vs 34% vs 42%) with higher poor disposition discharge to non-home destinations (19% vs 40% vs 62%), 4) worse 12-month mortality (11% vs 14 % vs 33%) and, 5) poorer Zubrod Performance status and objectively-measured physical function. The CCI cohort reached 76% of goal calories being recommended by the ICU nutritional protocol. Serial biomarkers showed that older and CCI patients remained persistently inflamed with ongoing stress metabolism and that despite receiving evidence-based protocol nutrition, had persistent catabolism and immunosuppression with more secondary infections.
Conclusion: Older sepsis survivors demonstrate poor in-hospital and long-term functional outcomes and greater aberrations of PICS biomarkers. CCI patients also fail to respond to recommended ICU nutrition, which warrants further research on optimization of ICU feeding protocols.

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R4 *(15 minutes)*

The metabolic response to critical illness – a therapeutic target?

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Critically ill patients undergo major changes in metabolism, caused by a combination of malnutrition, tissue damage, inflammation, anesthesia and inactivity. Increases in resting energy expenditure are usually compensated by reduced activity energy expenditure. Metabolism changes are related to increased protein breakdown and lipolysis, leading to a high production of essential amino acids (EAA) and non-EAA (NEAA) like alanine, glutamine and glutamate.

An innovative stable isotope approach has been developed by us to study an array of amino acid productions and conversions on a whole body level and within certain compartments in critically ill patients. A pulse of a combination of many stable isotope tracers is given and 5 times blood sampled for 2 hours. Calculation of decay parameters makes compartmental analysis possible which is needed to calculate whole body production (WBP), extra- and intracellular appearance and flux rates to/from the intracellular compartment after ANCOVA and inclusion of confounders like age, sex, muscle mass.

Analysis of changes in metabolism in 51 ICU patients and 49 matched healthy subjects (1) showed a very weak relation between plasma concentrations and WBP of many amino acids, suggesting that only WBP measurements give a good insight of metabolic changes in critically ill patients. The main observations were an overall reduction in net catabolism and substantially increased protein synthesis and breakdown rates and increase of glutamine (150%), glutamate (260%) and decrease of arginine de novo (50%) and citrulline (75%). Sicker critically ill patients (SOFA >8) had a lower glutamine and de novo arginine production and higher muscle protein breakdown, suggesting exhausting catabolism of muscle protein pools.

Secondary analysis (2) revealed that females that have lower ICU admission rates and better long term ICU survival are able to increase protein breakdown and glutamine production more than males, while limiting muscle protein breakdown increase.

Our observations in critically ill patients also point to a possible therapeutic target that can reduce protein breakdown and NEAA productions, limiting the burden on metabolism. Critically ill patients experience substantial and long lasting muscle weakness during rehabilitation. Treating malnutrition and increasing protein intake show beneficial effects, albeit that the amount and timing of this approach is critical. So an intervention should aim at lowering energy expenditure, reducing muscle weakness and lower nutritional needs. Our recent studies all indicate that HMB (beta-hydroxy-beta-methylbutyrate) is an effective reducer of protein breakdown. Combined increased intake of protein and HMB reduce mortality in hospitalized malnourished older adults with COPD, CHF and Pneumonia (3, 4). A recent HMB trial in 37 critically ill patients in which HMB is given from day 4 to 15 and general characteristics, muscle mass and metabolism were assessed (5) showed, although HMB had no effect on muscle mass, a reduction was found in disease severity (sofa) and increase in BIA phase angle and energy expenditure. In addition, protein breakdown and related metabolism including WBP of glutamine and glutamate were reduced.

In conclusion, measuring whole body production and conversion of amino acids with the pulse stable isotope approach gives insight into metabolic targets in critically ill patients. We suggest that this new approach can be used to design nutritional supplements that match better their metabolic profile. Also, HMB can reduce protein breakdown in critically ill patients that possibly will improve their overall condition and recovery.

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S1 *(15 minutes)*

Gut microbiota alterations in patients with cancer cachexia

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The underlying mechanisms of cancer cachexia involve systemic inflammation and insulin resistance, both of which have long been known to be influenced by the gut microbiota in the context of obesity and its associated metabolic disorders. Only recently, preclinical studies have provided support for a role for the gut microbiota and their metabolites such as short-chain fatty acids in cancer cachexia. Cachectic mice were shown to display various gut microbiota composition shifts accompanied by increased gut permeability, translocation of pro-inflammatory microbial compounds, and muscle atrophy-related processes. Furthermore, some positive effects of microbiota-modulating interventions on the progression of cachexia in animals have been reported.
Despite of this, human studies on the role of the gut microbiota in cancer cachexia are still scarce. A recent study from our lab showed that specific alterations in gut microbiota composition and fecal short-chain fatty acid concentrations were present in a heterogeneous cohort of cachectic patients with several cancer types, although overall microbial diversity and community structure were not altered.1 The abundance of Proteobacteria, and the Veillonella, Megamonas, Peptococcus, and an unknown Enterobacteriaceae genus was correlated with weight loss. Two other recent human studies confirmed a lack of alpha-diversity changes in cachexia but showed differences in beta-diversity between cachectic and non-cachectic lung cancer patients.2,3 Klebsiella oxytoca was more abundant in cachectic patients, in line with previous preclinical C26 mouse data. Functional metagenomics analyses showed decreases in microbial synthesis pathways of certain amino acids, in line with decreased plasma amino acid levels frequently observed in cachexia. Furthermore, increased microbial synthetic potential of pro-inflammatory lipopolysaccharide was reported in cachectic individuals.
These insights only represent the first steps towards exploring the potential of using the gut microbiota as a therapeutic target in cancer cachexia. However, in view of the limited effectiveness of the current treatment approaches and the considerable impact of cachexia on prognosis and quality of life of patients, such a novel treatment strategy is eagerly anticipated.

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S2 *(15 minutes)*

Gut microbiota and muscle: from proof-of-concept to molecular mechanisms

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Cancer cachexia is characterized as “a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without fat mass loss) that can be partially but not entirely reversed by conventional nutritional support”1. Cachexia affects 85% of the cancer patients and is one of the primary causes of morbidity associated with cancer. There is currently no standard of care that effectively prevents or counteracts cancer-associated tissue wasting even though such interventions are anticipated to have an important positive impact on overall tumor disease outcome2,3.
The current literature clearly establishes the ability for the gut microbiome to modulate muscle function and mass. In this talk, I will discuss key articles demonstrating that bacterial metabolites can exert a beneficial or detrimental impact on muscle physiology. Most of the evidence concentrates on short-chain fatty acids (SCFAs), with an emerging role for bile acids, bacterial amino acid metabolites (bAAms), and bacterial polyphenol metabolites. Other molecular players worth considering include cytokines, hormones, lipopolysaccharides, and quorum sensing molecules.
The understanding of the mechanisms underlying this gut-muscle axis may lead to the delivery of novel therapeutic tools to tackle muscle wasting in cancer cachexia4. In the second part of my talk, I will therefore discuss how these mechanisms could apply to the muscle wasting observed in cancer cachexia.

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S3 *(15 minutes)*

Fecal microbiota transplantation (FMT) in cancer cachexia

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Presently, the only approved indication for FMT is recurrent Clostridium Difficile infection. However, gut microbiota alterations have been shown in many diseases including cancer and metabolic diseases. Thus, FMT may also a therapeutic option in cachexia.
In order to be efficient, an FMT likely has to interact with the intestinal barrier. The latter consists of the microbiota, the mucus layer and the gut mucosa, i.e. the gut epithelium, the gut-associated lymphoid tissue (GALT) and the enteric nervous system. We hypothesize that cancer is associated with gut microbiota alterations which in turn induce a systemic inflammation, an increased gut permeability and decreased energy harvest, and a dysbalance of appetite mediators in favor of anorexigenic mediators.
Animal studies show the link between FMT and body weight or muscle mass. FMT from control mice into germ-free mice induces an increase in muscle mass and muscle function (1). A delay in weight and muscle mass gain was shown in germ-free mice that received an FMT from malnourished children as compared to well-nourished children. This delay could be counteracted by the administration of well-defined bacteria (2). Finally, a pilot study showed that germ-free mice that received the FMT from a patient newly diagnosed with a pancreatic adenocarcinoma, tended to have a lower weight gain than when they received the FMT from healthy controls (3). Thus, the phenotype associated with cachexia seems to be transferrable to germ-free animals.
The link between FMT and a defined phenotype in humans is scarce. A recent pilot study found that a single FMT from healthy obese patients into cachectic gastro-oesophageal cancer patients did not influence body mass index, muscle mass, calorie intake and satiety (4). However, the number of patients responding to chemotherapy was significantly higher, and the overall survival and progression-free survival tended to improve.
Several hypothesis have been suggested to improve the chances of FMT success in the future. They include a matching of donors and recipients based on genetic, metagenomic and immune compatibilities, a thorough preparation of the gut (nutrition, antibiotics, bowel cleansing) and selected immunosuppressive drugs (5).

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S4 *(15 minutes)*

Targeting CXCR2 signaling counteracts cancer cachexia

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Tumor-secreted factors are well established to be important initiators of cancer-induced cachexia [1]. In recent work, we demonstrated that human pancreatic cancer cells secrete high levels of interleukin-8 (IL-8/CXCL8) and growth-related oncogene alpha (GRO-□/CXCL1), and that treatment of myotubes or mice with IL-8 is sufficient to induce myotube/muscle atrophy [2]. In the current study, we show that treatment of myotubes or mice with CXCL1 is also sufficient to induce myotube/muscle atrophy. Further, we identified that co-deletion, but not single deletion, of CXCL1 and CXCL8 from human pancreatic cancer cells, using CRISPR/Cas9, inhibited the development of muscle and fat wasting when orthotopically injected into mice. Since CXCL1 and CXCL8 both signal through the CXCR2 receptor, we treated pancreatic tumor bearing mice with the CXCR2 antagonist SB225002, or vehicle control. When matched for duration of tumor burden, mice in the SB225002 treated group had significantly larger body mass, fat mass, muscle mass and myofiber size compared to vehicle treated tumor bearing mice. Given that a prominent source of CXCR2 in mice are Ly6G+ neutrophils and myeloid derived suppressor cells (MDSCs), we tested whether depletion of these cells would attenuate the development of cachexia by injecting pancreatic tumor bearing mice with an anti-Ly6G antibody. When matched for duration of tumor burden, muscles from mice treated with the anti-Ly6G antibody were protected against atrophy compared to mice injected with the isotype control antibody. Collectively, these data suggest that in mice bearing pancreatic tumors, inhibiting CXCL1/CXCL8-CXCR2 signaling may protect against the development of cachexia.

References

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2. Callaway, C.S., et al., IL-8 Released from Human Pancreatic Cancer and Tumor-Associated Stromal Cells Signals through a CXCR2-ERK1/2 Axis to Induce Muscle Atrophy. Cancers (Basel), 2019. 11(12).

POSTER SESSIONS

Poster Session 1.1 Cachexia – mechanisms, animal models I (posters 1-01 to 1-08)
Chairs: Denis Guttridge, Jochen Springer

1-01
Growth of GL261 glioblastoma tumors induced delayed body weight gain and stunted skeletal muscle growth in pediatric mice
Joshua R. Huot[1], Nicholas A. Jamnick[2], Patrick D. Livingston[2], Fabrizio Pin[1], Andrea Bonetto[2]
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1-02
Sexual dimorphism in the development of cancer cachexia in *Apc*$^{Min/+}$ mice
Bénédicte Guegan[1], Anne-Cécile Durieux[1], Esra Elmali[1], Valentine Allibert[1], Benjamin Buhot[1,2], Christophe Hourde[3], Julien Gondin[4], Damien Freyssenet[1]
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1-03
Metabolic dysfunction during recovery from colorectal cancer chemotherapy: a role for skeletal muscle AMPK signaling
Jessica Halle[1], Quan Zhang[1], Hector Paez[2], Stephen Alway[2], James Carson[1]
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1-04
Renal cell carcinoma in kidney specific Tsc1 knocked out mice cause cachexia in the skeletal Muscle
Suvham Barua[1], Sara Clerici[3], Elia Angelino[1,2]., Michella Ferrara[3], Lorenza Bodo[1], Daniela Talarico[3], Alessandra Boletta[3], Andrea Graziani[1,2]
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1-05
Hepatic metabolism alterations and effects of niacin supplementation in experimental cancer- and chemotherapy-induced cachexia
Natalia Cortez[1], Yuki Nakamura[2], Fabien Riols[3], Marc Beltrà[4], Mark Haid[3], Shinpei Kawaoka[2], Fabio Penna[1]
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1-06
The effects of a novel long-acting ghrelin on ameliorating cancer cachexia in mice
Haiming L. Kerr[1], Kora Krumm[1], Ian (In-gi) Lee[1], Barbara Anderson[1], Anthony Christiani[1], Lena Strait[1], Beatrice A. Breckheimer[1], Brynn Irwin[1], Alice (Siyi) Jiang[1], Artur Rybachok[1], Amanda Chen[1], Lucas Caeiro[1], Elizabeth Dacek[1], Daniel B. Hall[2], Caroline H. Kostyla[2,3], Laura M. Hales[2], Tarik M. Soliman[2], Jose M. Garcia[1]
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1-07
Sex differences in amino acid metabolism is linked to cachexia outcomes in mice treated with chemotherapy drugs
Olasunkanmi A.J. Adegoke, Stephen Mora
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1-08
Unraveling the mechanisms of muscle atrophy: focus on lipocalin 2 and iron homeostasis
Elisabeth Wyart [1], Myriam Hsu[1], Erica Mina[1], Alessio Menga[1], Paolo E Porporato[1]
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Poster session 1.2 **Cancer Cachexia I** (posters 2-01 to 2-09)
Chairs: Joanne Reid, Florian Strasser

2-01
Neutrophil-derived S100a8/a9 as a mediator of adverse cardiac remodeling in cancer-associated cachexia
Parham Diba[1,2], Abigail C. Buenafe[2], Mason A. Norgard[2], Peter R. Levasseur[2], Tetiana Korzun[1,2], Xinxia Zhu[2], Ariana Sattler[3], Xiaolin Li[2], Brennan Olson[1,2], Daniel L. Marks[2,3]
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2-02
Mechanistic insights from an integrative analysis of biological sex differences in two colorectal cancer cachexia models
Ana Regina Cabrera[1], J. William Deaver[1], Francielly Morena da Silva[1], Eleanor Schrems[2], Tyrone A. Washington[2], Kevin A. Murach[3], Nicholas P. Greene[1]
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2-03
The dialogue between metastatic cells and the host
Blanca Majem[1], Josefina Martin[1], Claudia Bigas[1], Gloria Pascual[1], and Salvador Aznar Benitah[1,2]
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2-04
Microbiota-derived secondary bile acids to tackle cancer cachexia
Morgane M. Thibaut[1], Justine Gillard[1,2], Martin Roumain[3], Adeline Dolly[1], Nathalie M. Delzenne[1], Giulio G. Muccioli[3], Laure B. Bindels[1]
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2-05

Cancer induces cachexia by reprogramming the nuclear SUMOylation landscape in striated muscle cells

Luis V Gand[1], Bushra Khan[1], Natalie Weber[2], Dongchao Lu[2], Christian Bär[2], Andreas Pich[3], Theresia Kraft[1], Mamta Amrute-Nayak[1], Arnab Nayak[1]

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2-06

Skeletal muscle microRNAs profile in patients with gastrointestinal cancer

Federica Tambaro[1], Giovanni Imbimbo[1], Giulia Lauteri[2], Antonietta Gigante[1], Maria Ida Amabile[3], Giuseppe Nigri[2], Cesarina Ramaccini[1], Alessio Molfino[1], Maurizio Muscaritoli[1]

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2-07

First-in-patient (Phase 1b) study of the GDF-15 inhibitor ponsegromab in patients with cancer and cachexia: safety, tolerability, and exploratory measures of efficacy

Jeffrey Crawford[1], Roberto A. Calle[2], Susie M. Collins[3], Yan Weng[4], Shannon L. Lubaczewski[5], Clare Buckeridge[2], Ellen Q Wang[6], Magdalena A. Harrington[7], Anil Tarachandani[8], Michelle I. Rossulek[2], James H. Revkin[2]

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2-08

Two phase 3 studies to evaluate the ghrelin receptor agonist anamorelin for malignancy-associated weight loss and anorexia in adults with non-small cell lung cancer (NSCLC): updates to the ongoing SCALA program

Richard J.E. Skipworth[1], Barry J.A. Laird[2,3], Eric J. Roeland[4], Tora S. Solheim[5,6], Jann Arends[7], Jose M. García[8], Mariana S. Sousa[9], David C. Currow[10]

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2-09

Scalable and privacy-preserving AI can characterize and discover more cachectic cancer patients compared to ICD codes and NLP based approaches

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Poster session 1.3 **Physical activity & training, nutrition & appetite** (posters 5-01 to 5-05 and 6-01 to 6-07)
Chairs: Stuart Phillips, Adrian Slee

5-01

The association between protein intake and skeletal muscle parameters in patients with localized renal cell cancer

Mark Nieuwenhuis[1], Jake S.F. Maurits[1], J.P. Michiel Sedelaar[2], Katja K.H. Aben[1,3], Lambertus A.L.M. Kiemeney[1], Alina Vrieling[1]

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5-02

An evidence based protocol for early identification of nutritional risk patients with cancer

Maurizio Muscaritoli*[*1], Gil Bar-Sela[2], Nicolo M L Battisti[3, 4], Borislav Belev[5], Jorge Contreras-Martínez[6], Enrico Cortesi[7], Ione de Brito-Ashurst[8], Carla M Prado[9], Paula Ravasco[10, 11], Suayib Yalcin[12]

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5-03

Preoperative supportive nutrition at major cancer surgery in weight-losing patients. Effects on muscle transcriptome

Britt-Marie Iresjö, Ulrika Smedh, Cecilia Engström, Jan Persson, Christian Mårtensson, Kent Lundholm

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5-04

Cancer-associated anorexia: DNA methylation signatures in patients with lung cancer

Giovanni Imbimbo[1], Federica Tambaro[1], Francesca Ambrosani[2], Silvia Udali[2], Sara Moruzzi[2], Annalisa Castagna[2], Michele Melena[1], Maurizio Muscaritoli[1], Simonetta Friso[2], Alessio Molfino[1]

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5-05

Combined nutritional and exercise interventions for cachexia in chronic diseases: a systematic review

Masatsugu Okamura[1,2,3], Kengo Shirado[3,4], Nobuyuki Shirai[3,5], Takuma Yagi[3,6], Tatsuro Inoue[3,7], Masato Ogawa[3,8], Erin Stella Sullivan[9], Stephan von Haehling[10], Jochen Springer[11], Stefan D. Anker[12,13], Ryo Momosaki[14]

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6-01

Exercise decreases catabolic protein signaling in rat skeletal muscle 40 days post-burn

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6-02

Effect of exercise on sarcopenic obesity (SO) patients: research progress and perspectives

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6-03

Effect and Mechanism of Exercise on Diabetic Sarcopenia：a Systematic Review

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6-04

Higher fibroblast growth factor 23 levels are associated with low exercise capacity in patients with chronic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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

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6-05

Associations of Exercise Habits in Adolescence and Old age with Phase Angle in Older Adults: the Bunkyo Health Study

***Hiroki Tabata*[1], Hikaru Otsuka[2], Shi Huicong[2], Hideyoshi Kaga[3], Hitoshi Naito[3], Abulaiti Abudurezake[1], Saori Kakehi[1], Yasuyo Yoshizawa[4], Ryuzo Kawamori[1,2,3], Yoshifumi Tamura[1,2,3,4]**

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6-06

Loss of hypoxia signalling-mediated PGC-1a expression underlies age-related loss of muscular adaptation to exercise

Yori Endo, Mehran Karvar, Yuteng Zhang, Christina Zhu, Daniel Koh, Indranil Sinha

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6-07

Body cell mass to fat-free mass ratio and extra-to-intracellular water ratio are related to maximal oxygen uptake

Yosuke Yamada, Tsukasa Yoshida, Haruka Murakami, Yuko Gando, Ryoko Kawakami, Harumi Ohno, Kumpei Tanisawa, Kana Konishi, Julien Tripette, Emi Kondo, Takashi Nakagata, Hinako Nanri, Motohiko Miyachi

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Poster session 1.4 **Diagnosis of cachexia /sarcopenia I** (posters 3-01 to 3-12)
Chairs: Swarnali Acharyya, Philip Atherton

3-01

Prognostic value of weight loss in hospitalized patients with acute heart failure

***Takanori Nagahiro*[1], Masaaki Konishi[1, 2, 3], Nobuyuki Kagiyama[4, 5, 6], Kentaro Kamiya[7], Hiroshi Saito[8], Emi Maekawa[9], Takeshi Kitai[10], Kiyoshi Hibi[1, 2, 3], Kouichi Tamura[1], Yuya Matsue[4]**

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3-02

Circulating microRNA-22 as an innovative biomarker in patients with sarcopenia and heart failure: results from the SICA-HF

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3-03

Novel biomarkers as possible prognostic tools in the determination of muscle wasting in HF patients

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

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3-04

Association between bioimpedance phase angle and post-stroke dysphagia: pilot study

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3-06

Screening for malnutrition, sarcopenia, and physical frailty in liver transplant recipients: a long-term cross-sectional study

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3-07

Creatinine to cyscatin C ratio as a marker of skeletal muscle mass and mysteatosis in patients before gastrointestinal cancer surgery

Hao Liu, Junjie Wang, Shanjun Tan, Zhige Zhang, Shuhao Li, Mingyue Yan, Guohao Wu

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3-08

Sarcopenia is uncommon, despite significant loss of weight and skeletal muscle, in patients undergoing oesophagogastric cancer surgery

Lisa Murnane[1,2]; Adrienne Forsyth[1,3]; Audrey Tierney[1,4]; Paul Burton[5,6]

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3-11

Sarcopenic obesity is predictive of critical weight loss in patients with head and neck cancer

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3-12

Body composition phenotype sarcopenic obesity is associated with poor physical fitness assessed by cardiopulmonary exercise testing in patients undergoing colorectal cancer surgery

***Jason Rai*[1], *Edward T Pring*[1], *Katrina Knight*[2], *Henry Tilney*[3], *Fiona Taylor*[4], *Laura E Gould*[1], *Dinh V C Mai*[1], *Ioanna Drami*[1], *Campbell Roxburgh*[2], *John T Jenkins*[1]**

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Poster session 2.1 **Cachexia – mechanisms, animal models II** (posters 1-09 to 1-17)
Chairs: Denis Guttridge, Jochen Springer

1-09

Exploring the lived experience of cachexia for individuals with end-stage kidney disease and the interrelated experience of their carers

***Carolyn Blair*[1], *Adrian Slee*[2], *Andrew Davenport* [3], *Denis Fouque* [4], *William Johnston* [5], *Kamyar Kalantar-Zadeh* [6], *Peter Maxwell* [7], *Clare McKeaveney* [1], *Robert Mullan* [8], *Helen Noble* [1], *Sam Porter* [9], *David Seres* [10], *Joanne Shields* [11], *Ian Swaine* [12], *Miles Witham* [13], *Joanne Reid*[1]**

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1-10

Induction of adipose lipolysis by acidosis-adapted cancer cells to meet their increased fatty acid demands

***Camille Lefevre*[1], *Olivier Feron*[2], *Laure B. Bindels*[1]**

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1-11

Role of fibroadipogenic progenitors in pancreatic cancer cachexia

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1-12

Mechanisms of skeletal muscle atrophy in patients with early breast cancer treated with chemotherapy: insights from acute and chronic measurements

***Joris Mallard*[1,2,3], *Elyse Hucteau*[1,2,3], *Laura Bender*[3], *Fabien Moinard-Butot*[3], *Roland Schott*[3], *Carole Pflumio*[3], *Philippe Trensz*[3], *Michal Kalish-Weindling*[3], *Antoine Grandperrin*[1,2], *Fabrice Favret*[1,2], *Xavier Pivot*[3], *Thomas J Hureau*[1,2], *Allan F Pagano*[1,2]**

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1-13

Lung tumor derived factors impair myogenic capacity and mitochondrial function of muscle progenitor cells

***Nikki Wanders*[1], *Wouter van de Worp*[2], *Chrysa Kapsali*[1,2], *Paula Bilbao Fraile*[2], *Hubert Smeets*[1], *Ramon Langen*[2]**

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1-14

Regulation of pancreatic cancer-induced muscle wasting through the obestatin/GPR39 system

***Icía Santos-Zas*[1], *Andrea Calviño-Lodeiro*[1,2], *Tania Cid-Díaz*[3], *Saúl Leal-López*[2], *Silvia Costas-Abalde*[1,2], *Carlos Seoane-Mosteiro*[1], *Rosalía Gallego-Gómez*[4], *Juan Enrique Domínguez-Muñoz*[2], *Yolanda Pazos-Randulfe*[2], *Jesús Pérez-Camiña*[1]**

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1-15

Tumor organoid-derived factors from cachectic pancreatic cancer patients induce a pro-inflammatory macrophage phenotype – role of macrophage migration inhibitory factor

***Valerie D'Antonio*[1], *Min Deng*[1], *Rianne Vaes*[1], *Alisa Huber*[1], *Mo Hadfoune*[1], *Steven Olde Damink*[1], *Sander Rensen*[1]**

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1-16

Leucine supplementation alters inflammatory gene expression in male, but not female *Apc*$^{Min/+}$ cancer cachectic mice

***Eleanor R. Schrems*[1], *Francielly Morena Da Silva*[1], *Ana Regina Cabrera*[1], *Kevin A. Murach*[1], *Nicholas P. Greene*[1], *Tyrone A. Washington*[1]**

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1-17

Using adipose tissue organoids – a new avenue for cancer cachexia research in vitro

Abdolreza Nazari, Jochen Springer

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Poster session 2.2 **Cancer Cachexia II** (posters 2-17 and 2-19 to 2-26)
Chairs: Joanne Reid, Florian Strasser

2-17

Non-steroidal anti-inflammatory drugs for treatment of cancer cachexia: a systematic review

***Megan Bowers*[1], *Brittany Cucchiaro*[2] *Adrian Slee*[3]**

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2-19

The role of body composition and pulmonary function in predicting survival after surgery for resectable lung cancer

***Koen C.H.A. Verkoulen*[1], *Yvonne L.J. Vissers*[1], *Karel W.E. Hulsewé*[1], *Steven W.M. Olde Damink*[2], *David P.J. van Dijk*[1 2*], *Erik R. de Loos*[1,*]**

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*Authors contributed equally

2-20

Prospective Characterisation of Cancer Cachexia in Patients with Advanced Cancer

***Judith Sayers*[1,2,3], *Leo R. Brown*[1], *Richard J.E. Skipworth*[1] *Barry J.A. Laird*[2,3]**

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2-22

Assessment of lipolysis biomarkers in subcutaneous adipose tissue of gastrointestinal cancer patients

***Giovanni Imbimbo*[1], *Federica Tambaro*[1], *Elisabetta Ferraro*[2], *Martina Andreini*[1], *Michele Melena*[1], *Maria Ida Amabile*[1], *Giulia Lauteri*[3], *Giuseppe Nigri*[3], *Maurizio Muscaritoli*[1], *Alessio Molfino*[1]**

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2-23

Effect of malnutrition risk on the association between skeletal muscle index and health-related quality of life and survival in upper gastrointestinal cancer

***Lauren Hanna*[1,2], *Kay Nguo*[2], *Judi Porter*[2,3], *Daniel Croagh*[4,5], *Catherine E Huggins*[2,6]**

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2-24

Adipose tissue radiation attenuation is an independent predictor of chemotherapy toxicity and shorter overall survival in metastatic colorectal cancer patients

***Yan Sun*[1], *Isabel M. van Ruijven*[2], *David P.J. van Dijk*[1], *Ralph Brecheisen*[1], *Nicolette Wierdsma*[2], *Sander S. Rensen*[1], *Steven M.W. Olde Damink*[1,3]**

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2-25

The Prognostic Impact of Pre-Treatment Cachexia in Resectional Surgery for Oesophagogastric Cancer: A Systematic Review, Meta-Analysis & Meta-Regression

***Leo R. Brown*[1*], *Judith Sayers*[1], *Michael S. Yule*[1], *Thomas M. Drake*[2,3], *Ross D. Dolan*[4], *Donald C. McMillan*[4], *Barry J.A. Laird*[5], *Stephen J. Wigmore*[1],*Richard J.E. Skipworth*[1]**

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2-26

Progressive loss of bone density in patients with esophageal cancer

***Miles Cameron*[1,2], *Ziad Awad*[3], *Sarah Judge*[1], *Andrew Judge*[1]**

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Poster session 2.3 **Muscle wasting & sarcopenia I** (posters 4-01 to 4-10)
Chairs: Marielle Engelen, Olav Rooyackers

4-01
Involvement of the CXCR4/CXCL12 axis in skeletal muscle dysfunction in an early murine model of COPD
***Pauline Henrot*[1,2], Pierre Schilfarth[1,2], Marilyne Campagnac[1], Elise Maurat[1], Marina Gueçamburu[1,2], Pauline Estèves[1], Jean-William. Dupuy[3], Maéva Zysman[1,2], Patrick Berger[1,2], Isabelle Dupin[1]**
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4-02
A novel *in vitro* model of senescent murine myoblasts and sarcopenic myotubes to highlight skeletal muscle involvement in the aging phenotype
***Laura Gerosa*[1], Marta Gomarasca[1], Amir Mohammad Malvandi[1], Martina Faraldi[1], Veronica Sansoni[1], Giovanni Lombardi[1]**
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4-03
The effect of Doxorubicin on skeletal muscle mass and myokine expression in Lewis Lung Cancer bearing mice
***Birgit Van Asbroeck*[1]; Dorien Dombrecht[1] Emeline Van Craenenbroeck[2,3] Pieter-Jan Guns[4] Eric Van Breda[1]**
[1]Department of Rehabilitation Sciences & Physiotherapy, Research group MOVANT, University of Antwerp; [2]Research group Cardiovascular Diseases, University of Antwerp; [3]Department of Cardiology, Antwerp University Hospital; [4]Laboratory of Physiopharmacology, University of Antwerp

4-04

The Rho GTPase inhibitor, RhoGDIα is a negative regulator of muscle mass and upregulated in sarcopenic human muscle
***Lisbeth L. V. Møller*[1,2], Kevin I. Watt[3,4], Jakob Agergaard[5,6], Anders Karlsen[5,6,7], Nicoline R. Andersen[2], Peter Schjerling[5,6], Hongwei Qian[8], Michael Kjær[5,6], Paul Gregorevic[8], Erik A. Richter[2], and Lykke Sylow[1,2]**
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4-05
ADAR2 deficiency alleviates muscle atrophy in HFD-induced obese mice
***Chia-Chi Lin*[1], Yun-Wen Chen[1*]**
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4-06

Urocortin 2 modulates muscle mass associated with insulin/IGF-1 signaling pathway stimulation in skeletal muscles of obese and denervated mice

***Natalia Lautherbach*[1], *Dawit Albieiro Pinheiro Gonçalves*[2], *Ana Paula Assis*[1], *Rafael Rossi Valentim*[3], *Lilian do Carmo Heck*[3], *Luiz Carlos Carvalho Navegantes*[3], *Isis do Carmo Kettelhut*[1,3]**

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4-07

Cyp27b1 ablation in skeletal muscle impairs muscle regeneration

***Hiu-tung Jessica Lo*[1,2], *Tszlam Yiu*[1,2], *Daniel Kam-Wah Mok*[3, 4, 5], *and Man-Sau Wong*[3, 4, 5], *Wayne Yuk-wai Lee*[1,2,6,7,8]**

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4-08

Role of mechanosensitive components in the regulation of myogenic differentiation

***Alexander Pacolet*[1,2], *Mathias Vanmunster*[2,3], *Inge Derese*[1], *Maxime Smits*[4,5], *Lies Langouche*[1], *Rik Gijsbers*[4,5]**

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4-09

MRI-based characterization of muscles in ageing mice fed on high-energy diet and sedentary lifestyle

Beatrice Matot*, *Ericky Caldas de Almeida Araujo, Pierre-Yves Baudin, Harmen Reyngoudt, Benjamin Marty, Yves Fromes

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4-10

MR-based characterization of aging in human muscles

Alfredo Lopez, Béatrice Matot, Jean-Marc. Boisserie, Sophie.Jouan, Ericky. Caldas, Pierre-Yves. Baudin, Benjamin Marty, Harmen Reyngoudt, Yves Fromes

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Poster session 3.1 **Muscle wasting & sarcopenia II** (posters 4-12 to 4-22)
Chairs: Nick Hoogenraad, Robert Mak

4-12
Long-term musculoskeletal consequences of chemotherapy in pediatric mice
Joshua R. Huot[1,2,3], Fabrizio Pin[1,2,3], Nicholas A. Jamnick[4], Patrick D. Livingston[4], Andrea Bonetto[4,5]
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4-13
Extracellular vesicles are possible mediators of the liver-muscle axis in sarcopenia associated to liver disease
Laura Barberi[1], Manuela Merli[1], Simone di Cola[1], Cristiana Porcu[2], Stefano Fonte[1], Lorenzo Ridola[1], Antonio Musarò[2]
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4-14
Skeletal muscle transcriptional dysregulation of genes involved in senescence is associated with prognosis in severe heart failure
Eric Rullman, Alen Lovric, Michael Melin, Rodrigo Fernandez-Gonzalo, Thomas Gustafsson
Division of Clinical Physiology, Department of Laboratory Medicine, Karolinska, Institutet, and Unit of Clinical Physiology, Karolinska University Hospital Huddinge, Stockholm, Sweden

4-15
Cachexia, sarcopenia and bone markers in patients with heart failure and hyperkalemia: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)
Guglielmo Fibbi[1], Tania Garfias-Veitl[1,2], Mirela Vatić[1,2], Ryosuke Sato[1], Wolfram Doehner[3,4,5], Stefan D. Anker[3,5,6], Stephan von Haehling[1,2]
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4-16
Low serum creatinine to cystatin C ratio predicts injurious falls in older men – the prospective STRAMBO study
Pawel Szulc, Roland Chapurlat
INSERM UMR1033, University of Lyon, Hospices Civils de Lyon, 69437 Lyon, France

4-17
Myeloid-Derived Growth Factor protects skeletal muscle from damage and is required for its repair and regeneration
Guo-Zheng Zhu, Zhao-Ming Zhong
Division of Spine Surgery, Department of Orthopaedics, Nanfang Hospital, Southern Medical University, Guangzhou, China

4-18

Metabolic remodeling during skeletal Muscle hypertrophy: role of glycolysis-derived intermediates in anabolic pathways

Philipp Baumert[1*], Sakari Mäntyselkä[2†], Martin Schönfelder[1†], Marie Heiber[1], Anandini Swaminathan[3], Petras Minderis[3]; Mantas Dirmontas[4], Karin Kleigrewe[5], Chen Meng[5], Michael Gigl[5], Tomas Venckunas[3], Hans Degens[3,6], Aivaras Ratkevicius[3,4], Juha J. Hulmi[2] & Henning Wackerhage[1]

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4-19

Vitamin D signaling plays an inhibitory role in intramuscular adipogenesis of FAPs

Tohru Hosoyama[1], Minako Kawai-Takaishi[1], Hiroki Iida[1], Tsuyoshi Watanabe[2], Yasumoto Matsui[2], Akiyoshi Uezumi[3], Ken Watanabe[1]

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4-20

To investigate the mechanism of adipose-derived stem cells in an in vitro model of dexamethasone-induced myotubes atrophy

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4-22

Inhibiting serine synthesis pathway by PHGDH inhibition reprograms skeletal muscle cell metabolism and impairs anabolic processes

Sakari Mäntyselkä[1], Kalle Kolari[1], Philipp Baumert[2], Laura Ylä-Outinen[1], Lauri Kuikka[3], Suvi Lahtonen[4], Perttu Permi[4,5,6], Henning Wackerhage[2], Elina Kalenius[5], Riikka Kivelä[1,7,8], Juha J Hulmi[1]

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Poster session 3.2 **Therapeutic development pre-clinical/clinical** (posters 7-01 to 7-13)
Chairs: Paola Costelli, Sander Rensen

7-01

Anti-RANKL treatment attenuates mitochondria deterioration and suppresses macrophage infiltration during sarcopenia

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7-02

Enhanced glutamine availability exerts different effects on protein and amino acid metabolism in muscles of healthy and septic rats

Milan Holeček, Ludek Šišpera

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7-03

Exploring Lonafarnib's Potential for Sarcopenia Treatment in Dexamethasone-Induced Muscle Atrophy Models

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7-04

Muscle Protein Synthesis with a Hybrid Dairy and Plant-based Protein Blend (P4) is Equal to Whey Protein in a Murine Aging Model after Fasting

Francina J. Dijk[1], Zandrie Hofman[1], Yvette C. Luiking[1], Matthew J.W. Furber[1], Justin D. Roberts[1,2], Ardy van Helvoort[1,3], Miriam van Dijk[1]

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7-05

A novel first-in-class USP19 inhibitor for the treatment of cancer-induced muscle atrophy

Richard D. A. Wilkinson[1], Vignesh Karthikaisamy[2], Darren M. O'Hara[1], Aaron N. Cranston[1], Colin R. O'Dowd[1], Xavier Jacq[1], Stephanie Burton[1], Hayley Gibson[1], Joana Costa[1], Daniel Longley[1], Matthew Helm[1], Chris McGivern[1], Steven Shepherd[1], Christina Bell[1], Steven Shepherd[1], Peter Hewitt[1], Mary McFarland[1], Hugues Miel[1], Steven Whitehead[1], Lauren Proctor[1], J. S. Shane Rountree[1], Mark Wappett[1], Natalie Page[1], Mauricio Berriel Diaz[2], Stephan Herzig[2], Timothy Harrison[1]

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7-06

Changes in CaCo-2 mRNA expression pathways affected by in vitro testosterone exposure

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7-07

CaCo-2 intracellular calcium changes following testosterone treatment

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7-08

Developing an evidence and theory based multimodal integrative intervention for the management of renal cachexia: a theory of change

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7-09

TERESA feasibility study (TEstosterone REplacement therapy (TRT) in SArcopenic male colorectal cancer patients) – Lessons from low recruitment numbers

Ioanna Drami[1,2], Dinh Mai[1,2], Edward T Pring[2], Harry Dean[1,2], Christos Kontovounisios[1], Adam Stearns [3], Channa Jayasena[1], John T Jenkins[1,2]

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7-10

Phase 2 study to assess the efficacy, safety, and tolerability of the GDF-15 inhibitor ponsegromab in patients with cancer cachexia

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7-11

Ruxolitinib's Nutritional Effects In patients with Myelofibrosis: preliminary results

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7-12

Assessing the effect of intra-abdominal malignancy on the impact of a short-term homebased unsupervised exercise on skeletal muscle mitochondrial OXPHOS function

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7-13

Association between sarcopenia and urinary dysfunction in patients with dysphagia

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Poster session 3.3 **Diagnosis of cachexia and sarcopenia II** (posters 3-14 and 3-16 to 3-22)
Chairs: Swarnali Acharyya, Philip Atherton

3-14

Sexual dimorphism in *masseter* thickness as anthropometric prognostic biomarker in head & neck cancer cachexia: a retrospective cross-sectional study

Julián Balanta-Melo[1,2], Alexander J. Jones[3], Michael G. Moore[3], Andrea Bonetto[4]

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3-16

The relationship between muscle strength and quality with functional performance in women mid-term after Roux-en-Y gastric bypass

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3-17

Height-adjusted appendicular skeletal muscle mass is overestimated due to height loss in Japanese middle-aged and older women: The Japanese Population-based Osteoporosis (JPOS) study

Kazuki Kaji[1], Jun Kitagawa[2], Takahiro Tachiki[3], Kouji Tsuda[4], Masayuki Iki[5], Junko Tamaki[4], Katsuyasu Kouda[6], Naonobu Takahira[2], Etsuko Kajita[7], JPOS Study Group[4]

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3-18

Functional physical parameters are more associated with falls than with the diagnosis of sarcopenia by EWGSOP2

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3-19

Validation of accuracy and reliability of automated segmentation of body composition from single-slice ct images at l3 level using data analysis facilitation suite (dafs) in patients with non-metastatic colorectal cancer

Mushfiqus Salehin[1], Vincent Tze Yang Chow[2], Parsa Moheban[3], Hyunwoo Lee[4], Bette J Caan[5], Elizabeth M Cespedes Feliciano[5], Da Ma[6], Mirza Faisal Beg[2], Karteek Popuri[1]

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3-20

Deep learning-driven volumetric CT body composition analysis: new metrics for long-term postoperative risk stratification in colorectal cancer patients

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3-21

Automated volumetric BC quantification by the Data Analysis Facility Suite (DAFS): external validation for preoperative CT abdomen and pelvis in colorectal cancer

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3-22

Compared to single lumbar slice, volumetric body composition analysis from regional CT scans is more representative of skeletal muscle and adipose tissue volume and radiodensity

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Poster session 4.1 **Diagnosis of cachexia and sarcopenia III** (posters 3-23 to 3-30)
Chairs: Nicholas Greene, Yi-Ping Li

3-23

Elevated epicardial adipose tissue and aortic calcification, quantified from volumetric regional CT scans, are associated with postoperative complications in complex rectal cancer

***Dinh V C Mai*[1,2], *Ioanna Drami*[1,2], *Edward T Pring*[1,2], *Laura E Gould*[1,2], *Jason Rai*[1] , *Philip Lung*[1,2], *Vincent Chow*[3], *Karteek Popuri*[4], *Mirza Beg*[3], *Thanos Athanasiou*[2], *John T Jenkins*[1,2]**

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3-24

Evaluation of body composition at L3 from computed tomography (CT) images using DAFS software, a 3D fully automated multi-slice multi-organ extraction platform

***Michelle V. Dietz*[1], *Karteek Popuri*[2], *Lars Janssen*[1], *Mushfiqus Salehin*[3], *Da Ma*[2,5], *Vincent Tze Yang Chow*[2], *Hyunwoo Lee*[4], *Cornelis Verhoef*[1], *Eva V.E. Madsen*[1], *Mirza Faisal Beg*[2], *Jeroen L.A. van Vugt*[5]**

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3-25

Mosamatic: a user-friendly, web browser-based platform for automatic analysis of body composition using CT scans

***Ralph Brecheisen* [1], *David P.J. van Dijk*[1], *Sander S. Rensen*[1], *Leonard Wee*[1,2], *Andre Dekker*[2], *Steven W.M. Olde Damink*[1]**

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3-26

Using MRI to Measure Head Muscles: An Innovative Method for Opportunistically Determine Muscle Mass and Detect Sarcopenia

***Miguel German Borda*[1,2,3], *Gustavo Duque*[4,5], *Mario Ulises Pérez-Zepeda**[6, 7] , *Jonathan Patricio Baldera*[1,8], *Eric Westman*[9], *Anna Zettergren*[10], *Jessica Samuelsson*[10], *Silke Kern*[10,11], *Lina Rydén*[10], *Ingmar Skoog*¥[10,11], *Dag Aarsland*¥[1,12]**

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3-27

Assessing the accuracy of estimating whole body SKM from L3 single slice and whole illiopsoas SKM

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3-28

Is single-slice (L3mid) regression-based assessment of SKM, VAT, SAT accurate for individual patient level analysis?

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3-29

Automated preoperative body composition may predict pancreatic fistula risk after whipple surgery

Chet W Hammill[1], Mohammadali Mirmojarabian[2], Hyunwoo Lee[3], Sanghee Lee[1], Rohit Srivastava[1], Da Ma[4], Vincent Chow[5], Mirza Faisal Beg[5], Karteek Popuri[2]

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3-30

Validation of a deep learning model for automatic segmentation of skeletal muscle and adipose tissue on L3 abdominal CT images

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Poster session 4.2 **Muscle wasting & sarcopenia III** (posters 4-23 to 4-34)
Chairs: Nick Hoogenraad, Hidetaka Wakabayashi

4-23

Antisense oligonucleotides as a potential therapy in muscle wasting disorders

***Andrea García-Rey*[1,2,3], *Estefanía Cerro-Herreros*[1,2,3], *Mouli Chakraborty*[1], *Nuria Barquero*[1], *Isabel Campillo*[1], *Sheila Soriano Santafé*[1], *Judit Núñez-Manchón*[4], *Neia Naldaiz-Gastesi*[5], *Marc Carrascosa-Sàez*[3], *Irene González-Martínez*[1,2] , *Adolfo López de Munain*[5] , *Mònica Suelves*[4], *Gisela Nogales-Gadea*[4], *Rubén Artero*[2,3] and *Beatriz Llamusí*[1]**

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4-24

Sex-specific molecular features of clear cell renal cell carcinoma are associated with muscle loss

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4-25

Influence of IGF-I serum concentration on muscular regeneration capacity in patients with sarcopenia

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4-26

Dynapenic abdominal obesity as a risk factor for the incidence of metabolic syndrome in individual 50 years of age or older: evidence from the English Longitudinal Study of Ageing

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4-27

Type II myofiber atrophy is not underpinned by deficits in acute anabolic signaling after resistance exercise and amino acid intake in healthy, lean older adults

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4-28

Autophagosomes and protein aggregates accumulation in the skeletal muscle of septic patients, a pilot study

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4-29

Hand grip strength as a prognostic factor for mortality among COVID-19 patients admitted to the intensive care unit (ICU)

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4-30

Validation of a bedside ergometer dedicated to longitudinal evaluation of neuromuscular function in intensive care unit patients

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4-31

Electrical stimulation (ES) exhibits a local and systemic restoring effect on muscular disarrangements associated with critical illness myopathy (CIM)

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4-32

The effect of awakening on leg muscle size in patients with critical illness who received early functional rehabilitation

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4-33

Non-acidotic hypercapnia limits the loss of force of diaphragm muscle fibers in mechanically ventilated rats for 5 days

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4-34

Long Covid: a combination of self-reported symptoms, lower muscle function and disrupted inflammation

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Poster session 4.3 **Cancer cachexia III** (posters 2-10 to 2-18)
Chairs: Mauricio Berriel-Diaz, Marcus Goncalves

2-10

Correlation of preoperative body composition with postoperative complications and 30-day-mortality in 255 patients in resectable pancreatic cancer

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2-11

Body Composition Endpoints in Cancer Cachexia Clinical Trials: A Systematic Review from the Cachexia Endpoints Series

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2-12

Oncological Endpoints in Cancer Cachexia Clinical Trials: Systematic Review of Cachexia Endpoints

Iain Phillips[1], Olav Dajani[2], Ester Størckson[2], Barry Laird[3], Richard Skipworth[3], Tora Solheim[4], Jann Arends[5] *on behalf of cachexia clinical trials endpoints group.*

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2-13

Biomarkers in cancer cachexia clinical trials: systematic review of the cachexia endpoints series

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2-14

The relationship between appetite and lean body mass as endpoints in cancer cachexia interventional clinical trials. A systematic review.

Eilidh Fraser[1], Tora Solheim[2], Richard Skipworth[3], Inger Ottestad[2], Asta Bye[4], Trude Balstad[2], Christine Greil[5], Ola Magne Vagnildhaug[2]

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2-15

The impact of acute systemic inflammation and the metabolic response to surgery on computed tomography body composition analyses

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2-16

An International Survey on Nutritional Issues in Patients with Cancer: Preliminary Results

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2-18

The mortality burden of cachexia in patients with non-small cell lung cancer: A meta-analysis

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POSTER ABSTRACTS

1-01

Growth of GL261 glioblastoma tumors induced delayed body weight gain and stunted skeletal muscle growth in pediatric mice

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Introduction: Up to 80% of adult cancer patients will develop involuntary body weight loss associated with skeletal muscle wasting, which altogether lead to increased morbidity and mortality. However, there is minimal understanding or research on the influence of pediatric cancers on muscle development and physiology. Given that brain tumors alone are responsible for 1/4 of all pediatric cancers, the aim of the current research was to investigate the skeletal muscle consequences associated with growth of these tumors in young mice.
Methods: In vitro atrophy was assessed by co-culturing C2C12 myotubes with GL261 murine glioblastoma cells. GL261 cells (1.0x106) were injected subcutaneously into 4-week-old male C57BL/6J mice. Body mass was monitored daily. Vehicle (n=5) and experimental mice (n=14) were culled 28 days after GL261 implantation. Skeletal muscle and organ weights were measured at the completion of the study. Muscle cross sectional area (CSA) was assessed via immunofluorescent stain of dystrophin. In vivo and ex vivo muscle function testing was completed at baseline and prior to completion of the study. Muscle protein synthesis was measured via the SUnSET method, and gene expression via qPCR.
Results: C2C12 cells exposed to GL261 exhibited myotube atrophy. Carcass, heart, and fat mass were mitigated ($p < 0.05$) in the tumor bearers, whereas growth of skeletal muscles (tibialis anterior and quadriceps) was impeded in the GL261 hosts ($p<0.05$), in line with significantly lower muscle fiber cross sectional ($p<0.05$). In vivo gastrocnemius torque was not significantly different between groups, while the ex vivo EDL muscle force was reduced in the GL261 hosts ($p<0.05$). Tumor hosts displayed reduced muscle protein synthesis ($p<0.05$). MuRF-1, MUSA1 and Atrogin1 muscle ubiquitin ligase mRNA expression was lower in the GL261 hosts.
Conclusions: Our research highlights the impact of GL261 glioblastoma on pediatric mice. GL261 hosts yielded a stunted development of skeletal muscle, as evidenced by decreased skeletal muscle mass, smaller muscle fiber CSA, diminished muscle protein synthesis, and reduced cell signaling associated with protein catabolism. Future research should focus on the mechanisms responsible for the systemic long-term effects of cancer in pediatric patients and investigate potential therapeutic targets to mitigate the blunted muscle development.

1-02

Sexual dimorphism in the development of cancer cachexia in *Apc*$^{Min/+}$ mice

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Introduction: Cancer cachexia is a devastating hypo-anabolic and catabolic syndrome characterized by a progressive unintentional loss of body mass, essentially due to a severe depletion of skeletal muscle compartment. Despites extensive studies over the last decade, little is known about the effects of sex and sex hormones on the development of cancer cachexia. Here, we determined whether the progression of cancer cachexia was different in male and female *Apc*$^{Min/+}$ mice, a model of intestinal and colon cancer cachexia that mimics the human adenomatous polyposis.
Methods: Male and female *Apc*$^{Min/+}$ mice aged of 11 and 15 weeks have been analyzed for body weight, the extent of polyposis, body composition (X-ray technology Lunar PIXImus), muscle weights and muscle force (Aurora Scientific). Age- and sex-matched wild type littermate mice were used as controls.
Results: The number of polyps (27 ± 9.8 in male *vs* 27.8 ± 3.2 in female) as well as the hematocrit (35.7 ± 2.5 in male *vs* 40.6 ± 2.4 in female), were similar in 15-week-old *Apc*$^{Min/+}$ mice, indicating no sex difference in the development of the polyposis. Male *Apc*$^{Min/+}$ mice started to lose weight at 12 weeks (-9%, $P<0.05$). At the age of 15 weeks, muscle weight loss was about 16% ($P<0.001$). By contrast, body weight was not statistically significant between wild type and *Apc*$^{Min/+}$ female mice. This was also associated with a better preservation of fat mass and bone mineral density in female *Apc*$^{Min/+}$ mice. *Gastrocnemius* muscle weight was also lowered in 15-week-old (-10%, $P<0.001$) male *Apc*$^{Min/+}$ mice compared to wild type male mice, whereas it was unchanged between female genotypes. Similar results were obtained for *extensor digitorum longus*, *quadriceps*, *soleus*, and *tibialis anterior* muscle weights. Functionally, maximum muscle force, which was lowered in 15-week-old male *Apc*$^{Min/+}$ mice compared to wild type male mice (-22.5%, $P<0.05$) was similar between female genotypes.
Conclusion: These data indicate that that while the progression of the disease *per se* seems to be the same in males and females *Apc*$^{Min/+}$ mice, 15-week-old female *Apc*$^{Min/+}$ mice display resistance to the development of cancer cachexia, clearly indicating the existence of a sexual dimorphism. Ongoing analyses will provide information to understand the molecular mechanisms involved in sexual dimorphism.

1-03

Metabolic dysfunction during recovery from colorectal cancer chemotherapy: a role for skeletal muscle AMPK signaling.

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Introduction: The FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) chemotherapy regimen is used to treat colorectal cancer and can induce acute metabolic dysfunction. While skeletal muscle loss can negatively regulate systemic metabolism, gaps remain in our understanding of how changes in the biochemical properties of muscle contribute to long-lasting chemotherapy toxicities. We investigated the effects of FOLFOX chemotherapy on systemic and skeletal muscle metabolism in mice and the direct effects of FOLFOX on AMPK and autophagy flux in cultured myotubes.
Methods: Male C57BL6/J (12wks) completed four cycles of FOLFOX or PBS treatment. Chemotherapy recovery was examined at 0 (n=8), 4 (n=11), or 10 weeks (n=8-13) after the fourth chemotherapy cycle. Metabolic measurements were done in CLAMs cages for 5-days. C2C12 myotubes were dosed with FOLFOX for 24-hrs. Bafilomycin A1 (100nM) and protein expression of LC3B and p62 were used to assess autophagy flux.

Results: FOLFOX attenuated body and fat mass accretion independent of lean mass, cage activity, or food intake. Fat mass remained reduced at 4-wks recovery. Acute FOLFOX decreased oxygen consumption (VO2), energy expenditure (EE), carbohydrate (CHO), and lipid oxidation ($p<0.01$). Deficits in VO2 and EE remained at 10-wks recovery. CHO oxidation was reduced at 4-wks but returned to control levels at 10-wks recovery. FOLFOX significantly decreased soleus (-29%, $p=0.01$) and plantaris (-26%, $p=0.03$) muscle COXIV enzyme activity. Acute FOLFOX reduced gastrocnemius muscle AMPK(T172) (-25%, $p=0.03$) and ULK1(S555) (-40%, $p=0.01$) phosphorylation and LC3B-II protein expression (-43%, $p=0.02$). The LC3B-II/I ratio was positively correlated to CHO oxidation ($r=0.75$, $p=0.03$) in FOLFOX mice. Recovery for 4-wks normalized muscle AMPK and ULK1 phosphorylation. FOLFOX treatment exerted direct effects on cultured myotubes; AMPK(T172) phosphorylation was reduced (-42%, $p<0.01$). Interestingly, FOLFOX administration suppressed myotube autophagy flux ($p<0.01$).
Conclusions: FOLFOX chemotherapy disrupted systemic metabolism, which did not recover after cessation of chemotherapy. Interestingly, FOLFOX-induced disruptions to muscle AMPK and autophagy signaling improved independent of systemic metabolism deficits. The activation of AMPK signaling during chemotherapy treatment warrants further investigation as a therapeutic target to prevent chemotherapy toxicities.

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1-04

Renal cell carcinoma in kidney specific Tsc1 knocked out mice cause cachexia in the skeletal Muscle

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Introduction: Cancer cachexia is a comorbidity that impacted significant skeletal mass reduction; patients undergoing this condition exhibit reduced functional ability, leading to a lower quality of life and compromised tolerability for chemotherapy treatments. Considering this situation, our study decided to investigate how pro-inflammatory cytokines released from a tumor played their role in driving protein breakdown and muscle atrophy in cancer cachexia. Thus, we analyzed tumorigenesis occurring within the kidneys of Tsc1-/- mice which leads to renal cell carcinoma by up-regulation of mTORC1 pathway. We investigated whether the tumorigenesis in the kidney of Tsc1-/- mice releases pro-cachectic factors causing muscle atrophy, reduced body weight, and muscle function compared to their wild type littermates. Based on our experiment's findings which provided an excellent insight for understanding the underlying molecular mechanisms that contribute to cancer cachexia from renal cell carcinoma and highlight potential targets for therapeutic interventions to improve the quality of life of cancer patients.
Method:
Mice – To generate Tsc1f/f:KspCre mice we intercrossed Tsc1f/+:KspCre mice (Pema et al., 2016).
Histological & immunofluorescence - Cross sectional area analysis.
Tumor conditioned medium from Tsc1-/- mice kidney of Post natal P50 & P80
Real-Time PCR analysis – Total RNA isolated from the muscles and C2C12 treated with TCM for the gene expression analysis.
Western blot analysis – Protein harvested from the C2C12 treated with TCM from P50, P80 and their wild type littermate kidney for western blot analysis.
Stat3 & NFkB Luciferase reporter assay
Results: Reduced body &muscle weight in Tsc1-/- mice at P50 & P80.
Gene which are downregulated and upregulated in various cancer cachexia model such as Calm2, Col1a1, Phka1 and Eif4ebp1, Foxo1 were regulated in the same manner in muscles of Tsc1-/- mice at P50 & P80, respectively. Atrogene (Atrogin-1 & MuRF1) are upregulated in muscles at P50 & P80.
Reduced cross-sectional area of myofiber at P50 & P80.
In vitro Smaller diameter of C2C12 myotubes treated with TCM P80.
In vitro Downregulation mTOR pathway (reduced phosphorylation of AKT and P70-S6K) in C2C12 myotubes upon exposure with TCM P50 & P80.
Increased phosphorylation and transcriptional activities of Stat3 and NFkB in C2C12 myoblast upon treatment with TCM P50 & P80.
Conclusion: The tumor in the kidney of Tsc1-/- mice releases pro-cachectic factors, potentially causing muscle atrophy by altering the cross-talk and signalling pathways of many proteins that include Akt, S6K, Stat3, and mTOR, among others which suggest that targeting the pro-cachectic factors may be a promising therapeutic strategy to treat cancer.

1-05

Hepatic metabolism alterations and effects of niacin supplementation in experimental cancer- and chemotherapy-induced cachexia.

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Introduction: Alterations in hepatic function influence energy expenditure in cancer patients and could play an important role in the development and progression of cancer cachexia, a progressive metabolic syndrome that results in depletion of skeletal muscle [1,2]. In cachectic mice, niacin (NA) supplementation ameliorated cancer- and chemotherapy-induced cachexia while repleting hepatic NAD metabolite levels, suggesting that a relevant part of the NA effects may be mediated by the improvement of liver metabolism [3]. Therefore, the objective of this project was to evaluate the differences in the liver metabolism of healthy mice and cancer/chemotherapy cachectic mice with or without niacin supplementation.
Methods: Two in vivo experiments were performed and compared with healthy controls. First, for an acute model of cachexia, female tumor-bearing C26 mice (n=7/group) were treated with chemotherapy (Folfox) and either treated daily with 150 mg/kg niacin (C26+F+NA) or given water (C26+F). Second, for a chronic model of cachexia, Msh2 loxP/loxP Villin-Cre (VCM) 12-month-old male mice (n=6/group) were either treated with a daily dose of NA or non-treated. Liver samples were lysed and processed to isolate high-quality RNA, RNA-seq libraries were generated, and sequencing experiments were performed. Lipidyzer technology was used to quantify lipid species in the liver.
Results: Diverse fatty acid, energy, immune, and NAD metabolism gene sets were impacted in tumor bearing mice when compared to healthy controls, plus enrichments profiles differed between the cachectic groups supplemented with NA and those not supplemented. Moreover, the acute and the chronic cachexia models showed distinct hepatic gene expression profiles. Importantly, when comparing tumor bearing mice per cachexia model, gene sets associated to NAD

metabolism were impacted by NA supplementation in the VCM mice, but not in the C26. Additionally, the lipidomic analysis demonstrated that hepatic lipid composition was also altered in tumor bearing mice with either acute or chronic cachexia when compared to controls, plus that lipid profiles change with NA repletion.
Conclusion: Our preliminary results indicate that in both acute and chronic models of cancer cachexia, gene expression and lipid metabolism profiles are altered in the liver, and that niacin supplementation has an impact in such changes. Further studies are needed to better understand the effects of such hepatic metabolic changes in different stages of cancer cachexia and the potential benefits of niacin supplementation, while also considering the impact of sex, age, and chemotherapy.

References:
1.doi:10.1139/apnm-2019-0407
2.doi:10.1002/jcsm.12798
3.doi:10.1038/s41467-023-37595-6

1-06

The effects of a novel long-acting ghrelin on ameliorating cancer cachexia in mice

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Introduction: Ghrelin has been investigated as a potential therapy for cachexia because of its orexigenic and anabolic effects on protecting against weight and muscle loss. However, its clinical application is limited due to its short half-life (~11 minutes in humans). EXT418 is a novel long-acting, constitutively active ghrelin analog created by covalently linking it to a vitamin D derivative. To evaluate the effects of EXT418 on cancer cachexia and elucidate the underlying mechanisms, we evaluated this compound in a cancer cachexia model in mice induced by Lewis Lung Carcinoma (LLC).
Methods: Adult male C57BL/6J mice were implanted with 1x10^6 heat-killed (HK) or live LLC cells subcutaneously. After ~7 days, when the tumor was palpable, mice were treated with vehicle (T+V) or EXT418 daily (T+418 Daily, 0.25mg/kg/day) or every other day (T+418 EOD, 0.5mg/kg/EOD) for up to 14 days, while HK-treated mice were given vehicle (HK+V). Subsets of T+418 Daily or EOD-treated mice were pair-fed to the T+V group. Body composition and grip strength were assessed at baseline (before tumor implantation) and at the end of the experiment. Skeletal muscles were collected after euthanasia and used for molecular analysis. Statistical analysis was performed by one-way ANOVA or Kruskal-Wallis tests to detect differences between groups (p<0.05).
Results: LLC tumor led to significant decreases in food intake, body weight, fat mass, lean body mass, and grip strength in mice. Administration of EXT418 daily or EOD prevented these decreases in weight and muscle strength, which was partially independent of food intake. Fiber size in tibialis anterior muscles was improved by EXT418 daily administration, and IIB fiber size in red gastrocnemius muscles was improved by EXT418 EOD in tumor-bearing animals. In skeletal muscles, EXT418 administration with both schedules attenuated tumor-induced increases in atrogenes (Fbxo32 and Trim63) and the gene level of Il-6, which were independent of food intake. A similar pattern of inflammatory markers Il-6 in adipose tissue and Il-10 in circulation was observed but the modification from EXT418 was not significant. Tumor-induced increases in mitophagy markers (Bnip3 and p62) in skeletal muscles were also attenuated by EXT418 EOD and/or daily. Meanwhile, tumor size was not altered by either of the EXT418 treatment.
Conclusions: EXT418 protects against LLC-induced cachexia by reducing skeletal muscle inflammation, proteolysis, and mitophagy without affecting tumor mass and is partially independent of food intake.

1-07

Sex differences in amino acid metabolism is linked to cachexia outcomes in mice treated with chemotherapy drugs

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Introduction: Cachexia is a body and skeletal muscle-wasting syndrome that affects ~80% of cancer patients. Given the differences in physiology between the sexes, it is likely that the severity and contributors to cachexia are different between the sexes Although negative effects of chemotherapy on skeletal muscle are documented, the majority of the studies were completed in male animals.
Branched-chain amino acids (BCAA: leucine, isoleucine, and valine) activate anabolic signalling in skeletal muscle. While BCAA may mitigate some measures of cachexia, BCAA nutritional support does not fully reverse cachexia. This may be related to altered metabolism of these amino acids in cachexia, a subject that has been little studied. The objective of this study is to compare the effects of chemotherapy on cachexia outcomes and BCAA metabolism in male and female mice.
Methods: Three-month-old CD2F1 male and female mice were treated with either the chemotherapy drug combination folfiri (50mg/kg 5-fluorouracil (5FU), 90mg/kg Leucovorin, and 24mg/kg CPT11, (drug)) or vehicle for six weeks.
Results: Between sexes, drug-treated female mice lost more body (-15%) and gastrocnemius muscle (-30%) weights compared to drug-treated males (-10 and -19%, respectively; P<0.05). Consistent with these, drug-treated females showed greater loss of anabolic signalling compared to males. Greater reductions were seen in muscle BCAA concentrations in male (-53% to -74%) compared to female (-27 to -41% (P<0.05). This was especially so for valine whose level was reduced by ~75% in male but by <30% in female. This correlated with greater reductions in muscle LAT1 (the BCAA transporter), but not in SNAT1, in female treated with the drugs compared to male (55% vs 40%, P>0.05). Conversely, plasma levels of BCAA were increased by 60% and concentrations in liver by >100% in male but with much smaller changes in females (no change in plasma, ~45% increase in liver in female). Among the key enzymes involved in BCAA metabolism, the inhibitory phosphorylation of branched-chain alpha-ketoacid dehydrogenase complex (BCKD) tended to be greater in drug-treated male animals. Although BCKD activity was higher in drug-treated animals, no significant sex differences were observed.
Conclusions: Our data suggest a link between body/muscle wasting and decreased BCAA metabolism during chemotherapy, and that these differences are likely regulated at the level of amino acid transport. Interventions that seek to mitigate cachexia need to consider these sex-related changes.

1-08

Unraveling the mechanisms of muscle atrophy: focus on lipocalin 2 and iron homeostasis

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Introduction: Cachexia is a wasting syndrome characterized by severe skeletal muscle atrophy that substantially increases mortality in various diseases. The mechanism of cancer-induced cachexia is still poorly understood, highlighting the need for effective treatment. We previously identified major alterations of iron metabolism in the skeletal muscle of tumor-bearing mice and in particular a decrease in mitochondrial iron, resulting in mitochondrial dysfunction. However, the underlying causes of these alterations in muscle iron metabolism remain unknown. Lipocalin 2 (LCN2), an iron-sequestering protein, has been identified as one of the most upregulated genes in various models of skeletal muscle atrophy. Therefore, we investigated the role of LCN2 in skeletal muscle atrophy associated with cancer and chronic glucocorticoid treatment.
Materials and Methods: We analyzed iron metabolism and muscle LCN2 expression both in the cancer-cachexia C26 model and in glucocorticoid-induced atrophy *in vivo.* To gain a better understanding about the role played by LCN2 in skeletal muscle atrophy, we silenced and overexpressed LCN2 in C2C12-derived myotubes and assessed myotubes diameter, atrophy markers, mitochondrial iron, and the expression of iron-related proteins.
Results: We observed a dramatic increase of LCN2 in the skeletal muscle of both C26 tumor-bearing and dexamethasone-treated mice. In *vitro* experiments showed that LCN2 overexpression decreased the diameter of C2C12 myotubes while silencing of LCN2 protected myotubes from dexamethasone-induced atrophy, confirming the implication of LCN2 in the atrophic process. In *vivo*, we found that aminoglutethimide, a drug inhibiting glucocorticoids synthesis, suppressed LCN2 expression in the skeletal muscle of C26 tumor-bearing mice thus suggesting that elevated levels of glucocorticoids are responsible for the upregulation of LCN2 in the C26 model. Additionally, treatment with dexamethasone both *in vitro* and *in vivo* led to a significant decrease in mitochondrial iron levels which mirrored the alterations in iron metabolism observed in the C26 model.
Conclusion: Overall, our findings provide new mechanistic insights in both cancer-induced and glucocorticoid-induced skeletal muscle wasting and support targeting lipocalin 2 as a potential therapeutic option for muscle wasting diseases.

1-09

Exploring the lived experience of cachexia for individuals with end-stage kidney disease and the interrelated experience of their carers

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Introduction: Cachexia is an important consideration in the person-centred care that is needed in end-stage kidney disease (ESKD). However, given that clinical guidelines relating to cachexia in ESKD are largely absent, this is an unmet care need. To inform guidelines and future ESKD service planning, there is an urgent need to understand individuals' experiences of cachexia in ESKD and the interrelated impacts on carers in their lives.
Methods: A purposive sampling strategy is being used to recruit individuals living with ESKD who have cachexia and their carers (n=12) across two nephrology directorates, within two healthcare trusts in the United Kingdom. Interviews are audio-recorded, transcribed verbatim and analysed using interpretative phenomenological analysis. Ethical approval for this study was granted by the Office for Research Ethics Committees Northern Ireland (REC Reference: 22/NI/0107).
Results: Analysis has generated five preliminary themes: reduced appetite; reduced functionality; weight loss interpreted as a bad sign; social impact of cachexia; tension over feeding. Data reflects the multidomain impact of cachexia on patients with ESKD, impacting on biological, psychological and social domains. Furthermore, analysis confirms that the impact of cachexia in ESKD affects not only patients but also their loved ones who care for them in the domiciliary setting.
Conclusion: These preliminary insights are a critical first step in the development of care that both recognises and responds to the needs of this population. The findings of this study will help healthcare providers understand the challenges that individuals with ESKD and their carers face in relation to cachexia and inform future clinical practice guidelines. Further research and supportive interventions which are co-designed to address the multifaceted impact of cachexia in ESKD are urgently required.

1-10

Induction of adipose lipolysis by acidosis-adapted cancer cells to meet their increased fatty acid demands

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Introduction: Cancer cachexia is characterized by an involuntary weight loss which cannot be restored by nutritional support, often due to adipose tissue depletion, and limits both the survival and the anticancer response in patients. Advanced tumors which are associated to cachexia present an altered microenvironment with large hypoxic and/or acidic areas. We know from previous work that acidosis-adapted cancer cells develop a fatty acid-dependent metabolism, the latter further supporting cancer cell invasion and metastases.
As fatty acid consumption by acidosis-adapted cancer cells increases, we reasoned that fatty acids derived from adipose tissue lipolysis could sustain this fatty acid craving leading to the subcutaneous and visceral adipose tissue depletion observed in the context of cancer cachexia. We formulate the hypothesis that acidosis-adapted cancer cells foster this adipose lipolysis by releasing pro-lipolytic soluble factors.

Methods: To evaluate the pro-lipolytic capacities of acidosis-adapted cancer cells, primary mouse adipocytes from subcutaneous and visceral adipose tissues were exposed to conditioned medium from human acidosis-adapted cancer cells (pH6.5), compared to naïve cancer cells (pH 7.4), from pharynx (Fadu), cervix (Siha), and colon (HCT). In parallel, rt-PCR and RNA sequencing were performed to identify pro-lipolytic mediators. Because of the ability of tumors to develop spontaneously an acidosis *in vivo*, Fadu and HCT cancer cells were injected in immunodeficient mice.
Results: Conditioned media from pH 6.5 cells triggered an increase in lipolysis of both subcutaneous and visceral primary adipocytes. Both Fadu and HCT injections *in vivo* support the *ex vivo* phenotype by promoting the subcutaneous and/or visceral adipose tissue weight loss. Known pro-lipolytic mediators were distinctly modulated with acidosis according to the cancer cell type, while RNA sequencing reveals 24 common predicted secreted proteins with a potential role in the induction of lipolysis.
Conclusion: Microenvironmental acidosis promotes the mobilization of fatty acids derived from adipocytes via the release of soluble factors by cancer cells. Some of these factors are currently being examined for their pro-lipolytic potential with the goal to identify attractive candidates for dualistic innovative treatments tackling both cancer progression and cachexia.

1-11

Role of fibroadipogenic progenitors in pancreatic cancer cachexia

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Background: Different signaling pathways are associated with muscle atrophy in cancer cachexia. However, the role of muscle microenvironment, particularly the contribution of specific cell types to overall muscle wasting has not been comprehensively explored. The current study aims to understand the role of fibroadipogenic progenitors (FAPs) in muscle wasting using an experimental model of pancreatic cancer cachexia. FAPs provide trophic signals to muscle stem cells for efficient regeneration during injury. However, when chronic inflammation ensues, as often the case in cachexia, the muscle microenvironment is altered where FAPs may produce pathologic fibrogenic and/or adipogenic progeny, leading to fibrofatty infiltration in muscle- a hallmark of cachexia.
Aim: Investigate (i) if FAPs in muscle are dysregulated, (ii) the role of microRNAs (miRNAs, small non-coding RNAs which modulate gene expression) in FAP dysregulation and (iii) if modulating miRNAs in tumor reduces FAP dysregulation and muscle wasting.
Methods: C57BL/6J mice were orthotopically implanted with 2 million KPCY cells. Control group received sham surgery. Muscle and adipose weights were measured at different time points following surgery (Weeks 2,3 and 4). FAPs were subjected to RNA sequencing and metabolomics. miRNA from tumor and FAPs were profiled using Nanostring.
Results: No significant difference was observed in muscle weights in weeks 2 and 3 between cancer and control. However, several genes implicated in cachexia such as *Il1b, Inhbb, Bmp7* were altered in 2 weeks muscle indicating early molecular changes. *Trim 63, Fbxo32* and *Il6ra* were significantly upregulated in 3 and 4 weeks. Significant difference was observed in muscle weights and gene expression at 4 weeks. RNAseq in FAPs from week 2 identified genes associated with decreased lipid synthesis and inflammation. Fibrosis associated pathways were predominantly present in weeks 3 and 4 potentially indicating a sustained negative effect on FAPs. Metabolomics analysis in FAPs identified downregulation of branched chain amino acids such as leucine, valine, and isoleucine along with other amino acids. 30 and 194 differentially expressed miRNAs were identified in FAPs and tumor, respectively. miR-27a-3p was selected as candidate molecule for further characterization in tumor and FAPs. Downregulation of miR-27a-3p in FAPs led to increased adipogenesis and its upregulation increased proliferation in cancer cells, exhibiting a cell/tissue type specific function of miRNA. Further characterization of miR-27a-3p in tumor and FAPs is ongoing.
Conclusion: The current study opens a new avenue of research in cachexia to understand the role of FAPs dysregulation in muscle wasting through miRNAs.

1-12

Mechanisms of skeletal muscle atrophy in patients with early breast cancer treated with chemotherapy: insights from acute and chronic measurements

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Introduction: Patients with early breast cancer are mainly treated with chemotherapy, which leads to skeletal muscle atrophy. To date, a comprehensive understanding of the underlying cellular processes, through skeletal muscle biopsies, is still needed. Moreover, there is no study investigating the acute effects of a single chemotherapy administration in patients while it would provide important insights on the mechanisms involved in skeletal muscle atrophy. Therefore, this study aimed to investigate both acute and chronic cellular mechanisms triggering skeletal muscle atrophy in breast cancer patients treated with chemotherapy.
Methods: Two separate experimentations were conducted. In study 1, 13 early breast cancer patients treated with chemotherapy were included and muscle biopsies from the vastus lateralis muscle were performed pre- and post-treatment (*i.e.,* after the whole chemotherapy treatment completion, 18 $\pm$ 1 weeks). In study 2, 10 early breast cancer patients were included and muscle biopsies were performed pre- and 4 days after the first chemotherapy administration. Histological and western blotting analyses were conducted.
Results: Four days after the first chemotherapy administration, a decrease in follistatin (-54%; $p<0.05$) protein expression was found, without change in myostatin levels. MuRF1 protein expression was drastically increased acutely (+523%; $p<0.05$) and remained upregulated at the end of the chemotherapy (+129%; $p<0.05$), along with NFκB (+163%; $p<0.05$), an important transcription factor implicated in its transcription process. Interestingly, key markers of the autophagy process were dysregulated four days after the first chemotherapy, as evidenced by a decrease in Atg7 (-72%; $p<0.05$), LC3B-II/I ratio (-50%; $p<0.05$), and no change in p62 marker expression. These results, combined with those obtained after the end of the chemotherapy treatment, demonstrate the fact that the autophagy process was downregulated in patients with breast cancer, which induces skeletal muscle atrophy. We therefore explored the cross-sectional area of the vastus lateralis muscle fibers and found a decrease in type I (-18%; $p<0.05$) as well as in type II (-22%; $p<0.05$) muscle fibers at the end of the chemotherapy treatment.
Conclusions: The skeletal muscle atrophy observed in breast cancer patients treated with chemotherapy is likely explained by an early upregulation of the ubiquitin-proteasome system and a decrease in the autophagy process. These alterations, highlighted as soon as 4 days after the first chemotherapy

administration, emphasize the need to develop countermeasures immediately after the start of chemotherapy to prevent skeletal muscle atrophy.

1-13

Lung tumor derived factors impair myogenic capacity and mitochondrial function of muscle progenitor cells

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Introduction: Cancer cachexia is a multifactorial syndrome, which can affect up to 60% of lung cancer patients. It is characterized by loss of skeletal muscle mass and leads to lower treatment response and reduced quality of life. Previous work has shown myogenesis impairments along with mitochondrial alterations in cachectic muscle. It is unclear whether tumor or host-responses drive these myogenic impairments and mitochondrial alterations. We tested the hypothesis that factors secreted by cachexia-inducing tumors inhibit myogenic fusion and mitochondrial function of muscle cells.
Methods: 344P lung adenocarcinoma cells, which induce lung cancer cachexia and muscle mitochondrial alterations *in vivo* (Van de Worp, 2023), were cultured *in vitro* to produce tumor conditioned medium (tCM). A conditional luciferase cassette reliant on myogenic fusion-dependent Cre-mediated recombination was expressed in a myoblast-myotube (MB-MT) co-culture to quantify myogenic fusion by assessing luminescence in cell lysates. During or prior to myotube fusion, MB-MT co-cultures were left untreated or treated with tCM or control lung epithelial cell-derived conditioned medium (cCM), or medium with a mitochondrial inhibitor (CCCP). In addition to luciferase activity, cells were lysed and mitochondrial DNA (mtDNA) copy number, ATP production and citric synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HAD) activity were assessed.
Results: When treated in the MB-MT co-culture stage, myogenic fusion was strongly reduced by tCM or CCCP exposure. A similar effect was observed when myoblasts were treated with tCM or CCCP prior to fusion. mtDNA copy number and ATP production were reduced in the co-cultures exposed to tCM during fusion as well, despite an increase in HAD and CS activity.
Conclusions: Our data demonstrate that tumor derived factors can cause mitochondrial impairments and can inhibit fusion of muscle cells. Disrupting mitochondrial function inhibits myogenic fusion as well, which could indicate a potential involvement of mitochondrial dysfunction in tumor-induced muscle wasting in cancer cachexia, although a causal role remains to be established.

References:
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1-14

Regulation of pancreatic cancer-induced muscle wasting through the obestatin/GPR39 system

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Background: we investigated whether the obestatin/GPR39 system, an autocrine signaling system acting on myogenesis and with anabolic effects on the skeletal muscle, could protect against pancreatic cancer-driven muscle cachexia and associated morbidity and mortality.
Methods: In this study, we used an *in vivo* model of muscle cachexia induced by orthotopic tumor implantation of pancreatic ductal adenocarcinoma (PDAC). We examined the molecules that define the interplay between the tumor and the skeletal muscle through the obestatin/GPR39 system. The findings were extended to *in vitro* effects on human myotubes co-cultured with PDAC cells (PANC-1 cells).
Results: A pilot study developed by using a co-culture system of human myotubes and PANC-1 cells showed that obestatin signaling decreased the expression of the E3 ubiquitin-ligase atrogenes (MuRF1/MAFbx). The protection against myotube atrophy was associated to the activation of anabolic signaling hallmarks (AKT/mTORC1/S6/4E-BP1) and autophagy flux, whereas NF-KB and iNOS signaling, hallmarks of muscle wasting, were attenuated. Of note, obestatin increased the expression of both slow- and fast-MHC that positively correlated with restoration of myotube phenotype. Simultaneously, obestatin treatment inhibited proliferation in PANC-1 cells. These actions acquire more significance considering the attenuation of preproghrelin expression, and thus obestatin, in human myotubes in the presence of PANC-1 cells. *In vivo*, we established an orthotopic PDAC model to examine the therapeutic efficacy of obestatin. Notably, obestatin treatment mitigated cancer-associated cachexia manifestations, reducing tumor associated skeletal muscle weight loss. In this model, obestatin suppressed the catabolic signaling hallmarks in tibialis anterior muscle, including AMPK, to regulate muscle catabolism via the downregulation of the E3-ubiquitin ligases and activation of autophagy flux.
Conclusions: These results highlight the potential of the obestatin/GPR39 system to fine-tune the effects of PDAC on skeletal muscle wasting.

1-15
Tumor organoid-derived factors from cachectic pancreatic cancer patients induce a pro-inflammatory macrophage phenotype – role of macrophage migration inhibitory factor

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Introduction: Systemic inflammation induced by tumor-derived factors is considered to play a key role in the pathogenesis of cancer cachexia. Macrophages mediate pro-inflammatory immune responses in several metabolic disorders. We

hypothesized that factors released by tumor cells from cachectic patients induce a pro-inflammatory macrophage phenotype, and focused on Macrophage Migration Inhibitory Factor (MIF), whose increased expression in several cancer types correlates with poor patient outcomes.
Methods: Human monocyte-derived macrophages were exposed to conditioned medium (CM) collected from pancreatic tumor organoids from cachectic (n=4) or non-cachectic (n=3) patients, or maintained in control medium. After 24 hours, zymosan-particle phagocytosis assays were performed by live cell imaging, and cytokine expression and secretion were determined by qPCR and ELISA. Mitochondrial respiration was assessed using a Seahorse analyzer. Macrophage morphology was assessed using Cellpose software to obtain shape descriptions and area measurements. Several assays were performed in the presence of ISO-1, a clinically approved MIF inhibitor. MIF concentrations in CM and plasma of 107 pancreatic cancer patients were determined by ELISA.
Results: Macrophage phagocytosis rates were increased after exposure to tumor organoid CM from cachectic vs. non-cachectic individuals (3.1±0.2 vs. 2.4±0.3, p<0.05). IL-6 and MIF secretion were increased after exposure to CM from cachectic vs. non-cachectic individuals (IL-6: 2.75±2.9 vs. 1.69±4.1 ng/ml, p<0.05; MIF: 2.84±0.49 vs. 1.87±0.48 ng/mL, p<0.05). Expression of IL-1alpha, Mcp-1, and TNF-beta followed a similar pattern, but IL-10 was not affected. Average macrophage area was higher after exposure to 'cachectic' CM vs. control (600±12 vs. 450±31 um2, p<0.01) and roundness was reduced (0.65±0.02 vs. 0.72±0.03, p<0.001). Oxygen consumption rates were lower after exposure to CM from cachectic vs. non-cachectic patients (81.7±29.0 vs. 100.8±21.4 pmol/min, p<0.001). Plasma MIF concentrations were higher in cachectic (n=73) vs. non-cachectic (n=34) patients (3.05±0.38 vs. 1.72±0.23 ng/mL, p<0.05) and in 'cachectic' vs. 'non-cachectic' CM (1.48±0.24 vs. 0.30±0.02 ng/mL, p<0.01). However, MIF inhibition during CM exposure did not affect macrophage phagocytosis or cytokine production.
Conclusion: Factors other than MIF released by tumor cells from cachectic patients induce a pro-inflammatory macrophage phenotype.

1-16

Leucine supplementation alters inflammatory gene expression in male, but not female *Apc$^{Min/+}$* cancer cachectic mice.

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Introduction: Cancer cachexia (CC) is a multifactorial wasting syndrome characterized by a significant loss in lean and/or fat mass, and is a leading cause of mortality in cancer patients. CC is often associated with enhanced proteolysis, mediated by pro-inflammatory cytokines. It is established that proinflammatory cytokines (IL-6 and IL-1β) are increased in several models of CC, promoting downstream catabolic functions. Nutraceutical treatments, such as the branched-chain amino acid, leucine, have been proposed as a potential treatment strategy to protect cancer patients against cachexia by targeting inflammation and muscle protein synthesis. However, contradictory findings warrant further investigation. **Purpose:** Examine the effects of leucine supplementation on the skeletal muscle inflammatory response across biological sexes during CC.
Methods: Male and female *Apc$^{Min/+}$* and their wild type (WT) littermates were used in this study. At ~5 weeks old, mice were given tap water (NL) or 1.5% leucine-supplemented water (L), with *ad libitum* food and water access (n=4-10/group/sex). The experimental endpoint for all groups was ~20 weeks of age. Skeletal muscles, fat, and organs were excised and weighed. *Il6*, *Il1b, Tnfa*, and *Nfkb* mRNA abundance in the tibialis anterior muscle was assessed via qPCR. Two-way ANOVAs (leucine supplementation x genotype) were conducted within biological sexes to determine significant main effects and interactions.
Results: The *Apc$^{Min/+}$* group had lower body mass, muscle mass, fat mass, and higher spleen mass in both sexes (p<0.05) compared to WT, confirming a cachectic phenotype independent of leucine supplementation. In males, *Il6* was higher in *Apc$^{Min/+}$* compared with WT independent of leucine supplementation (p<0.05). There was an interaction of genotype and treatment on *Il1b*, where *Il1b* was higher in APCNL compared with WTNL, but lower in APCL compared with APCNL (p<0.05). *Tnfa* was lower in WTL and APCL groups, independent of genotype (p< 0.054). *Nfkb* was not different between groups. In females, *Il6*, *IL1b, Tfna*, and *Nfkb* were all higher in *Apc$^{Min/+}$* compared with WT groups independent of leucine supplementation (p<0.05).
Conclusions: Results of this study demonstrate males appear to have a leucine dependent response on inflammatory gene expression in skeletal muscle, wheras females do not. Based on these differences in leucine supplementation between sexes indicates the existence of a sexual dichotomy. Our results demonstrate there may be a sex dependent response to leucine supplementation in cancer cachexia.

1-17

Using adipose tissue organoids – a new avenue for cancer cachexia research in vitro

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One of the primary pathophysiologies of cancer cachexia is systemic inflammation, which leads to weight loss through the breakdown of skeletal muscle and adipose tissue (AT) and the suppression of hunger. Significant crosstalk between AT and muscle loss suggests a strong interplay between the two. There is a dire medical need for effective treatments for the large number of patients suffering from cancer cachexia, as treatment options are extremely limited. Therefore, it is imperative to develop novel therapies. Traditional two-dimensional cell culture methods are inadequate for studying cancer cachexia due to the lack of interaction between different cell types. Animal models, typically rodents, are currently used for meaningful cachexia research. However, a significant gap exists in translating findings from animal models to clinical studies. In this project, we aim to address this gap by developing and validating 3D organoids of adipose tissue in the laboratory. These organoids will provide a better understanding of the molecular mechanisms involved in AT alterations at different stages of cancer cachexia.

2-01

Neutrophil-derived S100a8/a9 as a mediator of adverse cardiac remodeling in cancer-associated cachexia

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Introduction: Compromised cardiac function resulting from structural and functional remodeling is commonly observed in cancer patients and survivors, leading to a difficult treatment management course, reduced quality of life, and eventual death of approximately 15-20% of patients. While some cancer patients experience cardiac dysfunction as a result of chemotherapeutic agents, numerous studies in chemotherapy-naïve cancer patients revealed signs of cardiac insufficiency,

implicating cachexia as a contributing factor. Cachexia, a wasting syndrome, is commonly observed in cancer patients, leading to cardinal symptoms including anorexia, fatigue, and elevated basal metabolic rate. However, the mechanistic relationship between cachexia and adverse cardiac remodeling is unknown.
Methods: To investigate this question, we used a murine model of pancreatic ductal adenocarcinoma (PDAC) associated cachexia. To generate the model, a pancreatic tumor cell line was orthotopically implanted in the pancreas of WT mice. The cells are derived from tumors in C57BL/6 mice expressing a constitutively active mutant oncogene $KRAS^{G12D}$ and a point mutation in the tumor suppressor gene $P53^{R1172H}$ with expression induced and targeted to the pancreas via Cre recombinase expression under the Pdx-1 promoter. Mediators of cardiac remodeling were assessed at the cellular and molecular level using bulk-RNA sequencing, flow cytometry, and ELISA studies.
Results: Tumor bearing animals demonstrated a gene signature consistent with structural and functional remodeling of the heart and significant elevation in biomarkers of cardiac damage in plasma, including Troponin-I, Galectin-3, and creatine kinase-MB. RNA-sequencing analysis of the heart identified granulocyte-derived S100a8/a9 as a candidate driver of adverse cardiac remodeling. We validated the increase in cardiac S100a8/a9 both at RNA and protein level in various PDAC cells lines, and flow cytometry experiments revealed recruitment of neutrophils to the heart.
Conclusions: Our data identified neutrophils and S100a8/a9 as candidate drivers of adverse cardiac remodeling in cancer-cachexia. Neutrophil activation and NETosis in the heart can lead to release of S100a8/a9 heterodimer, activating inflammatory pathways in the heart and deteriorating cardiac structure and function. Therefore, our observations provide support for neutrophils and S100a8/a9 as potential therapeutic targets of adverse cardiac remodeling in cancer-cachexia patients.

2-02

Mechanistic insights from an integrative analysis of biological sex differences in two colorectal cancer cachexia models

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Introduction: Cancer-Cachexia (CC) is clinically characterized by an involuntary weight loss of >5% within six months. This study aimed to investigate the transcriptomic changes in skeletal muscle (SKM) during CC progression in male and female mice.
Methods: TA samples were collected from two colorectal-CC animal models: eight-week-old BALB/c mice injected with C26-cell allografts or PBS as control (samples collected after 10-, 20-, or 25-days of cancer injection), and 20-week-old $Apc^{Min/+}$mice and their WT-littermates (n=6-8/sex/group/model). Global gene expression analysis was performed, and differentially expressed genes were identified (FDR<0.05).
Results: $Apc^{Min/+}$ groups, both female and male mice, developed severe cachexia after 20-weeks, while C26-male mice experienced moderate body weight loss after 20-days and SKM mass loss after 25-days. In contrast, C26-females-25-days exhibited a mild cachectic phenotype, with preserved body weight and SKM despite exhibiting other hallmarks of CC such as hepatosplenomegaly. At the transcriptomic level, all groups had *Fbxo32* and *Trim63* upregulated (>+2.16-fold, except C26-male-20-days), suggesting protein degradation as a common factor between sexes and models. Additionally, *Map1lc3b, Bnip3, P62,* and ULK-1 and Beclin-1 complexes related genes were upregulated for C26-male-25-days and males and females $Apc^{Min/+}$ (>+1.5-fold), suggesting proteolysis and phagophore formation for mitophagy and autophagy. Moreover, in the same groups, genes related to ETC-complex subunits, pyruvate dehydrogenase (PDH) complex, TCA cycle and feeder pathway enzymes were downregulated (>-2.63-fold), potentially affecting mitochondrial energy production and pathways related to amino acid synthesis and their availability. Male and female $Apc^{Min/+}$ showed dysregulation of carnitine-palmitoyltransferase (CPT) and mitochondrial pyruvate carrier (MPC) genes (>-2.3-fold), suggesting deficiency in the transport of lipid and pyruvate for mitochondrial oxidation. Furthermore, upregulation in genes coding for malonyl-CoA decarboxylase (MCD) and AS160 (>+1.5-fold) was observed after 25-days in both C26 sexes, and in $Apc^{Min/+}$-males, suggesting an increase in fatty acid and carbohydrate oxidation. In contrast, C26-females did not exhibit dysregulation in the mRNA content of ETC subunits and TCA and feeder pathway enzymes.
Conclusion: This study highlights significant metabolic disruptions in SKM during CC with differences observed between sexes. Preservation of mitochondria function may play a crucial role in maintaining SKM, particularly during early time points in female mice, despite an upregulation in mRNA for common markers of muscle wasting. These findings help define underlying mechanisms of muscle wasting during CC and provide valuable insights into potential interventions to preserve SKM in both male and female populations.

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2-03

The dialogue between metastatic cells and the host

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Introduction: Malnutrition and cachexia are major problems of metastatic cancers and lead to depletion of the main energy depots. Importantly, the metabolic plasticity of metastatic cells allows them to adapt under certain nutrient-limiting conditions and to reach different organs; however, how metastatic cells metabolically outcompete with the host physiology to boost their energetic demands, is poorly understood. Our efforts are focused on understanding how metastatic tumors communicate with distant tissues rarely inhabited by metastatic cells, to unveil potentially targetable mechanisms underpinning cachexia, with the overarching goal of blocking metastasis, and improve quality of life of metastatic patients suffering from cachexia.
Methods: Tackling metastasis in the context of wasting requires understanding of i) how metastatic tumors communicate with the body through secreted factors, ii) how metastasis contributes to chronic inflammation, iii) which metabolic changes underneath of these inflammatory-secretory axes are key during tissue wasting in metastatic patients. We systematically tested this hypothesis by using an oral cancer syngeneic mouse model, and evaluate how tumor/metastasis growth correlates with cachexia parameters, including body weight loss, reduction in food intake and peripheral tissue loss. We performed high-throughput metabolomic and transcriptomic analyses in several tissues, tumors and plasma to comprehensively determine a wasting signature.

Results: We identified systemic metabolic alterations in metastatic bearing hosts in the MOC2 syngeneic mouse model. In particular, we defined by multiple omics a 2-stage cachexia process associated with changes in histological parameters of the liver, muscle and fats. This 2-stage cachexia progression leverages the host metabolism in a different way, associated to a more aggressive metastatic behavior when tumor cells were previously exposed to palm-rich diet. We also found potential factors that can be secreted by the metastatic cells in the lung metastasis compartment, and found important candidates that could be inhibited, which are related to increased lipid metabolism and cachexia.
Conclusions: We conclude that enhanced metastatic potential is associated with increased body weight loss and identified two stages of cachexia (early and late-cachexia), with no significant changes in food intake when body weight loss is initiated. Progressive peripheral tissue loss was found in the two stages suggesting either gradual or distinct metabolic changes in both stages of cachexia. Metabolic and transcriptomic analyses of these two stages are key to understand how metastasis influence the host metabolism. Finally, inhibition of secreted pro-cachectic factors by metastatic cells will validate the metastasis-to-the-host axes and prove its anti-metastatic and anti-cachectic therapeutic potential.

2-04

Microbiota-derived secondary bile acids to tackle cancer cachexia

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Introduction: Bile acids can act as powerful signaling molecules and exert diverse actions on host metabolism and immunity. The two main steps involved in the bacterial metabolism of bile acids are the hydrolysis of conjugated bile acids into free bile acids, catalyzed by bile salt hydrolases (BSH), and the 7α-dehydroxylation (7αDH) to generate secondary bile acids. We previously reported alterations in the gut microbiota composition and in bile acid pathways in cancer cachexia. We also showed that the modulation of the bile acid profile could affect cachectic features. Here, we investigated the gut microbiota-bile acid crosstalk in cancer cachexia.
Methods: We compared mice inoculated with cachexia-inducing C26 colon carcinoma cells (C26 mice), non-cachexia-inducing C26 colon carcinoma cells (NC mice), and sham-injected mice (CT mice). We performed hepatic and portal bile acid quantification using HPLC-MS and analysis of the gut microbiota composition using 16S rRNA gene sequencing of CT, C26 and NC mice. We also measured the BSH activity in CT and C26 mice and we estimated the 7αDH activity.
Results: Hepatic bile acid profiling revealed increased levels in conjugated primary bile acids and a four-fold decrease in total secondary bile acids in C26 cachectic mice as compared to CT mice, whereas they were not changed in NC mice compared to CT. We also revealed that the gut dysbiosis found in the C26 cachectic mice, marked by an increase in the *Enterobacteriaceae* family and decreased levels in the *Ruminococcaceae* and *Lachnospiraceae* families, was not observed in NC mice, displaying similar profile to CT mice. No significant difference in microbial BSH activity was found in fecal extracts from C26 mice as compared to CT. Interestingly, the *Lachnospiraceae* family, that has been shown to be able to perform the 7αDH activity, was found to be positively correlated with portal secondary bile acids in C26 mice. In accordance with our hypothesis, the predicted 7αDH activity (based on the secondary/primary bile acid ratio) decreased in the feces of C26 mice as compared to CT mice.
Conclusion: The alterations in bile acid profile and gut microbiota are intrinsically linked with cachexia itself, and cannot only be ascribed to the presence of the tumor in C26 mice. Moreover, our data suggest a major role for the gut microbiota in bile acid alterations. Altogether, this work highlights microbiota-derived secondary bile acids as promising candidates to improve cancer cachexia.

2-05

Cancer induces cachexia by reprogramming the nuclear SUMOylation landscape in striated muscle cells

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Introduction: Cachexia is a complex, debilitating muscle-wasting disorder prevalent in 80% of cancer patients, with mortality in 30% of patients. The molecular mechanisms underlying cancer-induced cachexia (CIC) remain largely unclear. Cells use the SUMO (Small Ubiquitin-like Modifier) machinery to respond rapidly to external challenges, particularly during the stress response. As cancer triggers oxidative stress, we hypothesize that the link between SUMO and CIC might prevail. In this study, we investigated this possibility.
Methods: To induce cachexia **(**CIC), we treated striated muscle cells (mature mouse myotubes and neonatal rat cardiomyocytes) with IFNγ and TNFα. To study the effect of CIC on muscle physiology, we checked calcium transient, muscle cell contraction, and sarcomere organization. By RNAseq, we determined global changes of in gene expression program in muscle cell. We performed quantitative endogenous SUMO proteomics, chromatin immunoprecipitations, epigenetic profiling of muscle-specific genes, confocal microscopy, and gene expression approaches to establish detailed molecular mechanisms in CIC.
Results: Here, we demonstrated that CIC affects muscle cell physiology at different levels. CIC-altered specific gene expression program that ultimately led to sarcomere disorganization, impaired calcium transient process, and severely disrupted muscle cell contraction. Mechanistically, CIC triggered an enhanced level of nuclear-soluble and chromatin-associated SUMO2/3-conjugated proteins. The mass spectrometry analysis revealed a reprogrammed network of increased SUMO-modified nuclear proteins, particularly the non-canonical polycomb repressor protein L3MBTL2 in CIC. Surprisingly, L3MBTL2 positively regulated genes involved in calcium transient and sarcomere organization. In line with this observation, depletion of L3MBTL2 phenocopied CIC. Preliminary observations showed enhanced SUMO modification of L3MBTL2 was associated with compromised active chromatin state of L3MBTL2 target genes particularly *Myosin heavy chain (Myh1)* and *Atp2a1.*
Conclusion: These outcomes revealed an unprecedented connection between SUMO and CIC. The paradoxical SUMO-associated transcriptional role of L3MBTL2 in regulating muscle-specific gene expression was targeted in CIC. Transcriptional activator role of L3MBTL2 is critical for muscle cell function. CIC-triggered higher SUMOylation of L3MBTL2 dampened transcriptional activator function leading to sarcomere organization, calcium transient process and thereby muscle function. This serves as one of the underlying mechanisms of CIC. Restoring balanced SUMOylation levels-particularly of L3MBTL2- in our ongoing experiments in the cancer cachexia models is expected to unravel possible strategies to ameliorate CIC.

2-06

Skeletal muscle microRNAs profile in patients with gastrointestinal cancer

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Introduction: The imbalance between catabolic and anabolic processes is the defining reason for skeletal muscle (SM) atrophy, a key feature of cancer cachexia (CC). microRNAs (miRs) were shown to mediate several signalling pathways associated to muscle wasting. However, their biological roles in CC are still poorly explored. This study aimed at evaluating the expression of muscle-derived miR486-5p and miR15b-5p, which both have been found to have a regulatory effect on inflammatory pathways as well as on modulation of protein synthesis and SM homeostasis, making them attractive as early non-invasive diagnostic tools and potential novel therapeutic targets in CC therapy.
Methods: SM biopsies were obtained from 25 newly diagnosed gastrointestinal (GI) cancer patients (CP) and 10 healthy controls (C), undergoing abdominal surgery for cancer resection or for a non-malignant condition, respectively. Total RNA was extracted from SM specimens and expression levels of miR486-5p and miR15b-5p were analyzed through RT-qPCR.
Results: BMI (Kg/m^2) did not differ in GI CP and C (24.57±4.11 vs 24.41±4.00). In GI CP, the expression of miR486-5p was lower, whereas miR15b-5p was overexpressed with respect to C (0.90±0.49 vs 1.90±1.98, p=0.038 and 1.5±0.49 vs 0.53±0.49, p=0.041, respectively). Both miR486-5p and miR15b-5p expression levels were higher in weight-losing (n=11) than in non-weight losing (n=13) CP (1.10±0.63 vs 0.69±0.25, p=0.042 and 1.84±2.14 vs 0.60±0.43, p=0.053, respectively).
Conclusion: These preliminary data suggest that miR486-5p and miR15b-5p are differentially modulated in the SM of GI CP. Moreover, unintentional weight loss, a main feature of CC, is also associated with changes in the expression patterns of these miRs. Further investigations are mandatory in order to better clarify their role in CC-related SM wasting.

2-07

First-in-patient (Phase 1b) study of the GDF-15 inhibitor ponsegromab in patients with cancer and cachexia: safety, tolerability, and exploratory measures of efficacy

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Introduction: Cachexia is common in patients with advanced cancer and has been associated with elevated serum growth/differentiation factor 15 (GDF-15) concentrations. This first-in-patient (phase 1b) study assessed the use of ponsegromab, a monoclonal antibody against GDF-15, in participants with advanced cancer and cachexia.
Methods: Adult participants (n=10) with cachexia, advanced cancer (non-small cell lung, colorectal, or pancreatic), and elevated serum concentrations of GDF-15 received open-label subcutaneous ponsegromab every three weeks (Q3W) for 12 weeks in addition to standard of care anti-cancer treatment. Study endpoints included assessment of ponsegromab safety, tolerability, and pharmacokinetics. Serum GDF-15 concentrations and exploratory measures of efficacy were also assessed.
Results: No treatment-related adverse events or injection site reactions were reported. No adverse trends in clinical laboratory tests, vital signs, or electrocardiogram parameters attributable to ponsegromab dosing were evident. Ninety-two adverse events deemed unrelated to treatment were reported; most were mild (Grade 1=58.7%) or moderate (Grade 2=28.3%) in severity. All participants were negative for anti-drug antibodies at baseline (n=10) and after receiving 5 doses (Q3W) of ponsegromab (n=9).
Mean unbound ponsegromab Ctrough ranged from 4.041–4383 ng/mL between Days 22–106. An elevated GDF-15 concentration was required for inclusion in the study. Following initiation of study treatment, median unbound GDF-15 concentration was reduced to below the lower limit of quantification (0.0424 ng/mL) on day 1 and remained suppressed until week 15 (3 weeks after final dose).
Increases in body weight were observed at all time points during the treatment (weeks 3, 6, 9, and 12) and follow-up (weeks 15, 18, and 24) periods. The mean (SD) body weight at baseline was 70.49 (16.97) kg. An LS mean (SE) increase of 4.63 kg (1.98) was observed at week 12 (end of treatment); representing an increase of approximately 6.5% relative to baseline. Improvements in actigraphy-based assessments of physical activity and in quality of life, including appetite, as assessed by Functional Assessment of Anorexia-Cachexia Therapy (FAACT) total and subscale scores, were also observed during the course of ponsegromab treatment.
Conclusions: In participants with advanced cancer, cachexia, and elevated baseline GDF-15, ponsegromab was well tolerated and suppressed serum GDF-15 concentrations to below the median concentration seen in healthy populations. Preliminary evidence of efficacy, including a mean observed weight gain of approximately 6.5% at 12 weeks, supports continued development of ponsegromab for the treatment of cancer cachexia.

ClinicalTrials.gov: NCT04299048

2-08

Two phase 3 studies to evaluate the ghrelin receptor agonist anamorelin for malignancy-associated weight loss and anorexia in adults with non-small cell lung cancer (NSCLC): updates to the ongoing SCALA program

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Introduction: Cachexia is a devastating multifactorial syndrome characterized by weight loss and anorexia affecting most patients with advanced cancer. With no standard of care or newly FDA- or EMA-approved drugs, therapy remains an unmet clinical need. Central to this challenge are the lack of agreement on acceptable clinical trial efficacy primary endpoints and the need to revisit predetermined trial endpoints due to ongoing developments within the field.[1] Formerly, regulatory agencies requested drug studies to demonstrate a meaningful change associated with morbidity/mortality, disease biology, and physical function. Consequently, lean body mass (LBM) and physical function measures have been required as suitable co-primary endpoints. However, the relevance of any association between them and of changes in physical function parameters remains theoretical,[2] and phase 3 trials with new agents have not surprisingly failed to meet the functional endpoint.
Anamorelin is an oral selective ghrelin receptor agonist recently approved in Japan for cancer cachexia treatment in NSCLC, gastric, pancreatic, or colorectal cancer. In the phase 3 ROMANA trials, anamorelin demonstrated significant increase in LBM versus placebo without significant effect on handgrip strength (co-primary endpoints). Subsequently, conforming to the anabolic and appetite-stimulating properties of anamorelin, the newer phase 3 SCALA program aimed to evaluate anamorelin superiority versus placebo in weight gain and anorexia. Herein, we report the updated efficacy endpoints of the ongoing SCALA program.
Methods: The SCALA program comprises two international, double-blind, phase 3 studies (NCT03743051/NCT03743064) with identical designs that enrolled adults with advanced NSCLC, weight loss (body mass index <20 kg/m^2, >2% weight loss within prior 6 months), and anorexia (≤17 points on the 5-item anorexia symptoms subscale [5-IASS] and ≤37 points on the 12-item Functional Assessment of Anorexia/Cachexia Therapy anorexia/cachexia subscale [12-FAACT A/CS]). In total, 632 patients received 100mg anamorelin or placebo (1:1) daily for up to 24 weeks. Updated co-primary efficacy endpoints are mean change in weight and 5-IASS from baseline over 12 weeks. Updated secondary efficacy endpoints (measured from baseline over 12 weeks) include: duration of treatment benefit (≥ a predefined threshold of clinical meaningfulness) in weight (≥5%) and anorexia symptoms (≥2 points in 5-IASS) (previous co-primary endpoints); duration of treatment benefit (≥0) in weight and 5-IASS, and mean change in 12-FAACT A/CS and fatigue (FACIT-F) (new endpoints added); FAACT total score (endpoint maintained). Exploratory efficacy endpoints are mostly maintained, and include mean change from baseline in weight, 5-IASS, and FAACT analyzed every 3 weeks, among others. Recruitment is completed.

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2-09

Scalable and privacy-preserving AI can characterize and discover more cachectic cancer patients compared to ICD codes and NLP based approaches

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Introduction: International Classification of Diseases (ICD) codes cannot be used to accurately discover cachectic cancer patients, due to significant miscoding. We present application of novel AI driven product (PIES) that improves on the limitations of ICD or pre-emptive keyword based methods by automatically characterising undiagnosed, misdiagnosed, and miscoded cachectic patients based on the discovery of clinical signatures (which otherwise clinicians have to ascertain through manual review) from electronic patient records (EPRs) in a scalable and privacy-preserving manner.
Methods: PIES uses AI to determine the clinical signature, i.e the key clinical features and their relationships, which characterise cancer patients with cachexia based on both structured and textual data within EPRs. 380 patient records were manually assessed by three clinicians, of which, 145 were used to configure PIES to discover the clinical signature for cachectic cancer patients and the remaining 235 were used as the test set to evaluate its performance.
Results: On the test set, ICD codes correctly discovered only 39 patients with cancer cachexia. In comparison, PIES correctly discovered 146 cachectic cancer patients (90.7% sensitivity) - meaning PIES found 274% more clinically validated cachectic cancer patients compared to ICD codes. These results corroborate those of our previous study, where PIES was applied on a dataset of 29,339 patients and found six times (316) more cachectic cancer patients than ICD codes (51).
Conclusions: PIES automatically discovers clinical signatures to characterise cancer patients with cachexia based on EPRs without external parties moving or touching patient data, which helped clinicians find more undiagnosed, misdiagnosed, and

miscoded patients in a privacy preserving manner. NHS Lothian will apply PIES to 8,000 lung and pancreatic cancer patients with a view to use PIES as part of the clinical care pathway and to help find more suitable patients for screening for new clinical trials and therapies. Additionally, PIES allows the clinical signature to evolve automatically, which helps clinicians address data heterogeneity and scale across multiple healthcare providers. PIES's ability to uncover novel insights through these clinical signatures across different hard-to-diagnose diseases will further facilitate research and drug development.

2-10

Correlation of preoperative body composition with postoperative complications and 30-day-mortality in 255 patients in resectable pancreatic cancer

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Introduction: This study aimed to demonstrate the association between body composition parameters and postoperative complications including 30-day-mortality in patients with pancreatic cancer who underwent surgical therapy.
Methods: A total of 255 patients with pancreatic cancer who underwent surgery between 2007 and 2021 were included in the retrospective data analysis. For the corresponding question, the body composition of these patients was determined by analysis of CT images, which were taken up to 4 weeks before surgery, using the sliceOmatic software. The parameters were skeletal muscle, intermuscular adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue at the level of the 3rd lumbar vertebra, standardized by body height resulting in SMI and FMI. Additionally examined variables included ASA score, unintentional weight loss within the last 6 months, BMI, as well as incidence and Clavien-Dindo classification of surgical complications and mortality within 30 postoperative days.
Results: SMI and FMI were determined in 255 patients with a mean value of 45.0 cm^2/m^2 (± 8.2 cm^2/m^2) and 102.6 cm^2/m^2 (± 50.1 cm^2/m^2) respectively.
133 patients had a low SMI (≤ 38.5 cm^2/m^2 for women and ≤ 52.4 cm^2/m^2 for men). 69.9% of patients with a low SMI had postoperative complications (Clavien-Dindo 1-5) and the 30-day mortality was 2.3%.
In addition, BMI was determined in all patients, with a mean value of 24.6 kg/m^2 (± 3.8).
8,6% had a BMI of < 20 kg/m^2 in this regard. Among this group of patients, 72.7% had postoperative complications (Clavien-Dindo 1-5) and 4.5% died within the first 30 postoperative days.
Unintentional weight loss of more than 5 kg within the last 6 months preoperatively occurred in 31 of 255 documented patients. In those patients, postoperative complications could be found in 80.6% (Clavien-Dindo 1-5) and the 30-day mortality rate was 6.5%.
In contrast, postoperative complications (Clavien-Dindo 1-5) occurred in only 67.9% of patients without this unintentional weight loss. In this group, 30-day mortality was 1.3%
Conclusions: Changes of body composition and cachexia influence postoperative outcomes and should be considered in the management of pancreatic cancer patients. Regardless of the quality of the surgery, which is measured by the postoperative complications, the postoperative mortality rate remains relatively high. This can be explained by the patient's pre-operative poor general and nutritional condition. Therefore, it would be recommended to apply the concept of pre-habilitation in such patients.

2-11

Body Composition Endpoints in Cancer Cachexia Clinical Trials: A Systematic Review from the Cachexia Endpoints Series

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Introduction: Significant variation exists in the chosen outcomes utilised by cachexia trials. Heterogeneity within the literature is likely to adversely impact the development and approval of targeted therapies. The aim of this review is to summarise the endpoints, related to body composition, that have been utilised in cancer cachexia trials.
Methods: A systematic search of MEDLINE, EMBASE and Cochrane Library databases was conducted to identify prospective clinical trials, published between January 1990 and June 2021, which considered interventions aimed at attenuating the effects of cancer cachexia. Inclusion was irrespective of the modality of intervention (e.g., pharmacological, nutritional, physical exercise, behavioural) or comparator. The present study is one of six systematic reviews on outcomes used in cachexia trials, and will focus on radiological, bio-electrical and anthropometric endpoints pertaining to body composition.
Results: A total of 83 clinical trials, comprising 13,048 patients, were eligible for inclusion. While numerous primary tumour sites were considered, non-small cell lung and pancreatic cancer were the most frequently studied. The majority of trial interventions (52%) were pharmacological or nutritional (34%) in nature. The most frequently reported anthropometric endpoint was body weight (69 trials, n=11,915) and over one third of trials (n=26) noted differences between groups using this endpoint. Bio-impedance analysis (BIA) was the most commonly utilised radiological modality for body composition (23 trials, n=3198). Only six studies (27%) identified a significant difference between trial groups using BIA-based measures. Sixteen trials (n=3052) considered dual-energy x-ray absorptiometry (DEXA) based endpoints with significant differences between groups found in over half of these (56%). Computed tomography (CT) body composition was considered by seven trials, with a move towards this modality in more recent years. However, none of these trials detected any significant between-group differences using CT based estimates of body composition.
Conclusions: This systematic review has described the most frequently utilised body composition outcome measures in cancer cachexia clinical trials. While it is difficult to comment on the optimal endpoint for body composition, based on the heterogeneity within the existing literature, we describe several considerations to aid the design of future cachexia trials.

2-12
Oncological Endpoints in Cancer Cachexia Clinical Trials: Systematic Review of Cachexia Endpoints

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Introduction: Cachexia affects outcomes for patients receiving anti-cancer treatment. These include reduced response rates to anticancer treatment, decreased survival and an increased incidence of adverse events.
To further understand the impact of cachexia on oncology outcomes, we aimed to identify which oncology endpoints have been reported in cachexia clinical trials.
Methodology: This systematic review was conducted according to the PRISMA statement and registered on the PROSPERO database. Six study groups collaborated to combine one search, creating one common data extraction table.
Ovid MEDLINE, EMBASE and Cochrane were searched for longitudinal studies and clinical trials. A hand search for additional relevant articles from references of key articles was conducted. Articles were eligible if they were: controlled trials aiming to treat/attenuate cachexia in adult patients with cancer, reported outcomes at >1 time point, published in full text from 1990 and were written in English. There were no restrictions on the type of intervention.
Primary outcomes investigated in this review were measures of oncological outcomes in cancer cachexia. These included: assessments of overall survival, progression free survival, response rate, completion of treatment and toxicity/adverse events.
Results: We identified 55 papers for further analysis. A further 101 papers met the manuscript criteria above, but did not include an oncology endpoint.
The commonest reported outcome was overall survival, reported in 85% of trials (see Table 1). Only 1 trial was positive. Toxicity/adverse events were reported in 21 trials (38%).
Twenty five (45%) of the studies were performed in a single tumour site: 8 in lung cancer, 6 in pancreatic cancer, 5 in Head and Neck cancers and 5 in GI cancers. The remaining 55% were basket studies. Forty-one studies (75%) were performed in stage 3-4 patients. Most studies (36/41, 65%) included patients receiving palliative anti-cancer drug treatment. Ten studies (18%) involved curative treatment and 4 studies (7%) included curative and palliative treatment.
The commonest interventions were pharmacological (47%) or nutritional (45%).

Endpoint	Primary or secondary outcome	Number of studies	Number of patients	Number of positive studies	Number of patients in positive studies
Overall survival	Primary	4	938	0	0
	Secondary	43	7367	1	54
Progression free survival	Secondary	5	644	0	0
Response rate	Secondary	8	1039	1	243
Completion of treatment	Secondary	4	891	2	421
Toxicity/adverse events	Primary	3	261	1	90
	Secondary	18	3121	3	473

Table 1: Oncology Endpoints reported in systematic review of oncology cachexia clinical trials.

Conclusion: Oncology endpoints are principally included as secondary endpoints. These studies are heterogeneous for cancer type and treatment received. This may be the reason for the majority of studies reporting negative oncology endpoints.
The choice of appropriate oncology endpoints are likely to depend on the setting of the clinical trial, including: type of cancer, whether patients are receiving curative or palliative treatment, the type of oncology intervention, the type of cachexia intervention and the likely prognosis of the patient population being investigated.

2-13

Biomarkers in cancer cachexia clinical trials: systematic review of the cachexia endpoints series

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Introduction: Over the course of the last decade systemic inflammation has moved towards central stage in the definition and diagnosis of cancer cachexia. While the basis of the systemic inflammatory response (SIR) in cancer patients is not fully understood, its prognostic ability is unquestioned. As a result, it is necessary for biomarkers including markers of the SIR to be incorporated into future endpoints for any cancer cachexia trials.
Methods: This systematic review is part of a series which examines multiples endpoints in cancer cachexia clinical trials and specifically addresses measures of SIR. The extensive literature review was carried out in the MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases. Clinical trials conducted between January 1990 to June 2021 that assessed SIR as a study endpoint were eligible.
Results: There were 56 controlled trials identified for inclusion with data from 6,488 patients. Interventions varied from pharmacological (n=23), multimodal (n=17) and nutritional (n=16). Most trials (n=28) included people with varied primary cancer sites, followed by trials specific to gastrointestinal (n=9), lung (n=8) and pancreatic cancers (n=4). Studies were conducted across the globe with multinational trials (n=8) most frequently reported, followed by trials based in the USA (n=7) and the UK (n=4) . The most frequently reported endpoint for SIR in cancer cachexia trials was albumin (n=32 trials) containing data on 2,969 patients. Out of these, about 40% noted significant results.
Conclusion: Work to date suggests albumin is the most used measure of SIR in cancer cachexia clinical trials.

2-14

The relationship between appetite and lean body mass as endpoints in cancer cachexia interventional clinical trials. A systematic review.

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Introduction: There are currently no approved therapeutics for cancer cachexia. Co-primary endpoints, assessing endpoints such as physical function and/or nutrition in addition to body composition endpoints, have been requested in cancer cachexia clinical trials. Failure of therapeutic regulatory approval has recently been due to inadequate improvement in function co-primary endpoints. It has been suggested this may be due to a non-linear relationship between physical function and lean body mass (LBM). This review aims to determine the relationship LBM and appetite. To understand if a linear relationship exists, and to determine the acceptability of utilising LBM and appetite as body composition and nutrition co-primary endpoints in cachexia clinical trials. This will aid the research regarding optimum endpoints in cancer cachexia clinical trials.
Methods: Relevant studies published between 1990-June 2021 were retrieved through an extensive literature search of electronic databases Medline, Embase and Cochrane. Eligible studies had sample sizes > 40, participants >18 years old with cancer cachexia interventions of ≥ 14 days. Included studies were required to measure appetite and LBM as endpoints. Records were reviewed by two independent reviewers and PRISMA guidance was followed.
Results: 5976 studies were identified from the literature search of which 14 were eligible to be included. Studies varied in intervention type (11 pharmacological, 3 multimodal), intervention time (2-26 weeks), mean baseline appetite (mean 4.7 ± 1.83), mean baseline LBM (40.2 ± 8.53kg), methods of recording appetite (VAS, NRS, EORTC QLQ-C30, QoL-ACD) and methods of recording LBM (DEXA, BIA, CT).
7 studies provided appropriate mean appetite change data, which was able to be correlated with mean LBM change. Peasons correlation between mean appetite change and mean LBM change was 0.539 (p=0.212). Controlling for numerical co-variables (baseline appetite, baseline LBM and intervention time) a partial correlation of 0.968 (p=0.032) was observed.
Conclusion: Inadequate evidence was available to conclude a valid correlation between appetite and LBM within cancer cachexia clinical trials. Further research is required to enhance findings.

2-15

The impact of acute systemic inflammation and the metabolic response to surgery on computed tomography body composition analyses

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Aim: Body composition has been used extensively for prognostication across malignant and benign diseases. Systemic inflammation is both a key driver of cancer cachexia and a common finding in patients presenting with acute pathology. However, its influence on body composition is poorly understood. This study aimed to longitudinally assess computed tomography (CT) body composition, in patients who experienced an anastomotic leak post-oesophagectomy, as a model of acute, severe systemic inflammation.
Methods: Consecutive patients who suffered an anastomotic leak, following oesophagectomy, between 01/01/2012 and 01/01/2022 were identified from a prospectively maintained database. Changes in body composition were assessed across staging, pre-operative, post-complication and follow-up scans at the L3 vertebral level.
Results: Twenty patients (median 65 years, 90% male) were included. Of these, fifteen underwent neoadjuvant chemo(radio)therapy. Body composition was not altered by neoadjuvant treatment. Following surgery and anastomotic leak, a decrease in skeletal muscle volume (mean difference: -68.06cm3, p=0.028) was noted. Estimates of intramuscular and

subcutaneous adipose tissue conversely increased (p=0.038 and p=0.039 respectively). Skeletal muscle density fell while adipose densities were higher following anastomotic leak. Although tissue radiodensity and subcutaneous fat volumes normalised on follow-up CT scans, skeletal muscle volume remained below pre-treatment levels.
Conclusion: Acute systemic inflammation has a marked effect on body composition analyses. Decreased muscle volume and increased volumes of adipose tissue were evident following the inflammatory insult. Radiodensity across muscle and adipose tissues trended towards that of water, likely secondary to oedema. Research utilising body composition variables should be interpreted with consideration of the potential of influence of underlying inflammatory status.

2-16

An International Survey on Nutritional Issues in Patients with Cancer: Preliminary Results

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Introduction: Nutritional disorders are common in patients with cancer and can lead to poor quality of life and survival. By the present international survey, we aimed at assessing the patients' perspectives on different nutritional aspects during cancer journey
Methods: This survey was developed by Das Lebenshaus with The European Cancer Patient Coalition (ECPC) and The European Nutrition for Health Alliance (ENHA), and designed and analyzed by researchers from Sapienza University of Rome. The majority of the participants were from Germany, Italy, United Kingdom and Hungary. The survey consisted of 46 questions on different nutritional issues. For this analysis, we considered the most relevant questions related to nutritional alterations
Results: The survey reached 1010 patients with cancer. The mean age of the participants was 55 ± 14 y. Based on the answers available, the most represented cancer type was breast (28%) and renal (16%); a recent diagnosis of cancer was performed in 35%, whereas 27% were diagnosed more than 8 years before. About 40% of the participants reported eating problems, such as loss of appetite (116/252) (46%), nausea (119/252) (47%), diarrhea (114/252) (45%). Regarding quality of life, patients answering on impact of nutritional problems reported a score of 3.5 ± 1.1 (from 1= no impact, to 5 = extremely negative impact). 441/672 (66%) reported that "rarely or never a physician or a member of the cancer care team asked about any feeding problems", and 483/670 (72%) believe that "oncology team do not take care of nutritional issues". 176/643 (27%) of the participants reported unvoluntary body weight loss and 138 out of 153 (90%) presented no awareness about the risk of not receiving anticancer treatment for this reason
Conclusions: Patients with cancer largely experienced nutritional alterations with a negative impact on quality of life. Well-structured health-care programs for nutritional intervention are needed.

2-17

Non-steroidal anti-inflammatory drugs for treatment of cancer cachexia: a systematic review

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Introduction: The objective of this review was to assess the efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) on patient-centred outcomes in patients with cancer cachexia (CC). This review is needed, as two systematic reviews on this topic, published in 2013, concluded there was not sufficient evidence to recommend the use of NSAIDs for clinical management of CC outside of clinical trials. However, recent clinical trials of multimodal CC interventions have included NSAIDs as an intervention component, so an up-to-date assessment of the evidence for NSAIDs in the treatment of CC is warranted.
Methods: Four databases (MEDLINE, EMBASE, CENTRAL, CINAHL) and three trial registers (clinicaltrials.gov, WHO ICTRP, ISRCTN) were searched on 16/12/2022. Randomised Controlled Trials (RCTs) comparing any NSAID (any dose or duration) with a control arm, in adult patients with CC, reporting measures of body weight, body composition, nutrition impact symptoms, inflammation, performance status or fatigue, were eligible for inclusion. Outcome classification was determined through patient involvement activities; primary outcomes were survival, changes in muscle strength, body composition, body weight, and quality of life. Included studies were assessed for risk of bias using the Revised Cochrane risk-of-bias tool for randomized trials.
Results: Five studies were included, which investigated Indomethacin (n=1), Ibuprofen (n=1) and Celecoxib (n=3). Risk of bias was high; four studies were judged to be at high risk for all outcomes, and one study was at high risk for some outcomes and raised concerns for all others. Considerable clinical and methodological heterogeneity amongst the studies meant that meta-analysis was not appropriate. There was insufficient evidence to determine whether Indomethacin or Ibuprofen are effective or safe for use in patients with CC; RCTs with lower risk of bias are needed. Results from Celecoxib studies indicated it was safe for use in this population at the doses tested (200-400mg/day), but found contrasting results regarding efficacy, potentially reflecting heterogeneity amongst the studies.
Conclusions: At present, there is inadequate evidence to recommend any NSAID for clinical practice in the management of CC. Whilst current clinical studies in the field of treating CC are shifting towards multimodal interventions, further research to determine the efficacy and safety of NSAIDs alone is necessary if they are to be included in such multimodal interventions. Furthermore, the lack of data on patient-determined primary outcomes in this review highlights the need for patient and public involvement in clinical trials for CC.

2-18

The mortality burden of cachexia in patients with non-small cell lung cancer: A meta-analysis

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Introduction: Cachexia and weight loss [WL] have been linked to poor outcomes in patients with cancer. This study's aim was to conduct a meta-analysis to estimate the mortality risk associated with cachexia in patients with non-small cell lung cancer (NSCLC) in studies identified through a systematic literature review (SLR).
Methods: Following a feasibility assessment, a meta-analysis evaluating cancer cachexia's impact (per International Consensus criteria [ICC] or previous WL ≥5% [without specifying a 6-month duration]) on overall survival (OS) in patients with NSCLC was conducted. The impact of heterogeneity was evaluated through sensitivity and subgroup analyses. Standard measures of statistical heterogeneity were calculated for each meta-analysis. We evaluated clinical heterogeneity by assessing variation in study characteristics, patient populations, and outcome definition.
Results: Of the 40 NSCLC publications identified in the SLR, 20 (50%) used the ICC definition or reported WL ≥5%. Sixteen studies (80%, n=6,225 patients, published 2016-2021) met the criteria for inclusion in the meta-analysis: 11 (69%) studies per ICC and 5 (31%) studies per WL ≥5%. Combined criteria (ICC or WL ≥5%) were associated with 82% higher mortality risk versus no cachexia or WL <5% (pooled hazard ratio [95% CI]: 1.82 [1.47, 2.25]). A subgroup analysis of studies using the ICC definition (hazard ratio [95% CI]: 2.26 [1.80, 2.83]) or WL ≥5% (hazard ratio [95% CI]: 1.28 [1.12, 1.46]) showed consistent findings. Although statistical heterogeneity (I-square=88%) was high across studies, a meta-influence analysis did not identify any potential outliers. Additionally, the results of sensitivity and subgroup analyses were consistent with the base-case analysis. Cumulative meta-analyses by publication year or data collection midpoint identified no time-varying effect, indicating results were robust to the differing timeframes of publication or data collection. No substantial publication bias, measured via funnel plot analysis, was identified in the meta-analysis.
Conclusions: ICC-defined cachexia or WL ≥5% were associated with inferior OS in patients with NSCLC. Identifying cachexia or WL ≥5% for patients with NSCLC has important implications for prognosis, treatment, and participant selection for interventional cachexia trials.

2-19

The role of body composition and pulmonary function in predicting survival after surgery for resectable lung cancer

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Introduction: TNM-classification is widely used to stage patients with non-small cell lung cancer (NSCLC) and is the major determinant of appropriate treatment and prognosis. Host factors such as body composition and pulmonary function are barely considered in predicting long term outcome for these patients. The goal of this study was to assess body composition and pulmonary function as predictors of overall survival in patients undergoing surgery for NSCLC. The second objective of this study was to assess the association of body composition with pulmonary function.
Methods: A prospective cohort of NSCLC patients undergoing surgical resection was used. Abdominal CT-scans were analyzed at the L3-vertebra level. Skeletal muscle (SM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) mass and radiation attenuation (RA) were assessed. Pulmonary function was defined as the forced expiratory volume in one second (FEV1). SM, VAT and SAT were corrected for sex and age by calculating Z-scores. Multivariable cox-regression analysis was used for survival analysis. Multivariate linear regression was used to assess the association between body composition and FEV1.
Results: 475 NSCLC patients had an abdominal CT-scan suitable for body composition analysis. The majority of patients underwent lobectomy (82%), followed by pneumonectomy (7%), bilobectomy (6%), and wedge resection (5%) one patient underwent segmentectomy. Overall mean survival was 59 months. Old age (HR 1.042, 95% CI 1.027-1.058), ASA III-classification (HR 2.152, 95% CI 1.170-3.960), and high SAT-RA (HR 1.155, 95% CI 1.031-1.294) were associated with shorter overall survival in multivariable analysis. High FEV1 (HR 0.987 95% CI 0.981-0.993) was associated with longer survival. Both ASA-III classification (B=-9.562, 95% CI -17.648 - -1.476, P=0.021) and SM-RA (B=2.197, 95% CI 0.232 – 4.161, P=0.028) were associated with FEV1 in multivariable linear regression analysis.
Conclusion: Both SAT-RA and FEV1 are strongly associated with overall survival in surgically treated NSCLC patients. SM-RA is significantly associated with FEV1. These are readily available parameters in the standard work-up of NSCLC patients and could play a role in decision making and possible enhanced prehabilitation.

2-20

Prospective Characterisation of Cancer Cachexia in Patients with Advanced Cancer

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Introduction: Cancer cachexia is a complex metabolic syndrome, with a multifactorial aetiology and widespread clinical effects. To date, there has been little work examining the different clinical phenotypes within the cachexia syndrome, or the interactions between tumour, systemic inflammation and clinical phenotype. Robust characterisation is required to direct future research, provide meaningful trial endpoints and improve patient care.
Methods: Patients with a diagnosis of incurable cancer were recruited from outpatient oncology, palliative care and hospice settings in Edinburgh, UK and enrolled in the Revolution Study, a prospective observational study aiming to characterise people with incurable cancer across five cachexia phenotypic areas. 1) *Body composition* was assessed using weight, BMI and CT-assessed sarcopenia, 2) *physical activity* was examined using physical activity monitors and Karnofsky performance status, 3) *symptoms* were examined using validated questionnaires (functional assessment of anorexia/cachexia therapy scale, Patient Generated Subjective Global Assessment–Short Form, Hospital Anxiety and Depression Scale (HADS) and Eating Assessment Tool– 10), 4) *quality of life* was assessed using the European Organisation for the Research and Treatment of Cancer–Quality of Life Questionnaire–C30, and 5) *systemic inflammation* was examined through analysis of blood samples for markers of the inflammatory response including white cell count, C-reactive protein, lactate dehydrogenase and albumin.
Results: We present the results for the first 90 patients recruited, with longitudinal data for 12 week follow up period available for a subset of patients (n=28). We compared demographic, pathologic and treatment data to clinical and biological phenotypic data and assessed for key differences between weight-losing, weight stable and sarcopenic patient groups. Modified Glasgow Prognostic Score (mGPS) was correlated with survival data.
Conclusion: There is a need for robust characterisation of people with incurable cancer, to understand underlying clinical phenotypes and guide future research. We present initial data from a prospective characterisation study which can be used to better understand the 'symptom phenotypes' within the cachexia syndrome and correlate these with systemic inflammatory and body composition profiles.

2-22

Assessment of lipolysis biomarkers in subcutaneous adipose tissue of gastrointestinal cancer patients

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Introduction: Lipolysis was shown to be involved in adipose tissue loss during cachexia. However, these mechanisms are not completely clarified in patients with cancer. We assessed the expression levels of lipolysis-associated genes in subcutaneous adipose tissue (SAT) of newly diagnosed gastrointestinal (GI) cancer patients according to the presence/absence of cachexia.
Methods: We considered patients with GI cancer at their first diagnosis and controls undergoing surgery for tumor resection and for benign diseases, respectively. Cachexia was defined as involuntary body weight loss > 5% in the prior 6 months. We collected SAT samples during the first phases of surgery. RNA was extracted from SAT and expression levels of ATGL, HSL, PPARα and MCP1 were analyzed by qRT-PCR.
Results: We enrolled 24 cancer patients (pancreatic, gastric and colorectal) and 15 controls. Cancer patients did not differ from controls in terms of BMI. We found significant upregulation of ATGL and HSL in GI cancer patients with respect to controls (p=0.008, p= 0.006). We observed a trend of increased mRNA levels of PPARα (p=0.055) in GI cancer patients compared to controls, whereas no significant difference was observed in MCP1 levels. Comparing to controls, we found an upregulation of ATGL in GI cancer patients with cachexia (p< 0.05), and also in the group without cachexia (p=0.02). HSL levels resulted upregulated in GI cancer patients with cachexia (p= 0.02), without cachexia (p= 0.02), compared to controls. We found an upregulation of ATGL in gastric patients compared to controls (p=0.01) and higher HSL levels in gastric cancer and in pancreatic cancer compared to controls (p< 0.04).
Conclusions: In our cohort of gastrointestinal cancer patients, we found a modulation in the expression of genes of lipolysis and significant differences in their levels according to cancer type.

2-23

Effect of malnutrition risk on the association between skeletal muscle index and health-related quality of life and survival in upper gastrointestinal cancer

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Introduction: Low skeletal muscle index (SMI) is an established prognostic indicator in cancer[1], and may also be associated with poor health-related quality of life (HRQOL)[2]. Presence or risk of malnutrition is also associated with poor survival and HRQOL outcomes[3,4], yet this confounding factor is rarely accounted for in studies investigating the consequences of low SMI. Malnutrition is prevalent in upper gastrointestinal (GI) cancer[5], therefore this study examined the effect of malnutrition risk on the association between SMI at diagnosis of upper GI cancer, and both HRQOL at diagnosis and survival over the following year.
Methods: A prospective study was conducted using data from participants enrolled in a randomised controlled trial at diagnosis of oesophageal, gastric or pancreatic cancer[6]. Baseline data included: SMI from diagnostic computed tomography imaging, malnutrition risk (PG-SGA Short Form, PG-SGA$_{SF}$[7]), and HRQOL (EORTC-QLQ C30)[8]. Low SMI was identified using sex-specific thresholds[9]. The correlation between SMI and PG-SGA$_{SF}$ scores was examined, and multiple linear regression was used to identify contributors to variation in HRQOL at baseline. Predictors of mortality within 12 months of diagnosis were investigated using Cox proportional hazards regression.
Results: The study included 105 treatment-naive patients with oesophageal (43%), gastric (20%), or pancreatic (37%) cancers. The cohort was 68% male, mean age 65.9 (SD±10.0) years. 56% of patients had low SM1, and 49% were at high risk

of malnutrition (PG-SGA_{SF} score ≥9)[10]. SMI was weakly, negatively correlated with PG-SGA_{SF} score (r=-0.268, p=0.006), and some HRQOL domains (physical and role functioning, summary score[11], all p<0.05). When adjusted for PG-SGA_{SF} score, SMI was not significantly associated with any measure of HRQOL at baseline. Higher PG-SGA_{SF} scores were independently associated with lower HRQOL across all scales. Advanced (unresectable) disease at diagnosis was independently associated with 12-month mortality (HR 2.643, 95% CI 1.041-6.711, p=0.041), adjusting for baseline $PGSGA_{SF}$ score and cancer type; baseline SMI was not prognostic. In a subgroup analysis of those with resectable/borderline resectable disease (n=52), high PG-SGA_{SF} score (≥9) at diagnosis was the only variable associated with 12-month mortality (HR 4.539, 95% CI 1.012-20.352, p=0.048).

Conclusions: Malnutrition risk measured by the PG-SGA_{SF} was a stronger predictor of poorer HRQOL and survival than SMI, and should be included as a covariate in future studies investigating the effect of low SMI on these outcomes in people with cancer.

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2-24

Adipose tissue radiation attenuation is an independent predictor of chemotherapy toxicity and shorter overall survival in metastatic colorectal cancer patients

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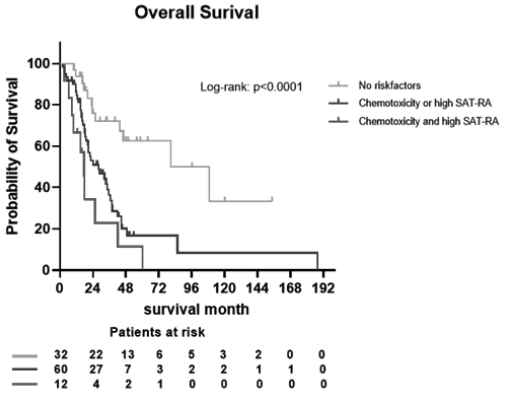
Introduction: Skeletal muscle mass and radiodensity have been shown to be associated with chemotherapy toxicity and survival of cancer patients. However, little is known about the clinical significance of adipose tissue radiodensity, which has been hypothesized to be associated with tissue inflammation and insulin resistance. We investigated the association between adipose tissue radiodensity, chemotherapy toxicity, and survival in patients with metastatic colorectal cancer (mCRC).

Methods: 104 patients of a prospective cohort of mCRC patients treated with standard first-line chemotherapy were included into this study. Using diagnostic abdominal CT scans, we assessed height adjusted area and radiation attenuation (RA) of skeletal muscle (SM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) at the third lumbar vertebra. Associations between these body composition parameters and overall survival as well as chemotherapy toxicity (CTCAE v4.03) were evaluated using univariable and multivariable logistic and cox regression analysis, respectively. Body composition variables were corrected for covariates including age, sex, nutritional support, and chemotherapy regimen.

Results: Forty-four patients (42.3%) developed grade 3-4 toxicity. Pre-treatment VAT-RA was independently associated with grade 3-4 toxicities (OR=0.912, 95%CI 0.843-0.987, p=0.022). Chemotherapy regimen and nutritional support were not associated with chemotoxicity. SAT-RA and chemotoxicity grade 3-4 were associated with shorter overall survival (HR=1.044, 95%CI 1.016-1.072, p=0.002 and HR=2.334, 95%CI 1.337-4.074, p=0.003, respectively). When stratifying patients for SAT-RA and chemotoxicity grade 3-4, patients with low SAT-RA and no chemotoxicity grade 3-4 had a significantly longer overall survival compared with patients with either high SAT-RA or chemotoxicity grade 3-4 or both (109.0 months compared with 28.2 months and 17.7 months, respectively, log rank p<0.001).

Conclusion: High SAT-RA and chemotoxicity are associated with shorter overall survival of patients with metastatic colorectal cancer. Low VAT-RA is an independent risk factor for grade 3-4 chemotoxicity. Body composition is an important risk factor for the occurrence of chemotoxicity in patients receiving chemotherapy and should be investigated in future chemotherapy studies.



2-25

The Prognostic Impact of Pre-Treatment Cachexia in Resectional Surgery for Oesophagogastric Cancer: A Systematic Review, Meta-Analysis & Meta-Regression

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Background: Cancer cachexia is not purely an end-stage phenomenon and can even influence the outcomes of patients with potentially curable disease. This review examines the effect of pre-treatment cachexia on overall survival, in patients undergoing surgical resection of an oesophagogastric cancer.
Methods: A systematic literature search of MEDLINE, EMBASE and Cochrane Library databases was conducted, from January 2000 to May 2022, to identify studies reporting the influence of cachexia on patients undergoing an oesophagogastric resection for cancer with curative intent. Meta-analyses of the primary (overall survival) and secondary (disease-free survival and postoperative mortality) outcomes were performed using random-effects modelling. Meta-regression was used to examine disease stage as a potential confounder.
Results: Ten non-randomised studies, comprising 7186 patients, were eligible for inclusion. The prevalence of pre-treatment cachexia was 35% (95% CI: 24-47%). Pooled adjusted hazard ratios showed that cachexia is adversely associated with overall survival (HR 1.46, 95% CI: 1.31-1.60, p<0.001). Meta-analysis of proportions identified decreased overall survival at 1-, 3- and 5-years in cachectic cohorts. Pre-treatment cachexia was not a predictor of disease-free survival and further data are required to establish its influence on postoperative mortality. The proportion of patients with stage III/IV disease was a significant moderator of between-study heterogeneity (p=0.027). Cachexia may have a greater influence on overall survival in studies where more patients have a locally advanced malignancy.
Conclusion: Pre-treatment cachexia adversely influences overall survival following resection of an oesophagogastric malignancy. Consideration of cachexia, during the shared decision-making process, may improve risk-stratification and facilitate targeted interventions.

2-26

Progressive loss of bone density in patients with esophageal cancer

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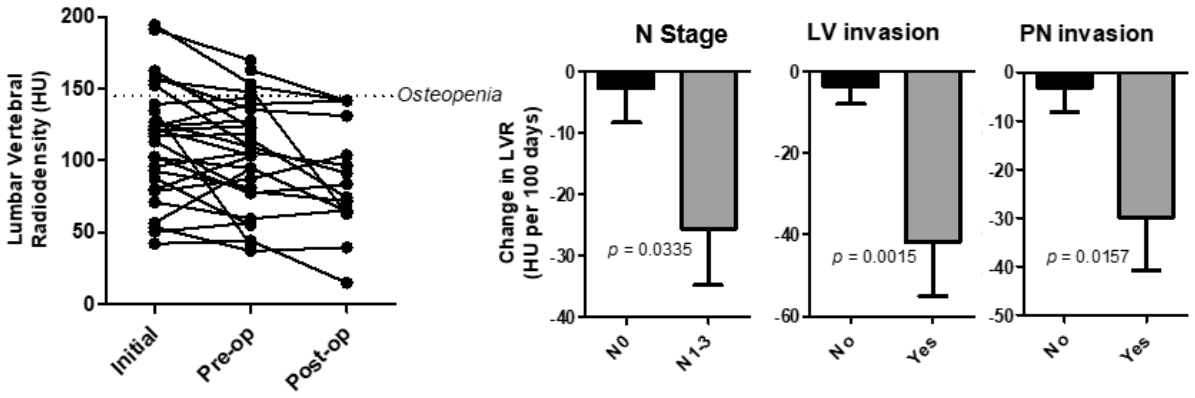
Background: Changes in body composition are common in esophageal cancer (EC). More than 60% of patients, regardless of stage, display signs of cachexia, including weight loss, skeletal muscle atrophy and fat wasting. In the current study, we questioned whether bone density also decreases in patients with EC and associates with oncologic outcomes.
Methods: We performed a retrospective review of all patients that received esophagectomy between 2015 and 2020 at University of Florida Health. Patients with pre-existing cardiac disease were excluded. Body composition was measured using PET/CT scans, and patients were classified as having cachexia/myopenia if having an L3 skeletal muscle index below sex- and BMI-dependent cutoffs. A p-value less than 0.05 was considered statistically significant.
Results: Bone density was significantly reduced in patients with cachexia relative to those with normal muscle mass (108±37.2 HU v. 146±55.0 HU, p=0.003). Furthermore, bone density correlated with muscle mass (p<0.0001, R=0.5055) and muscle quality/radiodensity (p=0.0002, R=0.4736). Mean rate of bone loss was -12.0±27.9 HU/100d between initial and re-staging imaging studies after neoadjuvant therapy. Patients with regional lymph node metastases at surgery (N1-3) had more bone loss than those with N0 disease (-26.6±30.8 HU/100d v. -2.71±22.1 HU/100d, p=0.03). Similarly, progressive loss of bone was observed in patients with positive Lymphovascular (LV) invasion (-41.8±32.6 HU/100d v. -3.53±20.1 HU/100d, p=0.005) and positive perineural (PN) invasion (-29.8 ± 32.4 HU/100d v. -3.12 ± 21.1 HU/100d, p=0.01).
Conclusion: Reduced bone mineral density is a key component of cachexia in patients with EC. We demonstrate herein that osteopenia in EC patients associates with several cachexia measures and that progressive loss of bone may predict a worse response to neoadjuvant therapy and a tumor's early metastatic potential. Bone density may serve as a strong predictor of survival and stratification tool for clinical trials. These findings further highlight the need to study mechanisms that lead to bone wasting in tumor bearing hosts.

Figure



3-01

Prognostic value of weight loss in hospitalized patients with acute heart failure

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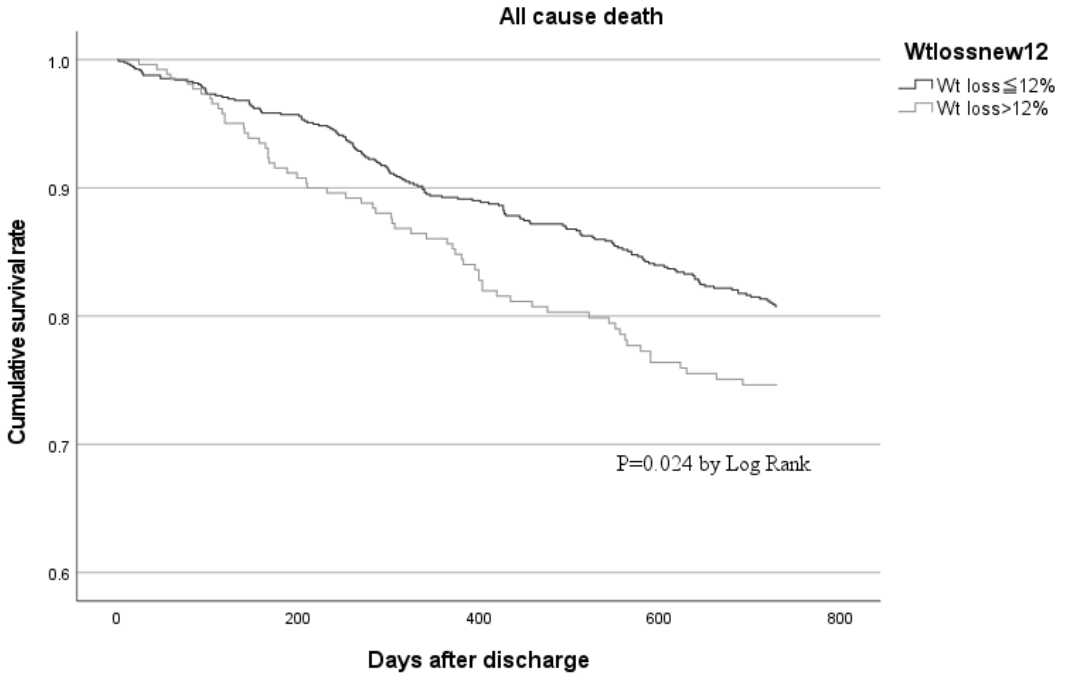
Introduction: Weight loss is a known poor prognostic factor in patients with chronic heart failure (HF). Whether weight loss is a poor prognostic factor in patients with acute HF is unknown. In this study, we aimed to investigate the prognostic value of weight loss in patients hospitalized for acute HF.

Methods and Results: This study was a post-hoc analysis of the FRAGILE-HF study, a prospective multicenter observational study that included 1,332 hospitalized older (≥65 years) patients with HF. The primary outcome was all-cause death within 2 years of discharge. The self-reported body weight 1 year prior to hospital admission was available in 1,106 patients (83.0%) and was compared with their weight before discharge after decongestion therapy. The mean weight change was -7.4±8.3% and 86.8% of the overall cohort experienced any weight loss. Whereas patients with weight loss ≥5%, which is a well-validated cut-off in chronic HF, showed comparable mortality to those with less weight loss (p= 0.955 by log-rank), patients with weight loss ≥12%, the lowest quartile value, showed higher mortality than those with less weight loss or no weight loss (p=0.024 by log-rank; figure). In a Cox proportional hazard model, weight loss ≥12% was associated with high mortality after adjustment with the known prognostic factors (age, gender, current smoking, NYHA class, ejection fraction, serum creatinine, systolic blood pressure, body mass index, past history of diabetes, chronic obstructive pulmonary disease, HF, medication, and log B-type natriuretic peptide; adjusted hazard ratio: 1.58 [1.14-2.19], p=0.006).

Conclusions: Our study showed that weight loss assessed before discharge was significantly associated with high mortality after discharge in patients aged ≥65 years who were hospitalized for acute HF.



3-02

Circulating microRNA-22 as an innovative biomarker in patients with sarcopenia and heart failure: results from the SICA-HF

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Background: Escalating loss of skeletal muscle mass and strength (sarcopenia) is a frequent comorbidity of heart failure (HF) and often present in the elderly. MicroRNA-22 (miR-22) targets several muscle function-related genes, such as myotubularin-related protein 2, myosin IXA, tropomyosin 3 or sarcalumenin and regulates skeletal muscle differentiation. Our aim was to assess the diagnostic value of miR-22 in sarcopenic HF patients and its association with variables deemed clinically relevant in sarcopenia.

Methods: We assessed miR-22 in 176 chronic HF patients ("Studies Investigating Comorbidities Aggravating Heart Failure" SICA-HF; overall prevalence of sarcopenia 15.9%). Sarcopenia was defined as appendicular skeletal muscle mass index <7.26 kg/m^2 in males and <5.45 kg/m^2 in females. Body composition was assessed by *dual-energy X-ray absorptiometry*. MiR-22 serum concentrations were measured by miR-specific TaqMan RT-qPCR analyses.

Results: In the present study, patients with HF and sarcopenia were older compared to non-sarcopenic HF patients (74.5 [68.7-80.2] *vs.* 68.4 [60.9-74.8]; p=0.001), had a lower BMI (25.1 [22.4-26.8] *vs.* 29.2 [26.0-32.9] kg/m^2; p<0.001), higher NT-proBNP levels (3693.2 [1183.3-5000.0] *vs.* 1066.4 [521.3-2453.6] pg/ml; p<0.001), lower left ventricular ejection fraction (16.8 [15.0-20.0] *vs.* 35.0 [30.0-40.0] %; p=0.025), lower maximal handgrip strenght (31.1±6.0 *vs.* 37.0±13.0 kg; p=0.016), lower absolute peak VO_2 (1181.3±379.5 *vs.* 1593.0±487.0 mL/min; p<0.001) and a lower 6-minute walk test distance (389.0±135.5 *vs.* 466.3±120.0 m; p=0.009). Cycle threshold (CT) value after RT-qPCR analysis showed that sarcopenic patients with HF had significantly higer serum levels of miR-22 compared to non-sarcopenic patients (5.2±0.8 *vs.* 5.7±0.9; p=0.032). In the ROC curve and Youden index analysis the optimal diagnostic cut-off CT-value of miR-22 was 5.39, providing the best trade-off between sensitivity (45.3%) and specificity (85.7%). In the multivariate regression model adjusted for age, diabetes mellitus, ejection fraction, NT-proBNP levels and absolute peak VO_2, miR-22 levels (adjusted OR 0.410, 95% CI 0.193-0.868, p=0.020) and BMI (adjusted OR 0.784, 95% CI 0.642-0.959, p=0.018) remained associated with presence of sarcopenia in HF patients.

Conclusion: MiR-22 is independently associated with sarcopenia in HF patients, proposing a novel epigenetic biomarker of alteration in skeletal muscle.

3-03

Novel biomarkers as possible prognostic tools in the determination of muscle wasting in HF patients

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Background: Muscle wasting is a comorbidity gaining attention among heart failure (HF) patients and older adults. According to the European Society of Cardiology, its prevalence in HF ranges from 20 to 50%. Identification of sarcopenia in the clinical practice can be challenging, firstly due to its multiple definitions in literature, secondly because of the lack of specific biomarkers that allow early recognition of deterioration of muscle mass. The present study therefore aimed to find possible biomarkers for early screening of muscle wasting.

Methods: Using ProcartaPlex Multiplex Immunoassay (ThermoFisher Scientific, Germany) 43 biomarkers were measured in 169 HF patients from the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF). Body composition was assessed by dual energy X-ray absorptiometry. Sarcopenia was defined as a low appendicular lean mass adjusted by height squared (≤7.26 kg/m^2 in men, ≤5.5 kg/m^2 in women).

Results: Patients with sarcopenia (21.3%) were all male, older (72.35±9 *vs.* 66.5±11 years, p=0.006) and presented with lower weight and body mass index (77.31±14 *vs.* 89.82±16 kg, 24.64 [22.18-26.79] *vs.* 29.11 [26-32.71] kg/m^2; both p<0.001), had more frequently ischaemic aetiology (77.8 *vs.* 57.3%, p=0.025) and higher prevalence of iron deficiency (72 *vs.* 36%, p<0.001) and anaemia (44 vs 23%, p=0.009) compared to patients without sarcopenia. Estimated glomerular filtration rate (65.61 [48.6-80.6] *vs.* 71.6[54.9-82.6] mL/min/1.73m^2, p=0.226) showed no difference between the groups. In sarcopenic patients concentrations of periostin (41.06 [32.92-47.89] *vs.* 33.21 [28.39-40.77] pg/mL, p=0.013), vascular endothelial growth factor-a (VEGF-a) (167.72 [84.89-238.21] *vs.* 110.36 [60.33-160.44] pg/mL, p=0.014) and tumor necrosis factor receptor 2 (TNF-R2) (58.93 [44.76-76.56] *vs.* 48.89 [40-63.86], p=0.027) were elevated in comparison to non-sarcopenic patients. Previously suggested biomarkers for sarcopenia, namely osteocalcin (18.6 [12.2-22.2] *vs.* 13.6 [9.83-18] µg/L, p=0.002), osteoprotegerin (5.88 [4.14-7.64] *vs.* 4.52 [3.64-6.08] pmol/L, p=0.016), parathyroid hormone (59.85 [34.5-91.8] *vs.* 42.1 [32.05-64.35] pg/mL, p=0.038) and fibroblast growth factor 23 (153.68 [78.74-819.32] *vs.* 82.9 [56.96-148.72] pg/mL, p=0.002) were higher in sarcopenic patients. Using univariate logistic regression models, VEGF-a (OR 3.51, 95% CI [1.19-10.31], p=0.023) and TNF-R2 (OR 1.02, 95% CI [1.002-1.036], p=0.029) were associated with sarcopenia. In a multivariate logistic regression model, VEGF-a remained an independent predictor of sarcopenia (adjusted OR 4.56, 95% CI [1.03-20.19], p=0.046).

Conclusions: VEGF-a showed a strong association with sarcopenia in HF patients. It is known that VEGF-a plays a role in angiogenesis but further investigation regarding its relation with muscle deterioration and heart failure is needed.

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3-04

Association between bioimpedance phase angle and post-stroke dysphagia: pilot study

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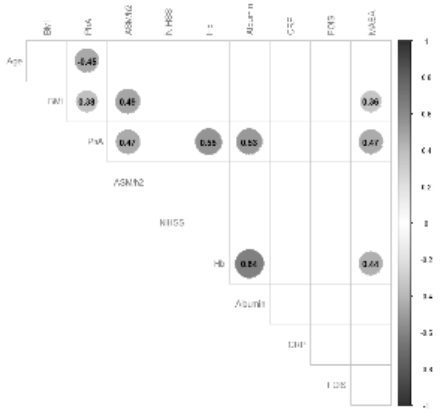
Introduction: Dysphagia is one of the common sequelae of stroke and can be observed in up to 60-70% of post-stroke patients. Post-stroke dysphagia is associated with various complications including aspiration pneumonia, prolonged length of hospital stay, and increased mortality. Bioimpedance analysis (BIA) is non-invasive tool to evaluate body composition and is commonly used in diagnosing and evaluating sarcopenia. Phase angle is one of the values obtained from BIA, which is useful in evaluating cellular health and known to be related with functional outcome in stroke patients. However, studies on association between phase angle and post-stroke dysphagia is scarce. Therefore, this study aimed to explore the association between phase angle and post-stroke dysphagia severity.
Methods: This study was retrospective observational pilot study, and first-ever stroke patients were included in the study. BIA (In-Body S10; Biospace Co. Ltd., Seoul, South Korea) was performed to measure appendicular skeletal muscle mass (ASM) and phase angle. Post-stroke dysphagia function was evaluated using functional oral intake scale (FOIS) and Korean Mann assessment of swallowing ability (K-MASA).
Results: A total of 34 post-stroke patients were included in the analysis. Sarcopenia accounted for 38.2% (n=13) of the included participants. Baseline characteristics of the participants are shown in Table 1. In Pearson correlation analysis, phase angle significantly negatively correlated with body mass index, ASM/(height)^2, hemoglobin, albumin, and K-MASA (Figure 1).
Conclusion: In this study, phase angle was significantly associated with K-MASA, one of the dysphagia evaluation tool including different aspects of swallowing, including oral motor function, sensation, pharyngeal swallowing, and laryngeal function. Phase angle may be utilized as feasible biomarker that may be associated with post-stroke dysphagia severity. Future studies with larger population are needed to support the result.
Table 1. Baseline characteristics of the participants

	Total (n = 34)
Age	74.5 [67.5 - 82.8]
Sex (male)	21 (61.8%)
Stroke type	
Ischemic stroke	23 (67.6%)
Hemorrhagic stroke	11 (32.4%)
BMI (kg/m2)	24.2 [22.2 - 26.4]
Hypertension (yes)	25 (73.5%)
Diabetes (yes)	16 (47.1%)
Atrial fibrillation (yes)	5 (14.7%)
Chronic kidney disease (yes)	5 (14.7%)
NIHSS	5.0 [2.3 - 10.5]
Hemoglobin (g/dL)	11.6 [10.7 - 13.0]
Albumin (g/dL)	3.8 [3.6 - 4.0]
CRP (mg/L)	5.6 [2.2-10.3]
Functional oral intake scale	4.0 [1.0-5.0]
Korean Mann assessment of swallowing ability	173.0 [151.2-189.5]

Figure 2. Association between phase angle and clinical parameters



3-06

Screening for malnutrition, sarcopenia, and physical frailty in liver transplant recipients: a long-term cross-sectional study

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Introduction: Despite the relative high survival rate after liver transplant (LT), malnutrition, sarcopenia and frailty are present in 47 %, 80% and 59%, respectively, 3 months after surgery. These complications are associated with adverse clinical outcomes and decreased quality of life after LT. However, there are no data regarding malnutrition, sarcopenia, and frailty in the long term after LT. The primary objective is to determine the prevalence of malnutrition, sarcopenia, and frailty at 1, 2 and 3 years after LT. The secondary objectives aim to describe muscle function, quality of life and employment status in LT recipients.
Methods: Cross-sectional observational study is conducted including 65 patients transplanted between 2019 and 2021. A single virtual meeting is performed with each patient during which nutritional risk (Canadian Nutrition Screening Tool), sarcopenia (SARC-F questionnaire), frailty (FRAIL questionnaire), muscle function (chair stand test), quality of life (SF-36) and employment status are assessed.
Results: To date, 64 patients (27 in 2019, 13 in 2020 and 24 in 2021) have completed the study (40 men and 24 women, mean age is 58.8 ± 10.2 years). 12.5%, 15.4% and 11.1% of LT recipients were at risk of malnutrition in the cohort of 1 year, 2 years and 3 years after LT, respectively. In LT recipients, 8.3%, 30.8% and 18.5% were at risk of sarcopenia in the cohort at 1 year, 2 and 3 years after LT, respectively. In addition, 1 year after LT, 50.0% and 12.5% were prefrail and frail, respectively. At 2 years after LT, 46.2% and 30.8% were prefrail and frail, respectively whereas, at 3 years after LT, 44.4% and 18.5% were prefrail and frail, respectively. Muscle function was impaired at 1 year after LT (15.8 ± 5.5 s vs. 12.6 s in healthy people) and the score remained unchanged until 3 years after LT. Regarding quality of life, the score of physical heath (62.6% ± 22.1) was slightly below normal and the scores remain unchanged until 3 years after LT. Finally, 68.4% of patients were unemployed, of which 46.2% were in early retirement for a liver disease-related cause.
Conclusion: Up to 3 years after LT, patients are still at risk of malnutrition, sarcopenia, and frailty. The physical component score of their quality of life score is below the score of the general population. The results of this project may help identify appropriate interventions in the long term after LT.

3-07

Creatinine to cyscatin C ratio as a marker of skeletal muscle mass and mysteatosis in patients before gastrointestinal cancer surgery

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Introduction: To evaluate the efficacy of creatinine to cyscatin ratio (CCR) as a marker of muscle mass and myosteatosis in patients before gastrointestinal cancer surgery.
Methods: Patients who received gastrointestinal cancer surgery from April 2020 to August 2021 were selected. Correlation analysis was used to identify the association between CCR and skeletal muscle imaging parameters before surgery. The predictive ability of CCR for muscle mass and myosteatosis in the target population was assessed based on the area under the receiver operating characteristic (ROC) curve (AUC). Optimal cutoff values for CCR were calculated and their relationship with clinical outcome was explored.
Results: A total of 1002 patients were included. There was a correlation between CCR and imaging parameters related to muscle adipose tissue. CCR was positively correlated with SMD (p<0.001), SMA (p<0.001), SMG (p<0.001), and SMI(p<0.001) and negatively correlated with IMAT (p<0.001) and IMAT% (p<0.001). CCR can be used to evaluate skeletal muscle mass reduction (AUC: 0.65) with an optimal cutoff of 76.190 and is superior to Cre (AUC: 0.64) and CysC (AUC: 0.53). CCR can be used to evaluate muscular steatosis (AUC: 0.72), with an optimal cutoff value of 77.532, and is superior to Cre (AUC: 0.63) and CysC (AUC: 0.57). When CCR was used to assess cachexia and sarcopenia, it was effective in distinguishing patients' risk of disease-free survival (P < 0.001).
Conclusions: CCR is a marker of skeletal muscle mass and steatosis in patients before gastrointestinal cancer surgery, which is helpful for auxiliary diagnosis of cachexia and can predict clinical prognosis.

Keywords: creatinine to cyscatin ratio; sarcopenia; cachexia; gastrointestinal cancer

3-08

Sarcopenia is uncommon, despite significant loss of weight and skeletal muscle, in patients undergoing oesophagogastric cancer surgery.

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Introduction: Low skeletal muscle is prevalent and associated with poorer outcomes after oesophagogastric (OG) cancer surgery. However, sarcopenia, including strength and function, is less commonly assessed. Therefore, we aimed to describe the prevalence of sarcopenia and changes in diagnostic criteria within 1-year of OG cancer surgery.
Methods: This prospective observational study included patients who had surgical resection of OG cancer between 2018-2021 at a tertiary hospital in Melbourne, Australia. Sarcopenia was defined using the EWGSOP2 definition. Body composition assessment using computed tomography (CT) measured skeletal muscle area (cm^2) and density (Hounsfield Units, HU). Low skeletal muscle index (SMI) was <52.4cm^2/m^2 for males and <38.5cm^2/m^2 for females. Low muscle density (myosteatosis) was defined using pre-determined HU and BMI thresholds. Bioimpedance spectroscopy (BIS) quantified muscle as fat-free mass (FFM, kg). Low fat-free mass index (FFMI) was <17kg/m^2 for males and <15kg/m^2 for females. Hand grip strength (HGS, kg) and 6-metre walk test (metre/second) measured strength and function. Sarcopenia was assessed preoperatively and up to 1-year postoperatively using CT (Sarc-CT) and BIS (Sarc-BIS) muscle measurements. Weight (kg) was recorded at each time point.
Results: Fifty patients, predominantly male (62%) and mean age of 64 years, were included preoperatively, with 32 patients at 1-year. The prevalence of Sarc-CT was 7.1% preoperatively and 10.7% at 1-year (p=0.32), with a significant reduction in SMI (47.2 vs 44.16 cm^2/m^2, p=0.03) between time points. Low SMI (46%) and myosteatosis (50%) were prevalent preoperatively and remained unchanged at 1-year (both p=0.21). The prevalence of Sarc-BIS was 2% preoperatively and 3.3% at 1-year (p=0.60). Figure 1 shows changes in weight and
FFM. Low FFMI occurred in 8% preoperatively and 12% at 1-year (p=1.00). Few patients met the low HGS (16%) and low walk speed (8%) criteria preoperatively without significant postoperative changes (both p=0.50).

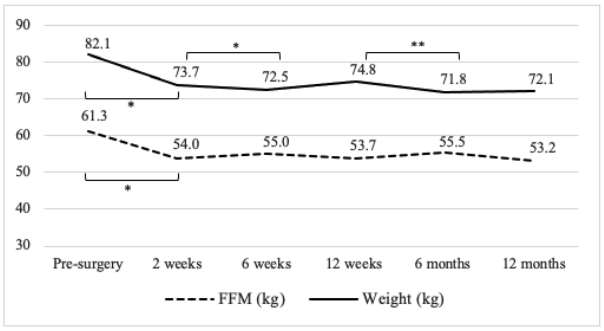

Figure 1. Change in weight and FFM. *p < 0.001, **p=0.01.

Conclusions: Despite the high preoperative prevalence of low SMI and myosteatosis and the significant loss of weight and skeletal muscle after surgery, sarcopenia was uncommon. The low prevalence of sarcopenia is predominantly attributable to the high number of patients with HGS above the low strength threshold. These results indicate that loss of skeletal muscle, without corresponding decline in strength or function, is a prominent feature in this patient cohort. Considering the known negative impact of low skeletal muscle on surgical complications and survival, muscle assessment remains a valuable and clinically meaningful measure.

3-11

Sarcopenic obesity is predictive of critical weight loss in patients with head and neck cancer

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Introduction: Patients with head and neck cancer (HNC) are at high risk of malnutrition and critical weight loss (CWL), either as a result of the tumour, and/or toxicities of treatment

modalities. Evaluation of skeletal muscle (SM) loss via computed tomography (CT) (CT-defined sarcopenia), has become an important nutrition assessment tool. We investigated predictors of CWL during radiotherapy (RT) and the impact of sarcopenia on overall survival (OS).
Methods: This retrospective study included adult patients with newly diagnosed HNC who completed radiotherapy (RT) (± other modalities) in our facility. SM was measured using PET-CT scans or RT planning CT scans at the third lumbar vertebra (L3) where available, and at the third cervical (C3) and second thoracic (T2) vertebra in patients with no visible L3 landmark. Validated equations were applied to C3 and T2 SM cross-sectional area (CSA) to predict L3-CSA. SM index (SMI, cm2/m2) was applied to determine sarcopenia, stratified by sex and body mass index (BMI). Predictors of CWL (≥5% during RT) were determined, and the impact of sarcopenia on OS was investigated with Kaplan Meier analysis.
Results: Scans of 415 patients were analysed (majority male 84%, mean age 60 years). Oropharynx cancer was the most prevalent (52%), with concurrent chemoRT used to treat 47% of patients. Sarcopenia was present in 43% (n=177), with 61% (n=116) also being overweight or obese (BMI≥25kg/m2). CWL was experienced by 58% (n=239), and 29% of these patients also had sarcopenic obesity at baseline. Patients with sarcopenic obesity were found to be 4.2 times more likely to experience CWL (OR 4.16, 95%CI 1.84-9.42, p=0.001). Other predictors on multivariate analysis were: concurrent chemoRT (OR 4.9, 95%CI 2.65-9.08, p<0.001), oropharynx tumour (OR 2.8, 95%CI 1.46-5.39, p=0.002), nasopharynx tumour (OR 3.6, 95%CI 1.32-9.97, p=0.012) and females (OR 2.17, 95%CI 1.05-4.49, p=0.037). Patients without sarcopenia at presentation were less likely to have CWL when not categorised by BMI (OR 3.9, 95%CI 1.76-8.62, p=0.001). Neither sarcopenic obesity or CWL significantly impacted on OS, however, sarcopenia without BMI categorisation was associated with worse OS (Log Rank p=0.006), median survival 8.4 versus 10.1 years (95%CI 4.00-12.00).
Conclusion: Patients with HNC who are overweight or obese are at risk of CWL during RT, and evaluation of SM prior to treatment may assist in early identification and appropriate nutrition intervention planning.

3-12

Body composition phenotype sarcopenic obesity is associated with poor physical fitness assessed by cardiopulmonary exercise testing in patients undergoing colorectal cancer surgery

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Introduction: Preoperative risk assessment for major colorectal cancer (CRC) surgery remains a challenge. Body composition (BC) analysis and objective physical fitness assessment can be used to evaluate risk. We aim to investigate if BC is associated with poor performance on cardiopulmonary exercise test (CPET) in CRC patients.
Methods: Stage I-III CRC patients undergoing CPET were identified between 2010 and 2020. BC analysis was done using a single axial slice preoperative CT image at third lumbar vertebra.
Sarcopenia was defined according to BMI <25 skeletal muscle index (SKMi) <43 cm²/m² in men, <41 cm²/m² in female, while BMI ≥25 SKMi <53 cm²/m² in men and <41 cm²/m² in female. Sarcopenic obesity was defined as having sarcopenia and BMI >30. Myosteatosis was defined as skeletal muscle mean attenuation in Hounsfield unit <41 in men and <33 in female. Visceral obesity was defined as visceral fat area >164 cm² in men and >80 cm² in female. CPET variables were oxygen uptake at anaerobic threshold (AT) <11.1 ml/kg/min and peak oxygen uptake (peak VO2) <18.2 ml/kg/min.
Relationships between clinicopathological, BC and CPET variables were investigated using binary logistic regression. Variables with a p-value <0.05 on univariate analysis were entered into the multivariate model.
Results: 218 CRC patients were identified from two different UK hospitals. On univariate analysis gender (0.32, 95% CI 0.18 - 0.59, p <0.001), ASA (3.52, 95% CI 1.90 - 6.52, p <0.001) and TNM (2.12, 95% CI 1.19 - 3.79, p 0.011) were associated with reduced AT. On multivariate analysis gender, ASA and TNM were independently associated with reduced AT.
On univariate analysis age (3.22, 95% CI 1.83 - 5.69, p <0.001), gender (0.32, 95% CI 0.18 – 0.59, p <0.001), ASA (3.08, 95% CI, 1.66 - 5.70, p <0.001), TNM (3.64, 95% CI 2.06 - 6.42, p <0.001), myosteatosis (2.28, 95% CI 1.28 - 4.05, p 0.005) and sarcopenic obesity (2.48, 95% CI 1.18 - 5.24, p 0.017) were associated with reduced peak VO2. On multivariate analysis age, gender, ASA, TNM and sarcopenic obesity were independently associated with reduced peak VO2.
Conclusions: We present novel finding that sarcopenic obesity is associated with poor physical fitness when objectively assessed with CPET in CRC patients.

3-14

Sexual dimorphism in *masseter* thickness as anthropometric prognostic biomarker in head & neck cancer cachexia: a retrospective cross-sectional study

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Introduction: Cancer cachexia (CA-CX) is characterized by progressive loss of skeletal muscle, with or without loss of fat, that cannot be reversed by nutritional support. Criteria for CA-CX include either one or a combination of: weight loss >5% (last six months; no starvation), Body Mass Index (BMI) <20 + weight loss >2% and Appendicular Skeletal Muscle index (ASMI) indicating sarcopenia + weight loss >2%. ASMI is generally obtained from computerized tomography (CT). However, full body CT is rarely available in head & neck cancer (HNC) patients. Here we analyze the *masseter* muscle thickness as an alternative method to discriminate between HNC-cachexia and non-cachexia (NCX) in adult males and females.
Methods: 60 HNC CT datasets (DICOM) from sex-, race-, height- and age-matched white males and females were analyzed. For three-group comparison, per sex, patients fulfilling all three criteria for CA-CX (CA-CX; n=10) and patients with cancer but no CX (CA-NCX; n=10) were analyzed relative to no cancer, non-cachectic, healthy control patients (CTRL; n=10). For two-group comparison we included: CA-CX and NCX (CA-NCX + CTRL) groups. Left masseter muscle was segmented with a 3D-imaging software. 3D distribution of *masseter* thickness (MT), body weight, and BMI were quantified. Area Under the Curve (AUC) of the Receiver Operating Characteristics (ROC) analysis was calculated. All statistical analyses were blinded. Male and female cohorts were analyzed separately.
Results: For both males and females, CA-CX subjects exhibited reduced body weight and BMI. Only in the male cohort, CA-CX MT was significantly reduced (CI95%: 2.33-3.38) relative to both CTRL (CI95%: 3.19-4.42) and NCX (CI95%: 3.33-4.06). When CA-CX relative to NCX, AUC-ROC (Males, 0.88, CI95%: 0.70-1.0; Females, 0.74, CI95%: 0.55-

0.93) was significant (p<0.05), with sensitivity (Males, 66.7%, CI95%: 30.0-94.1; Females, 50.0%, CI95%: 23.7-76.3), specificity (Males, 90.0%; CI95%: 59.6-99.5; Females, 90.0%, CI95%: 69.9-98.2) and likelihood ratio (Males, 13.3; Females, 5.0), at a MT cut-off <9.68 (Males) and <8.80 (Females).
Conclusions: MT showed a sexual dimorphism as an anthropometric prognostic biomarker to discriminate between CA-CX and NCX in HNC patients and represents a promising tool that will need validation in larger cohort studies including other ethnicities, both sexes and different age groups.

3-16

The relationship between muscle strength and quality with functional performance in women mid-term after Roux-en-Y gastric bypass

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Objective: To examine the association between muscle strength and quality with physical function in women mid- to long-term after Roux-em-Y gastroplasty (RYGB).
Methodology: A total of 133 women (mean age 43.7±9.9yrs) who have undergone RYGB for at least two years (mean 6.3±3.4yrs) were included. All patients underwent body composition evaluation using dual-energy X-ray absorptiometry, which provides fat-free mass (FFM) and fat mass values for the entire body as well as for regional body segments. Knee extensors strength was evaluated using an isokinetic dynamometer; for the procedure, volunteers performed 2 sets of 4 repetitions at 60º/s, being the peak torque (PT) recorded for subsequent analysis, which was considered in absolute values as well as relative to body weight. Specific torque was taken as a measure of muscle quality (MQ) and was obtained through the ratio between absolute PT and FMM of the dominant leg. Physical function was measured through the 30 seconds sit-to-stand, 6-minute walking, and the timed up-and-go tests.
Results: Significant differences between PT tertiles were observed for the 30-second sit to stand (p<0.01) and for the 6-minute walking (p<0.01) tests, however, statistical significances disappeared when adjusting for age. Regarding PT relative to body weight, all the functional tests were significantly different between tertiles (all p<0,01), which remained consistent when adjusted for age. Comparing functional performance according to MQ tertiles, significant differences were found for the sit-to-stand (p=0.01) and walking (p=0.02) tests, but statistical significances disappeared when adjusting for age. Absolute PT was significantly correlated to the sit-to-stand performance (r=0.21; p=0.02) and to 6-minute walking (r=0.34; p<0.01), while PT relative to body mass and MQ are correlated with all the functional tests (all p<0.05).
Conclusion: Both muscle strength and quality seem to be associated with physical function to some degree in women mid-to-long-term after RYGB, but strength relative to bodyweight outperformed absolute strength and muscle quality. These observations suggest that muscle strength relative to body weight may be a useful supplement to other functional indices in the evaluation of these patients.

Keywords: Obesity; Bariatric Surgery; Physical Function; Muscle Function; Body Composition

3-17

Height-adjusted appendicular skeletal muscle mass is overestimated due to height loss in Japanese middle-aged and older women: The Japanese Population-based Osteoporosis (JPOS) study

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Introduction: Both EWGSOP 2 and AWGS 2019 use height-adjusted appendicular skeletal muscle mass (ASM/ht^2) as a cut-off value for a definitive diagnosis of sarcopenia. However, the 2020 US Sarcopenia Definitions and Outcomes Consortium dispenses with ASM entirely, either absolute or after adjusting for body size, because there are no clear associations between ASM and adverse health-related outcomes.
We focused on age-related height loss (HL) that might cause overestimation of ASM/ht^2, attenuating the predictive value for poor clinical outcomes in the elderly.
The purpose of this study was to examine the effects of HL over the past 15 years on the absolute level of ASM and indices adjusted for body size in different ways, using height squared (ASM/ht^2), weight (ASM/weight), and body mass index (ASM/BMI) in Japanese middle-aged and older women.
Methods: This study was part of the 15/16-year follow-up survey of the Japanese Population-based Osteoporosis (JPOS) cohort study conducted in 2011/2012. The JPOS cohort study was started in 1996. The subjects of the 15/16-year follow-up were 762 women (mean: 67.4 years). Subjects were divided into quartiles by HL over the past 15 years (Q1 was the lowest; Q4 was the highest). ASM was measured by dual X-ray absorptiometry, and we calculated ASM/ht^2, ASM/weight, and ASM/BMI. Grip strength (kg) was measured as an indicator of muscle strength. Trend tests were used to examine the difference among quartiles of HL.
Results: The mean HL value over the past 15 years in all subjects was 1.95 cm. A trend test showed a significant increase in mean age from the lowest to highest quartile. While ASM and ASM/BMI were significantly decreased from Q1 to Q4, ASM/ht^2 was significantly increased from Q1 to Q4. There was no significant difference in ASM/weight among quantiles. Grip strength was significantly decreased from Q1 to Q4.
We compared differences among quartiles in each index of ASM after adjusting for age. There were no significant differences in ASM and ASM/weight among groups. ASM/ht^2 and ASM/BMI retained significant differences after adjusting for age.
These results indicate that middle-aged and older women who exhibit a greater HL show higher ASM/ht^2 along with low muscle strength.
Conclusions: This study suggests that ASM/ht^2 is overestimated due to HL in Japanese middle-aged and older women.

3-18

Functional physical parameters are more associated with falls than with the diagnosis of sarcopenia by EWGSOP2

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Introduction: Aging are associated with osteoporosis and progressive loss of muscle mass and quality. The risk of falls is especially troublesome in women with osteoporosis.
Objectives: to evaluate the presence of sarcopenia and the relationship of its components with the history of falls and fractures.
Methods: Cross-sectional study with women aged ≥ 65 years recruited during their visit to the osteoporosis clinic or from the community. Those with unstable chronic diseases or under medications, except treatment for osteoporosis, that could interfere with the assessment were excluded. The included participants answered a questionnaire (demographics, diseases characteristics, lifestyle and history of falls and fractures), performed functional and isometric strength tests including ankle evaluation (peak isometric strength (PIS), muscle architecture and muscle thickness [MT]. Muscle architecture was evaluated by ultrasound and the DXA exam (lumbar spine, femur, total body) was performed. Sarcopenia was diagnosed based on EWGSOP2. Participants were divided in sarcopenia group (SG) and non-sarcopenia group (NSG).
Results: Out of 340 screened, 116 were included (71.54 ± 3.19 years, body mass index 26.10 ± 3.66 Kg/m^2). Although 50% of individuals had low performance or strength, only 6.89% was diagnosed with sarcopenia (SG: 8; NSG: 108) following the EWGSOP2 criteria. Bone mineral density on all sites was lower in SG *vs* NSG, p<0.005 for all. The most affected performance test was the gait speed (GS) - 32.78% followed by the short physical battery test (23.27%). The seat to stand test was low in 46.55% of the individuals, while the hand grip strength was low only in 11.2%. All individuals had compromised ankle function. Surprisingly, more subjects had low calf circumference compared to appendicular lean mass index (ALMI) 20.3% *vs* 13.7% respectively, limiting sarcopenia diagnosis. Previous falls were negatively correlated with dorsiflexor range of motion (ROM) (R=-0.212, p=0.017) and PIS (R=-0.212, p=0.023). The PIS was related to the number of falls (R=- 0.194, p= 0.049) and fractures (R= -0.219, p=0.019). Similarly, the plantiflexion ROM correlated negatively with GS (R= -0.182, p=0.047) and ALMI (R= -0.256, p=0.005).
Conclusions: sarcopenia prevalence was low despite the high percentage of functional impairments; possibly the EWGSOP2 criteria may be underdiagnosing sarcopenia in Brazilian elderly women. Functional assessments, including ankle function, should be incorporated into the evaluation of sarcopenia and falls.

3-19

Validation of accuracy and reliability of automated segmentation of body composition from single-slice ct images at l3 level using data analysis facilitation suite (dafs) in patients with non-metastatic colorectal cancer

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Introduction: Assessing body composition using computed tomography (CT) can help predict clinical outcomes of cancer patients as it can be related to surgical complications, chemotherapy toxicity, and survival. However, manual segmentation of whole-body CT images is labor-intensive and requires expertise in body anatomy and composition, which may lead to a significant amount of inter-observer variability. To overcome this limitation, automated methods such as the Data Analysis Facilitation Suite (DAFS) software have been developed to segment body tissues in 3D CT scans. In this study, we validate the accuracy and reliability of DAFS in segmenting body composition from single-slice CT images.
Methods: The study analyzed single-slice CT images at the third lumbar vertebra (L3) level of patients with non-metastatic colorectal diagnosis at Kaiser Permanente. The cohort for analysis consists of CT images taken from 9067 subjects. Segmentation of skeletal muscle mass (SKM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) at L3 were performed both manually and automatically using DAFS. Areas were calculated for these three tissue types. The accuracy of DAFS vis-a-vis manual segmentation was assessed by the Dice index, reliability was assessed by intra-class correlation coefficients, and agreement between automatic and manual segmentations was assessed by Bland-Altman analysis.
Results: The accuracy of automatic segmentation compared to manual analysis was high for all three tissue types, as indicated by the Dice scores and intra-class correlation coefficients (**Table 1**). The Bland-Altman plots (**Figure 1**) indicated that automated measurements tended to underestimate the tissue areas compared to the manual analysis for all three tissue types, with mean differences (±2 standard deviations) of -5.87 (4.68, -16.43) cm^2, -5.45 (4.85, -15.75) cm^2, and -6.30 (7.58, -20.18) cm^2 respectively.

Table 1: Dice scores and intra-class correlation coefficients for SKM, SAT, and VAT areas (n = 9067).

Tissue type	Dice score	ICC
SKM	96.0	0.99 (0.987 - 0.988)*
SAT	97.4	1.00 (0.999 - 0.999)*
VAT	95.4	1.00 (0.997 - 0.998)*

Statistically significant with p-value < 0.0001

Conclusions: The study validates that automated L3 segmentation using the DAFS platform is an accurate, reliable, and efficient method for measuring body composition that closely matches the manual segmentation in patients with non-metastatic colorectal cancer. This may help overcome the bottleneck of manual training and effort needed to measure body composition and may serve as a useful tool in assessing markers of sarcopenia, muscle loss, and adiposity, as well as in predicting clinical outcomes.

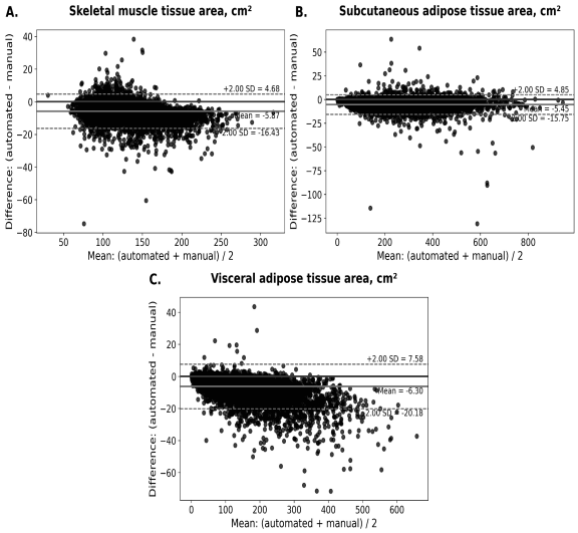

Figure 1: Bland–Altman plots showing the comparison of automated (DAFS) and manual analysis of computed tomography scans for measuring body composition parameters (n = 9067). The plots display the difference (y-axis) and the average (x-axis) of automated and manual measurements of skeletal muscle (SKM), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT). The blue reference line marks the zero difference between the manual and automated methods. The red solid lines indicate the overall mean difference between manual and automatic segmentation results. The red dashed lines indicate ±2 standard deviations (SD) of the difference, with limits of agreement from -16.43 to 4.68 for SKM, from -15.75 to 4.85 for SAT, and from -20.18 to 7.58 for VAT.

3-20

Deep learning-driven volumetric CT body composition analysis: new metrics for long-term postoperative risk stratification in colorectal cancer patients.

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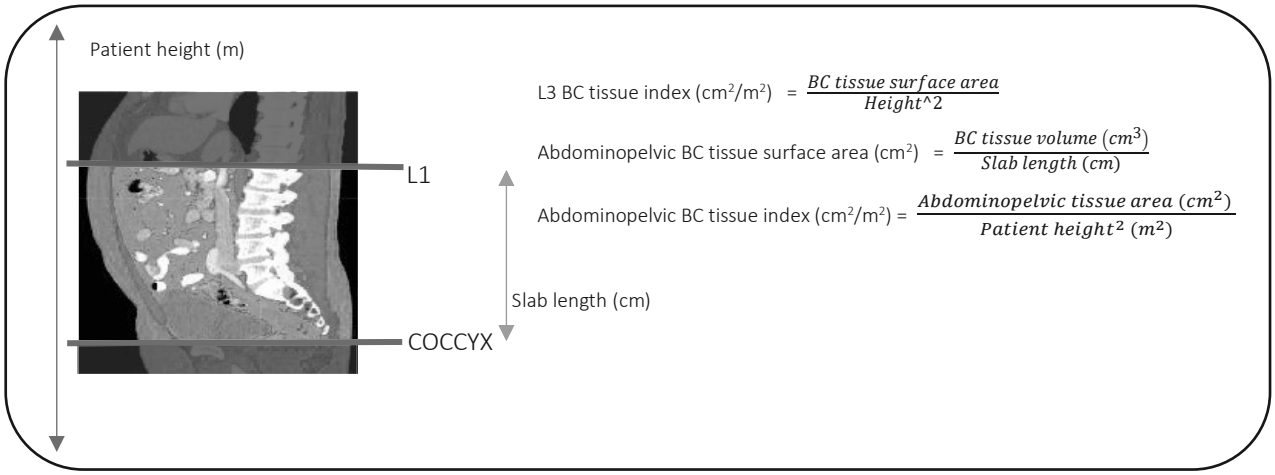
Background: A 2D single L3 CT slice has been de facto for studying body composition (BC) in cancer, with sarcopenia and myosteatosis predicting poorer short and long-term colorectal cancer (CRC) outcomes. Relationships with adipose tissue is less clear. The Data Analysis Facility Suite (DAFS) is a deep learning software enabling volumetric BC assessment from 3D regional CT scans. DAFS was used to study relationships between volumetric BC and CRC overall (OS) and disease-free survival (DFS) outcomes.
Method: Patients were sourced from a database of curative surgical resections for primary and non-complex CRC at a UK tertiary centre between 2006-13. DAFS segmented preoperative CT scans, providing abdominopelvic volumes of skeletal muscle (SM), subcutaneous, visceral, and total adipose tissue (SAT, VAT, TAT). This was defined from superior-most L1 to inferior-most coccyx. Division by abdominopelvic length and patient height^2 provided an abdominopelvic index (fig.1). Tissue radiodensity was quantified by mean Hounsfield attenuation (MA). Continuous metrics were categorised by quartiles, whilst additional literature cut-offs were applied to SM index. Multivariate Cox regression analysed relationships between BC and outcomes. Intravenous contrast use was included as a co-variate.
Fig. 1 Calculation of height and slab corrected body composition indices



BC – Body Composition; refers to either skeletal muscle, or subcutaneous, visceral, or total adipose tissue.

Results: At 60 months, 219 of 750 patients had died (29.2%). Reduced OS was predicted by sarcopenia (HR=1.309, CI 95% 1.027-1.668, p=0.029), the lowest quartile of TAT index (HR=1.466, CI 95% 1.1132-1.898, p=0.004), and myosteatosis (HR=1.334 CI 95% 1.025–1.736, p=0.032).The highest quartile of mean SAT (HR=1.390, 95% CI 1.065-1.814, p=0.015) or VAT MA (1.402, 95% CI 1.077-1.826, p=0.012) also had an elevated risk. Patients with simultaneous sarcopenia and low TAT index had a particularly heightened mortality: a 48% five-year rate (HR=1.650, CI 95% 1.194-2.279, p=0.002). Excluding metastatic disease, 125 of 659 (18.9%) suffered recurrences. Reduced DFS was independently associated with sarcopenia (HR 1.706, 1, 1.005-2.896, p=0.048) and the highest quartile of VAT MA (HR 1.576, 1.060-2.344, p=0.025).
Conclusion: Increased VAT MA coud be a novel predictor of CRC mortality and recurrence. Additionally, low TAT quantity is associated with mortality, particularly in combination with sarcopenia. Further research is required to validate concordance of regional CT scan BC with true whole body, allowing for standardised methodology in future volumetric BC studies.

3-21

Automated volumetric BC quantification by the Data Analysis Facility Suite (DAFS): external validation for preoperative CT abdomen and pelvis in colorectal cancer

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Introduction: The Data Analysis Facility Suite (DAFS) is a deep learning-driven software capable of automated segmentation of 3D clinical CT scans. This is relevant to researchers and clinicians interested in body composition (BC) as volumetric measures of skeletal muscle (SM) and subcutaneous, visceral and intermuscular adipose tissue (SAT, VAT, IMAT) are provided. This is the first external validation of DAFS' performance in quantifying of SM, SAT, VAT and IMAT.
Method: The validation test was conducted in a UK tertiary hospital, where 13 male and 13 female patients were randomly selected from a colorectal cancer database. The 26 CT abdomen and pelvis scans were segmented by DAFS. We calibrated DAFS to focus on the abdominopelvic region, defined from the superior-most aspect of the L1 vertebra to the inferior coccyx. Abdominopelvic volumes of SM, SAT, VAT, and IMAT were then produced without manual verification.
The segmentation files were then duplicated. Two clinicians checked through the automated segmentation for errors using the inbuilt manual annotation and segmentation tool. After corrections were made and saved, tissue volumes were reproduced for each clinician. Clinician interobserver agreement was assessed. Mean volumes of SM, SAT, VAT, and IMAT volumes between the two clinicians were calculated and compared to DAFS' initial unverified measurements by Bland-Altman plots. Volume percentage differences with 95% C.I limits of agreement (LoA) were also calculated.
Results: The Bland-Altman plots for clinician vs clinician and clinician vs DAFS interobserver agreements are shown in Fig. 1 and Fig. 2. There was strong clinician vs clinician agreement for SM, SAT, VAT and IMAT volumes, with mean percentage differences of 0.06±1.61%, 0.09%±1.18%), 0.13±1.15%), and 0.06±1.39% respectively.
Mean volumes of each tissue were then derived the two sets of clinician-verified measurements and compared to the unverified DAFS measurements. Mean percentage differences were 0.09±0.6%, 0.07±1.23%, 0.03±1.07%, and 0.03±1.39% for SM, SAT, VAT, and IMAT respectively.
Conclusions: There was high agreement between unverified and clinician-verified DAFS measurements of SM, SAT, VAT, and IMAT volumes from the abdominopelvic CT scans in this single UK colorectal cancer hospital. We recommend this as a convenient methodology for external validation of DAFS in other in other institutions.

Figure 1: Bland-Altman plots of clinician vs clinician verification of DAFS body composition measures

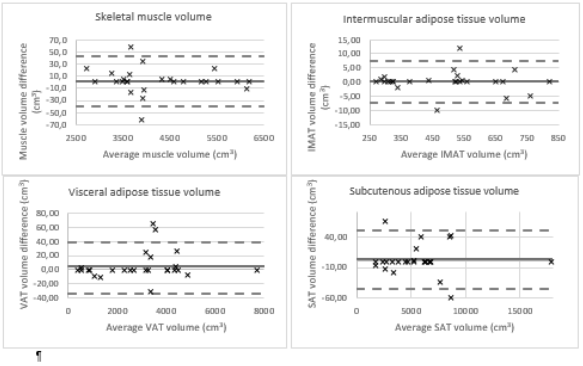
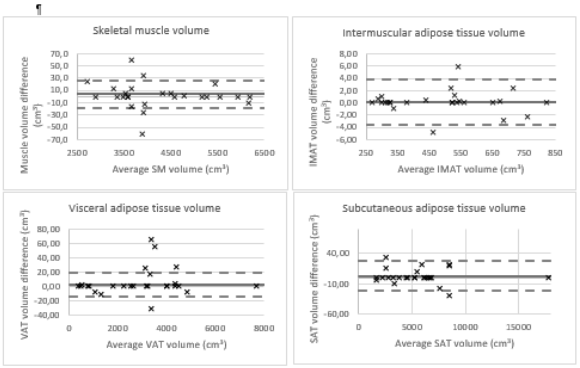


Figure 2: Bland-Altman plots of unverified versus clinician-verified DAFS body composition measures



3-22

Compared to single lumbar slice, volumetric body composition analysis from regional CT scans is more representative of skeletal muscle and adipose tissue volume and radiodensity

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Background: Body composition (BC) in the context of colorectal cancer (CRC) outcomes is a keen area of research. Using a single third lumbar (L3) CT slice has been a surrogate estimate of whole skeletal muscle (SM), subcutaneous and visceral adipose tissue (SAT, VAT) quantity. The Data Analysis Facility Suite (DAFS) is a deep learning software allowing 3D BC analysis of entire scans. Our group utilised DAFS to examine relationships between thoracic BC and outcomes in patients undergoing surgery for complex and recurrent CRC. We also assessed relationships between 2D SM, VAT and SAT L3 surface areas, with 3D volumes thoracic and abdominopelvic volumes on CT.

Methods: A 2009-2019 complex CRC database at St Mark's Hospital was reviewed. DAFS segmented preoperative CT thorax/abdomen/pelvis according to BC tissues. Segmentations were checked by a clinician. SM, SAT and VAT were quantified as three-dimensional thoracic (T2 to T11) and abdominopelvic (L1 to coccyx) volumes, and as surface areas at the mid-L3 level. Tissue radiodensity was measured by mean Hounsfield attenuation (MA) per 3D or 2D region.
Results: In 186 patients, thoracic and abdominopelvic volumetric BC strongly correlated (r= 0.905, 0.929, 0.845, all p<0.001, for SM, SAT and VAT respectively). Comparatively, L3 surface areas correlated weakly with thoracic SM (r= 0.187, p=0.02), SAT (r=0.200, p=0.013), and VAT (r=0.237, p=0.003) volumes, and with abdominopelvic volumes (SM, r=0.188, p=0.014; SAT, r=0.251, p=0.001; VAT, r=0.178, p=0.020). Whilst both abdominopelvic volumes and L3 surface area predicted thoracic BC, the abdominopelvic volume linear regression model had markedly stronger fit (SM R2 =0.820 vs 0.032; SAT R2 =0.830 vs 0.060; VAT R2 =0.706 vs 0.033).
3D L1-coccyx tissue MA were compared with 2D L3 surface area. Weak correlation existed for SM (r= 0.276, p<0.001) and VAT (r= 0.156, p=0.041), and no relationship was observed for SAT (r= 0.059, p=0.439). On comparing 3D thoracic and abdominopelvic regions, there was strong correlation for SM (r= 0.892, p<0.001) and SAT (r= 0.875, p<0.001), and moderate relationship for VAT (r= 0.676, p=0.041) MA.
Conclusions: Volumetric BC from regional CT scans could be more representative of SM and AT volume and radiodensity.

3-23

Elevated epicardial adipose tissue and aortic calcification, quantified from volumetric regional CT scans, are associated with postoperative complications in complex rectal cancer

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Introduction: Body composition (BC) research in colorectal cancer commonly focuses on measurements from the abdominal cavity. The Data Analysis Facility Suite (DAFS) is a deep learning-driven software platform capable of automated body composition analysis of three-dimensional (3D) regional CT scans. We used DAFS to study assessed relationships between volumetric thoracic BC and early postoperative outcomes in a cohort of patients undergoing surgery for complex rectal cancers (RC) at St Mark's Hospital.
Method: A database of resections of locally advanced or recurrent RC from 2009-2022 was reviewed. Available CT thorax scans were automatically segmented DAFS and visually checked by a clinician. Skeletal muscle (SM), aortic calcification (AC), thoracic and epicardial adipose tissue (ThAT, EpiAT) volumes were quantified from a 3D slab (a 3D region of multiple CT slices) between T2 and T11. Volumes were divided by slab length and patient height^2, excluding AOC which was divided by thoracic aortic volume. Each tissue index was divided into sex-specific tertiles for comparison.
Results: In 206 patients, postoperative cardiovascular events were significantly increased in the highest tertile of ThAT (11.8% vs 1.4% *p=0.036*), and EpiAT index (11.8% vs 1.4% *p=0.36*). Major wound complications were increased in the highest tertile of EpiAT (35.3% vs 16.7% *p=0.032*). Moderate correlation was observed between ThAT and EpiAT indexes (r=0.769, *p<0.*001).
Patients in the highest tertile of AOC were significantly likelier to suffer postoperative cerebrovascular events (14.7% vs 0%, *p=0.01*), and anastomotic leakage (8.8% vs 0%, *p=0.11*). Individuals in the highest tertile of SM index benefited from reduced rates of pelvic collection (8.8% vs 27.8, *p=0.027*), or any collection requiring radiological drainage (2.9% vs 18.1%, *p=0.034*)
Conclusions: ThAT, EpiAT and AC could be novel predictors of cardiovascular, cerebrovascular and anastomotic complications after complex RC surgery. In the context of abdominal pathology, thoracic BC should be additionally studied now that technology allows for analysis of 3D regional CT. EpiAT would be missed if focusing on the abdomen alone. Further study with a larger sample is required, allowing for multivariate logistic regression to confirm whether these observations are independent.

3-24

Evaluation of body composition at L3 from computed tomography (CT) images using DAFS software, a 3D fully automated multi-slice multi-organ extraction platform

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Introduction: Measures of body composition can be used to evaluate the nutritional status of patients, which may affect the clinical outcomes. To facilitate accurate and time-efficient body composition measurements, fully automated whole-body 3D computed tomography (CT) segmentation methods have been developed. The aim of the current study was to evaluate the performance of automated segmentation by the Data Analysis Facilitation Suite (DAFS) in an independent dataset.
Methods: The current study used preoperative CT scans of patients who had undergone cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases or pseudomyxoma peritonei from appendicular origin (n = 165) from March 2014 to May 2019 at the Erasmus MC Cancer Institute, Rotterdam, Netherlands. Manual and automated measurements of skeletal muscle mass (SMM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intramuscular adipose tissue (IMAT) were performed at the third lumbar vertebra (L3). Segmentation accuracies of the automated measurements were evaluated based on their Jaccard index and intra-class correlation coefficients with the manual measurements.
Results: Median age was 64 years (IQR 55 – 71) and 50.3% of the patients were men. Automatic segmentation provided accurate measurements compared to manual analysis, as indicated by Jaccard scores coefficients of 97.9 for SMM, 98.4 for VAT, 99.1 for SAT, and 79.4 for IMAT. In accordance, intra-class correlation coefficients ranged from 0.98 to 1.00. The Bland-Altman plots (**Figure 1**) showed that automated measurements on average overestimated SMM and SAT areas compared to manual analysis, with mean differences (±2 standard deviations) of 1.10 cm^2 (-1.91, 4.11) and 1.61 cm^2 (-2.26, 5.48) respectively. For VAT and IMAT, automated measurements on average underestimated the areas with mean differences of -1.24 cm^2 (-3.35, 0.87) and -0.93 cm^2 (-5.20, 3.35), respectively.
Conclusions: The current study showed that the commercially available DAFS software provides similar results compared to manual measurements of body composition at the level of L3. This software provides accurate and time-efficient body

composition measurements, both of which are necessary for implementation in clinical practice. Cervical and thoracic measurements will be added shortly.

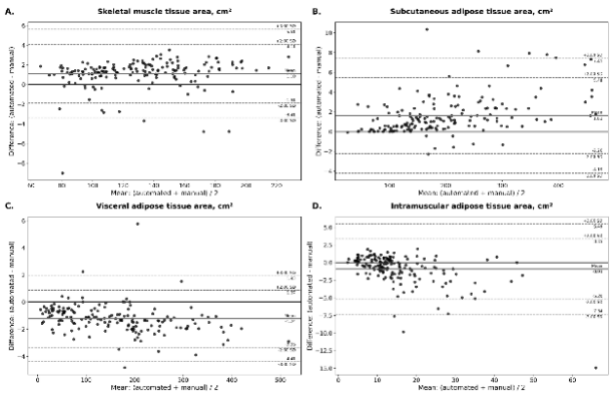

Figure 1: Bland–Altman plots depicting the agreement between automated (DAFS) and manual analysis of computed tomography scans for quantifying body composition parameters. The plots show the difference (y-axis) versus the average (x-axis) of automated and manual quantifications of skeletal muscle, subcutaneous adipose tissue, visceral adipose tissue, and intramuscular adipose tissue. The solid blue reference line indicates no difference between the manual and automated methods. The red dashed lines represent ±2 standard deviations (SD) of the difference, with limits of agreement ranging from 4.11 to -1.91 for muscle, 5.48 to -2.26 for subcutaneous adipose tissue, 0.87 to -3.35 for visceral adipose tissue, and 3.35 to -5.20 for intramuscular adipose tissue. The green dashed lines represent ±3 SD of the difference, with limits of agreement ranging from 5.61 to -3.41 for muscle, 7.41 to -4.19 for subcutaneous adipose tissue, 1.93 to -4.41 for visceral adipose tissue, and 5.49 to -7.34 for intramuscular adipose tissue. Mean differences were 1.10 for muscle, 1.61 for subcutaneous adipose tissue, -1.24 for visceral adipose tissue, and -0.93 for intramuscular adipose tissue.

3-25

Mosamatic: a user-friendly, web browser-based platform for automatic analysis of body composition using CT scans

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Background: Body composition assessment using abdominal computed tomography (CT) images is increasingly applied in clinical and translational research for assessing cachexia, sarcopenia, mortality risk, etc. Manual segmentation of body compartments on L3 CT images is time-consuming and requires significant expertise. Robust high-throughput automated segmentation is key to assessing large patient cohorts and, ultimately, to support implementation of body composition measures into routine clinical practice.
Methods: We trained a deep learning neural network (DLNN) on several clinical cohorts of various cancer types (>3400 patients) with expert-annotated ground truth images and performed external validation on another large independent cohort from a single center (>2500 patients).
To make the DLNN model more easily usable for clinical research both inside and outside our hospital, we designed and implemented a web browser-based platform called **Mosamatic.** This tool allows upload of thousands of L3 images at once and running body composition analysis on these images within hours. One image takes 1-2 seconds to process. Output can be downloaded as a single ZIP file and consists of:

- Original DICOM images
- Segmentations as NumPy arrays and PNG
- CSV file with, for each L3 image, (1) skeletal muscle area, (2) subcutaneous fat area, (3) visceral fat area, (4) skeletal muscle radiation attenuation, (5) subcutaneous fat radiation attenuation and (6) visceral fat radiation attenuation.

Results: Mosamatic was implemented in Python 3.9 and uses packages like Django, pydicom, TensorFlow, NumPy, Pandas, Redis and Django RQ. The application is wrapped inside a Docker container for easy deployment on any platform. The web interface of **Mosamatic** is shown in Figure 1. The web *site* for submitting requests to have your L3 CT images analyzed by us is www.mosamatic.com. Note this is *not* the URL of the web application.

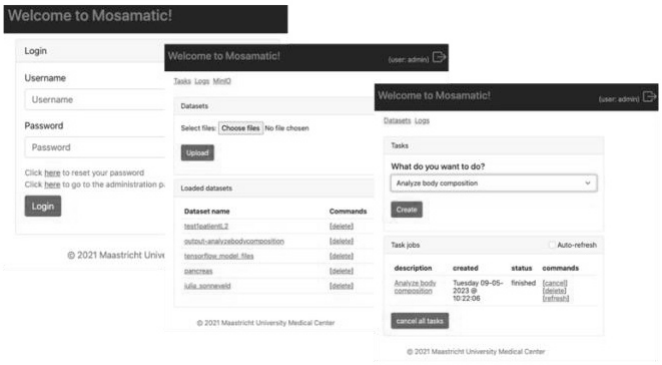

Figure 1: Login, datasets and tasks pages
The source code for the untrained AI model is publicly available here:
https://github.com/MaastrichtU-CDS/BodyCompL3_DLNN_Open_Code
The AI model has been externally validated as described in this pre-print:
https://doi.org/10.1101/2023.04.23.23288981
Conclusion: Mosamatic makes body composition analysis faster and more easily available. This will enable faster future implementation in clinical settings. We believe that body composition can have a major impact on treatment decisions in oncology applications. We encourage clinical researchers in the field to contact us and try out **Mosamatic**. For academic purposes the tool will be free of charge.

3-26

Using MRI to Measure Head Muscles: An Innovative Method for Opportunistically Determine Muscle Mass and Detect Sarcopenia

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¥ Shared last author

Background: Sarcopenia is associated with multiple negative outcomes. Traditional methods to determine low muscle mass for the diagnosis of sarcopenia are mainly based on Dual-energy X-ray absorptiometry (DXA), whole-body MRI and Bioelectrical Impedance Analysis. These tests are not always available and are rather time consuming and expensive. However, many brain and head diseases require taking a head MRI. Therefore, in this study, we aim to bring a more accessible way to detect sarcopenia by comparing the traditional method of DXA lean mass estimation vs. the tongue and the masseter muscle mass assessed in a standard brain MRI.
Methods: The H70 study is a longitudinal study of older people living in Gothenburg, Sweden. In this cross-sectional analysis, we included 791 participants, aged 70 year at baseline, with data and MRI images available. We used the appendicular lean soft tissue index (ALSTI) in DXA images as our reference measure of lean mass. Images from the masseter and tongue were analyzed and segmented using 3Dslicer. For the statistical analysis spearman correlation coefficient was used and concordance was estimated with the Kappa coefficient.
Results: The sample was constituted of 52.3% females. We found a significant correlation coefficient between both tongue 0.26 and masseter 0.33 with ALSTI $p<0.001$. Confirmed sarcopenia prevalence using the alternative muscle measure in MRI was *similar* to when calculated using ALSTI (*tongue= 2.0%, masseter= 2.2%, ALSTI= 2.4%).* Concordance between the different muscle measures with ALSTI as reference was close to 1 using both techniques.
Conclusion: ALSTI was significantly correlated with tongue and masseter muscle mass. In addition, when performing the sarcopenia diagnostic algorithm, the prevalence of sarcopenia calculated with head muscles did not differ from sarcopenia calculated using DXA and almost all participants were correctly classified using both methods.

3-27

Assessing the accuracy of estimating whole body SKM from L3 single slice and whole illiopsoas SKM

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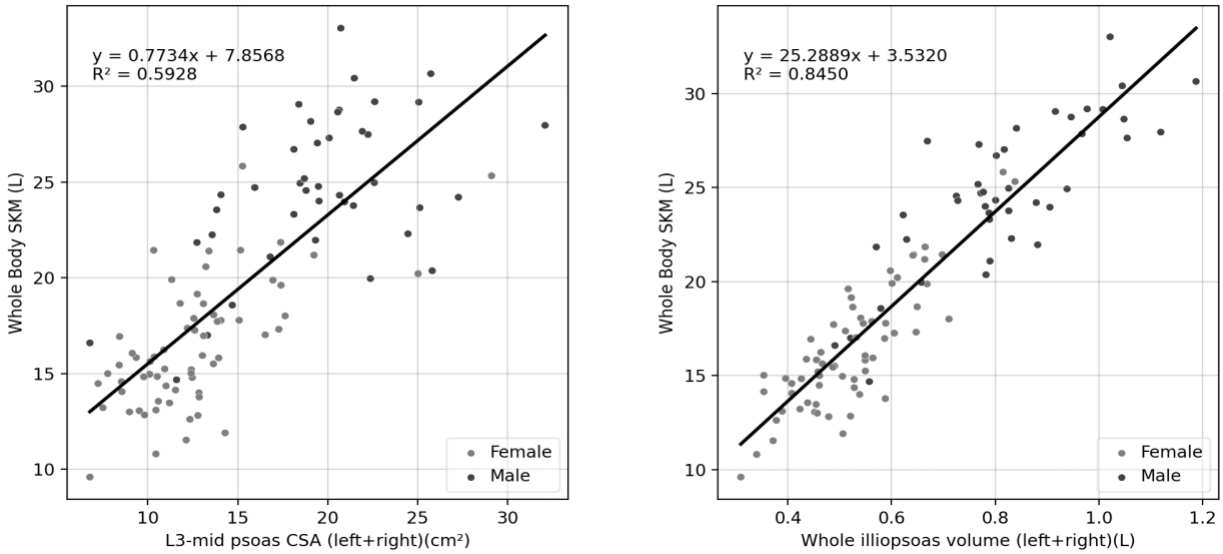
Introduction: Analysis of skeletal muscle (SKM) is important for assessing the presence of sarcopenia and has important ramifications in the oncology workflows for optimal intervention design for the individual patient. Since whole body computed tomography (CT) images are not routinely available, researchers have sought simpler proxy measurements, such as single-slice L3mid SKM cross-sectional area (CSA) [1], or the psoas muscle CSA at the L3mid level [2]. While regression-based analysis is accurate for group association studies as the group mean is preserved, of interest is if this regression-based approach can accurately estimate whole body measurements at the individual patient level measurements of the psoas. We hypothesize that multi-slice measurements of the psoas will be a better predictor of the whole body measurements compared to single-slice psoas CSA measurements, with larger multi-slice slabs offering increasingly more accurate estimation at the individual level.
Methods: From a whole body CT scan database, we measured SKM for the whole body as well as the entire illiopsoas muscle volume and psoas CSA at the L3mid slice for each individual whole body CT image. The non-contrast conventional dose scans of 106 patients (42 males, 64 females) analyzed were acquired on a Siemens Somatom CT at 100 KVP covering the full body, from head to toe, including the arms with axial resolution of 0.97x0.97x1.6mm for each scan. Average age was 65.94 ± 12.1 years for males and 66.26 ± 11.7 for females. A linear regression model was fitted between L3-mid, Lumbar, and whole body measurements.
Results: Figure 1 shows that single L3mid psoas CSA measurements and whole psoas volume measurements are correlated to whole body SKM measurements, with the correlation R^2 being higher for psoas volumetric measurements indicating stronger linear relationship, and reduced spread around the regression line for the volumetric measures, which decreases the ambiguity of estimating whole body measurements. Figure 2 shows the percentage error of estimating whole body SKM using L3mid psoas CSA within a regression

framework indicating errors from -29.37% to 58.87% with higher errors for females than males. For the whole illiopsoas measurement, the percentage of error computed using the regression line in Figure 1 shows lower errors in estimating whole body SKM as compared to using single-slice.

Conclusion: Psoas CSA at L3mid single-slice estimation of whole body SKM showed errors ranging up to 36.58% for males and 58.87% for females indicating that single-slice psoas CSA measurements may not be accurate enough for individual assessment. Assessment of whole iliopsoas muscle volume-based estimation of whole body SKM showed errors up to 25.55% for males and 37.25% for females, which are lower than single-slice based estimation. These findings have important implications for clinical research and practice, highlighting the need to carefully consider the selection of regions of interest when assessing body composition for individual patient assessment.

[1] Shen W et. al., Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333-8.
[2] Jones, K.I. et. al. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal disease*, 2015;*17*(1), pp. O20-O26.

Figure 1: Panel (a) shows the correlation between L3mid psoas cross-sectional area and whole body SKM volume. The correlation



coefficient of 0.59 shows medium correlation, and the spread shows considerable variability for the individual-level assessment based on regression. Panel (b) shows the correlation between whole psoas volume and whole body SKM volume with a larger correlation coefficient of 0.84 and reduced variability for individual-level assessment.

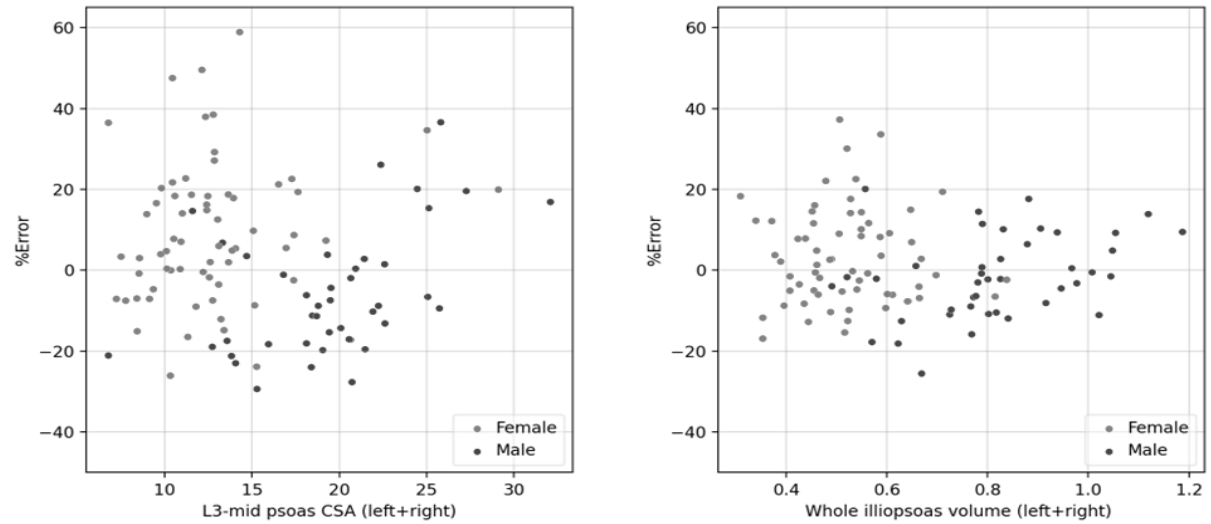


Figure 2: Panel (a) shows the percentage of error in estimating whole body SKM from regression-based prediction using L3-mid psoas cross-sectional area, and Panel (b) shows the error in estimating whole body SKM from whole illiopsoas volume. Overall reduction in error is observed when using whole illiopsoas volume as compared to single-slice cross-sectional area.

3-28

Is single-slice (L3mid) regression-based assessment of SKM, VAT, SAT accurate for individual patient level analysis?

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Introduction: Analysis of skeletal muscle (SKM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) is important for assessing the presence of sarcopenia or visceral obesity and has important ramifications in the oncology workflows for optimal intervention design for the individual patient. Since whole body computed tomography (CT) images are not routinely available, using a single-slice based assessment of body composition, typically at the L3mid level, is considered the established standard based on the high correlation of L3mid-based measurements and whole body measurements using linear regression [1]. While regression based analysis is accurate for group association studies as the group mean is preserved [1], of interest is if this regression-based approach can accurately estimate whole body measurements at the individual patient level. We hypothesize that multi-slice measurements will be a better predictor of the whole body measurements compared to single slice L3mid measurements, with larger multi-slice slabs offering increasingly more accurate estimation at the individual level.
Methods: From a whole body CT scan database, we measured SKM, VAT and SAT for the whole body as well as at a single L3mid slice and Lumbar (L1 - Sacrum) multi-slice slab for each individual whole body CT image. The non-contrast conventional dose scans of 106 patients (42 males, 64 females) analyzed were acquired on a Siemens Somatom CT at 100 KVP covering the full body, from head to toe, including the arms with axial resolution of 0.97x0.97x1.6mm for each scan. Average age was 65.94$\pm$12.1 years for males and 66.26$\pm$11.7 for females. A linear regression model was fit between L3-mid, Lumbar, and whole body measurements.
Results: Figure 1 shows that single L3mid and multi-slice L1-Sacrum SKM, VAT, SAT measurements are correlated to whole body measurements with the correlation R^2 being higher for multi-slice measurements indicating stronger linear relationship, and reduced spread around the regression line, which decreases the ambiguity of estimating whole body measurements from multi-slice measurements. Figure 2 shows the percentage error of estimating whole body SKM from the regression equation [1] indicating errors from -18.5% to 47.4% with higher errors for females than males. For the L1-Sacrum slab, the percentage of error computed using the regression line in Figure 1 shows lower errors in the range -21% to +22.1% in estimating whole body SKM as compared to using single-slice.
Conclusion: L3 single-slice based estimation of whole body SKM, VAT and SAT showed errors ranging from -18.5% to 47.4% for individual assessment indicating single-slice measurements may not be accurate enough for individual assessment. These findings have important implications for clinical research and practice, highlighting the need to carefully consider the selection of regions of interest when assessing body composition for individual patient assessment.

[1] Shen W et. al., Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333-8

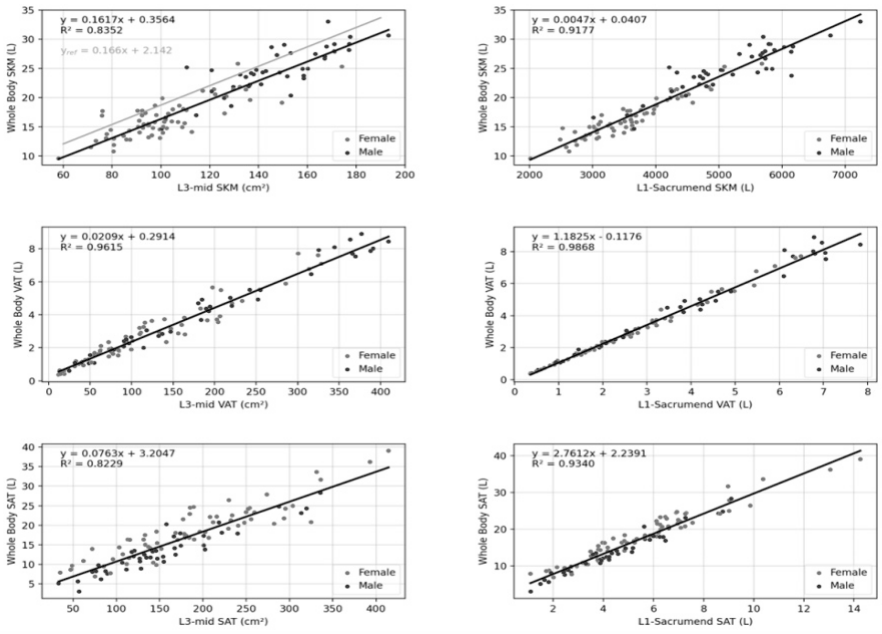

Figure 1: Correlation between whole body (y-axis) and 1) L3-mid, 2) L1-Sacrum end measurements for each of SKM, VAT and SAT body composition tissues showing that correlations are stronger when using a multi-slice slab (such as L1-Sacrum) as compared to single slice. The spread of points around the regression line is closer in the multi-slice slab L1-Sacrum field of view as compared to

single slice L3-mid based approach also showing that multi-slice measurements are better for individual assessment as compared to single-slice measurements. For the SKM L3-mid assessment, the orange regression line derived from 328 healthy individuals is taken from reference [1] as compared to the regression line in black derived from this cohort of older cancer patients showing sensitivity of regression approach to the particular age and disease status of individuals.

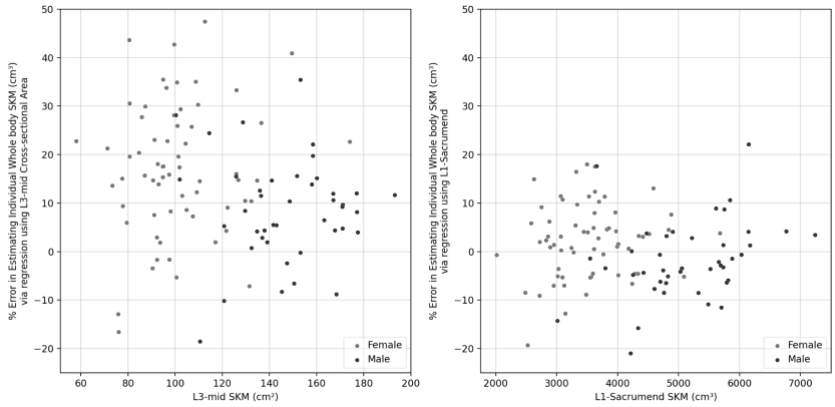

Figure 2: Left panel shows percentage error in estimating whole body SKM using regression based on L3-mid SKM cross-sectional area using the regression equation from reference [1] showing marked individual level errors in whole body SKM estimation. Right panel shows percentage error in estimating whole body SKM using regression based on L1-Sacrum multi-slice SKM volume showing lower errors for the individual patient in estimating whole body SKM.

3-29

Automated preoperative body composition may predict pancreatic fistula risk after whipple surgery

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Introduction: Postoperative pancreatic fistulas (POPF) pose a serious adverse risk for patients after Whipple surgery (pancreatoduodenectomy). Therefore, an accurate assessment of POPF risk is crucial for predicting recovery and ensuring positive postoperative outcomes. While conventional predictors of POPF risk include small pancreatic duct, soft pancreas, high-risk pathology, and excessive blood loss [1], recent evidence suggests that incorporating computed tomography (CT) imaging-based measures may better predict fistula risk scores [2]. Body composition measures, such as skeletal muscle (SKM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intramuscular adipose tissue (IMAT), reflect nutritional status and overall fitness level. We hypothesized that a lower proportion of muscle (i.e., SKM) and a higher proportion of body fat (i.e., VAT, SAT, and IMAT) are associated with an increased risk of POPF. Given the inherent sex-related differences in body composition, we further hypothesized a differential association between males and females.
Methods: The survey included 108 patients, with 57 males and 51 females, stratified in terms of having a higher risk of fistula (Fistula Risk+; Fistula risk score of 3 or above) or a lower risk of fistula (Fistula Risk-; risk score of 2 or below). Males in the Fistula Risk+ group had a mean age of 62, compared to 68 in the Fistula Risk- group. The corresponding values for females were 60 and 65, respectively. Using CT scans acquired prior to Whipple surgery, we measured SKM, VAT, SAT, and IMAT for the whole body. General linear models (GLM) were used to conduct the comparisons. Covariates included age and Charlson Comorbidity Index (CCI). GLM was fitted separately for Males and Females.
Results: For Males, significantly higher VAT (p=0.044), SAT (p=0.025), and IMAT (p=0.044) volumes were associated with higher fistula risk scores (Fistula Risk+). SKM volumes were similar between the Fistula risk groups. Associations between body composition and fistula risk were not observed in Females. See **Table 1**.
Conclusions: Males with higher risk for fistula were associated with higher body fat proportion (VAT, SAT, and IMAT), but not associated with higher muscle proportion (SKM). The lack of similar associations in Females suggests a potential sex-related effect that may stem from the different body composition between the sexes. Our findings suggest that automated CT-based markers of body composition may not only serve as a predictor of fistula risks, but also as a useful tool to investigate possible sex differences in outcome after pancreatic Whipple surgery.

***Table 1**: Metric values for SKM, VAT, SAT, and IMAT tissues in both males and females, as well as the t statistics and significance probability values for Fistula Risk groups (Fistula Risk+ vs. Fistula Risk-)*

	Metric* ± SD							
	Male (57)				**Female** (51)			
	Fistula Risk+	**Fistula Risk-**	**t-stat**	**p-value****	**Fistula Risk+**	**Fistula Risk-**	**t-stat**	**p-value****
Patients, (n)	29	28	—		12	39	—	
Age (Mean)	62.07 ± 9.35	68.04 ± 7.84	-2.61	**0.012**	59.83 ± 9.54	65.33 ± 9.25	-1.76	0.096
SKM	162.04 ± 20.52	153.32 ± 30.33	1.27	0.683	111.12 ± 16.94	108.27 ± 19.03	0.49	0.579
VAT	81.82 ± 35.36	67.41 ± 30.47	1.65	**0.044**	59.74 ± 38.59	51.51 ± 33.04	0.67	0.313
SAT	171.70 ± 102.73	129.37 ± 50.58	1.98	**0.025**	269.96 ± 136.77	202.02 ± 97.92	1.60	0.061
IMAT	27.86 ± 9.87	24.35 ± 9.00	1.40	**0.044**	28.32 ± 11.93	22.80 ± 9.20	1.48	0.050

* Metric = tissue volume [$(cm)^3$] / height [cm]
M:F (57:51)
** p-values represent GLM-based group comparison, adjusted for Fistula Risk Score groups (for *Age*, p-value is t-test based).

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3-30

Validation of a deep learning model for automatic segmentation of skeletal muscle and adipose tissue on L3 abdominal CT images

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Background: Body composition assessment using abdominal computed tomography (CT) images is increasingly applied in clinical and translational research. Manual segmentation of body compartments on L3 CT images is time-consuming and requires significant expertise. Robust high-throughput automated segmentation is key to assess large patient cohorts and ultimately, to support implementation into routine clinical practice. By training a deep learning neural network (DLNN) with several large trial cohorts and performing external validation on a large independent cohort, we aim to demonstrate the robust performance of our automatic body composition segmentation tool for future use in patients.

Methods: L3 CT images and expert-drawn segmentations of skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue of patients undergoing abdominal surgery were pooled (n = 3,187) to train a DLNN. The trained DLNN was then externally validated in a cohort with L3 CT images of patients with abdominal cancer (n = 2,535). Geometric agreement between automatic and manual segmentations was evaluated by computing two-dimensional Dice Similarity (DS). Agreement between manual and automatic annotations were quantitatively evaluated in the test set using Lin's Concordance Correlation Coefficient (CCC) and Bland-Altman's Limits of Agreement (LoA).

Results: The DLNN showed rapid improvement within the first 10,000 training steps and stopped improving after 38,000 steps. There was a strong concordance between automatic and manual segmentations with median DS for skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue of 0.97 (interquartile range, IQR: 0.95-0.98), 0.98 (IQR: 0.95-0.98), and 0.95 (IQR: 0.92-0.97), respectively. Concordance correlations were excellent: skeletal muscle 0.964 (0.959-0.968), visceral adipose tissue 0.998 (0.998-0.998), and subcutaneous adipose tissue 0.992 (0.991-0.993). Bland-Altman metrics (relative to approximate median values in parentheses) indicated only small and clinically insignificant systematic offsets : 0.23 HU (0.5%), 1.26 $cm^2.m^{-2}$ (2.8%), -1.02 $cm^2.m^{-2}$ (1.7%), and 3.24 $cm^2.m^{-2}$ (4.6%) for skeletal muscle average radiodensity, skeletal muscle index, visceral adipose tissue index, and subcutaneous adipose tissue index, respectively. Assuming the decision thresholds by Martin et al. for sarcopenia and low muscle radiation attenuation, results for sensitivity (0.99 and 0.98 respectively), specificity (0.87 and 0.98 respectively), and overall accuracy (0.93) were all excellent.

Conclusion: We developed and validated a deep learning model for automated analysis of body composition of patients with cancer. Due to the design of the DLNN, it can be easily implemented in various clinical infrastructures and used by other research groups to assess cancer patient cohorts or develop new models in other fields.

4-01

Involvement of the CXCR4/CXCL12 axis in skeletal muscle dysfunction in an early murine model of COPD

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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a vastly prevalent respiratory disease, currently the third leading cause of death, and is now considered as a systemic inflammatory disease. Sarcopenia affects up to 35% of the patients and increases mortality up to ten-fold. However, no effective treatment is available to date and triggering pathophysiological mechanisms remain unclear. The implication of the CXCL12/CXCR4 axis has been suggested in COPD development. We aimed here at studying its role in COPD skeletal muscle dysfunction.
Methods: We developped a murine model of early-phase COPD by exposing C57BL/6 mice for ten weeks to cigarette smoke (CS) and intranasal instillations of poly-IC to mimick exacerbations, thereby leading to bronchial obstruction, peri-bronchial fibrosis and right ventricle thickening (Dupin et al, submitted). A conditional inactivation of CXCR4 was also generated via a tamoxifen-inducible Cre/Lox system in CS and poly-IC-exposed mice. Skeletal muscle function was assessed using the grip test (muscle force) and the hanging test (muscle endurance), and skeletal muscle tissues were harvested for histological and proteomic analysis.
Results: There was no difference in muscle mass or muscle force between control and exposed mice, underlying the absence of sarcopenia features in this early-phase model. However, we evidenced a decreased endurance in exposed mice, which was not present in CXCR4$^{-/-}$ exposed mice (Fig. 1A). In agreement, the proportion of type IIx glycolytic myofibres was significantly increased in the Soleus of exposed mice, and was similar to controls in CXCR4$^{-/-}$ exposed mice (Fig. 1B). Capillarization was unchanged between the three groups. However, we evidenced moderately increased inflammation in Soleus muscle, evidences of moderate hypoxia, as well as indirect evidences of neuromuscular junction (NMJ) degeneration in exposed mice. Proteomic analysis evidenced inversely regulated contractile and inflammatory pathways in exposed mice and CXCR4$^{-/-}$ exposed mice, as well as an increase in mitochondrial proteins (Fig. 1C).
Conclusion: Decreased endurance linked to increased glycolytic myofibres proportion might be the initial event preceeding sarcopenia in COPD, and is prevented by CXCR4 deletion. The fiber-type switch is likely to be multifactorial and linked both to inflammation, NMJ degeneration and hypoxia, which might initially be compensated by an increased in mitochondrial proteins. These results provide a framework to study the CXCL12/CXCR4 axis and implicated cells in COPD early skeletal muscle dysfunction.

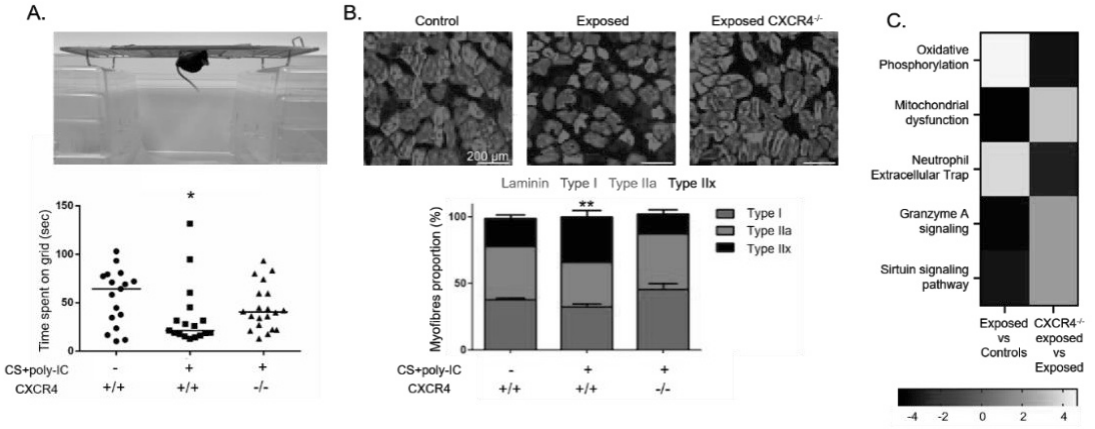

Figure 1: Murine model of early-phase COPD evidences decreased endurance, increased type IIx myofibres proportion in Soleus, and dysregulated mitochondrial and inflammatory pathways in Soleus muscle of exposed mice, which are normalized in CXCR4-/- exposed mice (n= 18 mice per group). A : Hanging test performed 9 ½ weeks after the beginning of the exposition protocol. B. Immunohistological staining for laminin, (blue), MHC1 (purple), MHCIIa (red). MHCIIx-positive fibres are identified as unstained fibres. C. Comparison analysis for global proteomic analysis of Soleus muscle. Negative Z-scores are indicated in dark colors and positive Z-scores in light colors.

4-02

A novel *in vitro* model of senescent murine myoblasts and sarcopenic myotubes to highlight skeletal muscle involvement in the aging phenotype

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Introduction: Although impairment of muscle mass and strength almost invariably features the human aging phenotype, availability of *in vitro* models of skeletal muscle senescence is limited and, where available, these models recapitulate only a restricted panel of phenotypic features of the senescent cells *in vivo*. Further, no studies have defined the role of muscle-bone cross-talk in the aging of the muscle-skeletal apparatus. With this work, we aimed at developing a new *in vitro* model of senescent myoblasts and sarcopenic-like myotubes to be used for the identification of biomarkers associated with sarcopenia that concurred to muscle-skeletal frailty phenotype of the elderly.
Methods: C2C12 mouse myoblasts were treated for 72h with 0µM, 0.4µM, 1µM and 2µM SYUIQ-5, an inhibitor of telomerase

activity. Senescent myoblasts were differentiated into myotubes for 4 and 7 days by supplementing the medium with horse serum (2%). The senescent phenotype of myoblasts and myotubes was characterized. Then, MC3T3 murine pre-osteoblasts were differentiated for 14 days, in presence or not of conditioned media derived from senescent myoblasts, and the osteogenic differentiation potential was analyzed.

Results: 2μM SYUIQ-5 treatment resulted cytotoxic for myoblasts, while increasing concentration of SYUIQ-5 significantly decreased myoblasts proliferation. 1μM SYUIQ-5 for 72h induced the expression of the typical hallmarks of senescence in myoblasts: enhanced expression of p21 transcript and protein, enhanced p53 and histone H2AX phosphorylation (γ-H2AX), accumulation of nuclear foci enriched in γ-H2AX, upregulation of senescence-associated β-galactosidase (SA-βgal) activity.

Confocal microscopy analysis revealed the impaired potential of senescent myoblasts to differentiate into myotubes and these resulting cells showed typical features of sarcopenic myotubes: downregulation of myosin heavy chain (MYHC), upregulation of MurF1 and atrogin, two markers of muscle catabolism, and reduced mitochondria content.

Supernatants from sarcopenic-like myotubes were enriched in myostatin, muscle growth inhibitor, and impoverished of osteoprotegerin, inhibitor of osteoclasts differentiation, as muscle-specific hallmarks of the senescence-associated secretory phenotype (SASP).

Finally, preliminary experiments showed that the osteoblastic differentiation of murine pre-osteoblasts cultured with conditioned media of senescent murine myoblasts was impaired.

Conclusions: Here we describe an *in vitro* model of senescent murine myoblasts recapitulating the main hallmarks of senescence and myotubes expressing a sarcopenic phenotype. Our model can be useful in future studies aimed at identifying the molecular mechanisms of muscle senescence and at finding out SASP markers with relevant roles in bone-muscle cross-talk during aging.

4-03

The effect of Doxorubicin on skeletal muscle mass and myokine expression in Lewis Lung Cancer bearing mice

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Introduction: Cancer cachexia is characterised by severe skeletal muscle mass loss. Chemotherapeutic treatment with Doxorubicin (DOX) worsens skeletal muscle mass loss but the underlying mechanisms through which DOX exerts its catabolic effect remain incompletely understood. Moreover, the role of myokines, secreted by skeletal muscle and involved in muscle homeostasis, is unknown. We examined the effect of DOX on myokine expression and pathways regulating skeletal muscle protein degradation in a Lewis Lung Carcinoma (LLC) mice model.

Methods: Sixteen 9 week-old C57BL6/J male mice were divided into: 1) Control, 2) LLC and 3) LLC receiving DOX groups. LLC mice were subcutaneously injected with $5x10^5$ LLC cells into the flank. DOX was administered intraperitoneally (2x/week 2.5 mg/kg) up to a cumulative dose of 10 mg/kg. Twenty-one days after tumour inoculation, mice were euthanized and the extensor digitorum longus (EDL), soleus (SOL) and gastrocnemius (GAS) muscle were collected. Myokine expression of myostatin, decorin and irisin and key proteins of skeletal muscle proteolysis (FOXO3a, MURF-1 and Atrogin-1) were evaluated by Western blotting. Differences between groups were considered significant if p<0,05(*).

Results: DOX-treated LLC mice showed a non-significant decrease in body weight that could be partly attributed to skeletal muscle mass loss, as shown by lower muscle/body weight ratios for GAS* and EDL. As anticipated, DOX treated mice developed smaller tumours (-35% tumour volume and weight). Interestingly, expression levels of myostatin*, FOXO3a*, MURF-1* and Atrogin-1* in the EDL were found to be increased in DOX-treated LLC mice compared to control and/or LLC mice. Additionally, a decrease of decorin* in the EDL was found for both DOX-treated and untreated LLC mice. Irisin levels were unchanged. For the SOL no alterations in myokine expression and protein degradation were observed.

Conclusion: We show that DOX increases protein degradation despite its important therapeutic effect in tumour reduction, revealing an effect of DOX to muscle wasting observed with cancer. Moreover, altered expression of myokines are likely to contribute to the development of muscle wasting. Finally, the catabolic effect of DOX seems to be muscle type dependent.

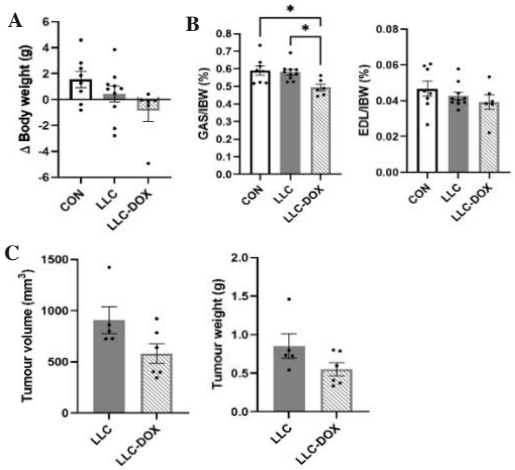

Figure 1: A) Body weight change, B) Muscle weight (g)/ initial body weight (g) ratios (%) for GAS and EDL and C) Tumour volume (mm³) and weight (g) 21 days after tumour inoculation. p<0.05 (*)

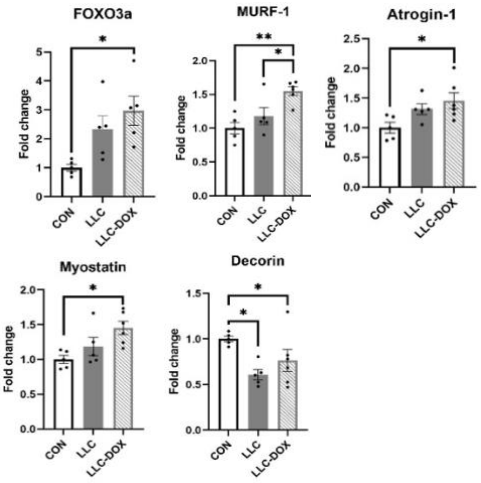

Figure 2: Western blot data represented in fold changes of normalised signals for the EDL. Markers of protein degradation (FOXO3a, MURF-1 and Atrogin-1) and myokines (myostatin and decorin) 21 days after

4-04

The Rho GTPase inhibitor, RhoGDIα is a negative regulator of muscle mass and upregulated in sarcopenic human muscle

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Introduction: Maintaining skeletal muscle mass is mandatory for upholding an independent lifestyle and muscle strength is inversely associated with all-cause mortality. Despite this, there are no clinically approved drugs to improve muscle growth and strength. Determining new molecular mechanisms regulating muscle mass would help identify new candidates for treatment. Rho GTPase signalling is one of the most regulated pathways in response to resistance exercise. Since resistance exercise potently increases muscle growth, Rho GTPases are exciting, yet, largely unexplored candidates for muscle mass control. Rho GTPases are promiscuously inhibited by the molecular chaperone Rho guanine nucleotide dissociation inhibitor α (RhoGDIα). By transgenically up- or down-regulating RhoGDIα muscle protein content (inhibiting or activating Rho GTPases, respectively), we investigated the role of Rho GTPases in muscle mass regulation and mechanisms of action.
Methods: RhoGDIα was overexpressed or knocked down specifically in the skeletal muscle of C57BL/6JBomTac mice after a single intramuscular injection using recombinant adeno-associated virus (rAAV)-mediated delivery of DNA or shRNA targeting RhoGDIα, respectively. Muscle mass was measured and by proteomic analysis and immunoblotting techniques, molecular markers of muscle wasting and hypertrophy were investigated. Human vastus lateralis muscle from healthy untrained young (age 20-30y), elderly (age 60-75y) and old, sarcopenic (age 83-94 y) men were analysed for RhoGDIα protein content.
Results: RhoGDIα overexpression reduced muscle mass (TA: -8%), while knockdown of RhoGDIα increased muscle mass (EDL: +20%, TA: +7-9%; Gast: +8%). Proteomics analyses revealed significant changes in the ubiquitin-proteasome system, which is involved in the regulation of skeletal muscle mass. Moreover, RhoGDIα overexpression-induced atrophy was associated with downregulation of the Hippo pathway-YAP/TAZ protein content with no changes in mTORC1 signalling. In contrast, RhoGDIα knockdown-induced hypertrophy was, despite reduced mTORC1 signalling and unchanged YAP/TAZ protein content, potentially partly explained by downregulated E3 ubiquitin ligase, MuRF1 protein content and autophagy indicator LC3-II protein content. Further suggesting a role for RhoGDIα in age-induced muscle wasting, RhoGDIα protein content was upregulated (+45%) in human skeletal muscle from old, sarcopenic patients and RhoGDIα protein content tended ($p = 0.0877$) to be negatively correlated with type II fibre cross-sectional area.
Conclusions: Altogether these data identify RhoGDIα as a negative regulator of muscle mass and possibly a mediator of age-induced muscle wasting. Accordingly, resolving the molecular mechanisms of RhoGDIα-induced muscle mass regulation can potentially provide novel pharmacological targets and therapeutic interventions, which are important because of the demographic evolution of an increasing proportion of elderly citizens.

4-05

ADAR2 deficiency alleviates muscle atrophy in HFD-induced obese mice

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Introduction/Background: Obesity is an extremely prevalent chronic disease that can induce metabolic syndrome and is associated with a more risk of muscular atrophy. Adenosine-to-inosine (A-to-I) editing, catalyzed by adenosine deaminase acting on RNA (ADAR), is an important post-transcriptional modification of genome-encoded RNA transcripts. Three fundamentally related members of ADAR family including ADAR1, ADAR2 and ADAR3 have been identified. In this study, we aim to investigate the role of ADAR2 in skeletal muscle atrophy.
Methods: $ADAR2^{+/+}$ (wild type, WT) and $ADAR2^{-/-}$ (ADAR2 KO) mice were subjected to feed with standard chow or high-fat-diet (HFD) for 20 weeks at the age of 5 weeks. Muscle mass, muscle strength, cross-sectional area, markers of protein synthesis/degradation, glucose/insulin tolerance were measured.
Results: ADAR2 KO alleviated the fasting blood glucose, insulin resistance and glucose intolerance in HFD-induced obese mice. ADAR2 KO increased muscle mass, muscle strength, and muscle endurance in HFD-induced obese mice. Muscle cross-sectional analysis of gastrocnemius revealed increases in fibre size distribution in ADAR2 KO mice fed with HFD. ADAR2 KO attenuates HFD-induced local skeletal muscle tissue Inflammation. Moreover, muscle atrophy-associated transcripts, such as FOXO1, MAFbx/atrogin-1, MuRF1/TRIM63, were decreased in ADAR2 KO mice fed with HFD compared to HFD-WT mice.
Conclusions: These results provide novel evidence that ADAR2 KO may mediate the protective effect of obesity-induced muscle wasting and weakness.

4-06

Urocortin 2 modulates muscle mass associated with insulin/IGF-1 signaling pathway stimulation in skeletal muscles of obese and denervated mice

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Introduction: Urocortin 2 (Ucn2) modulates skeletal muscle (SM) mass of rodents, however, the intracellular mechanisms responsible for these findings remained unclear. We have recently demonstrated that the hypertrophic effect promoted by Ucn2 *in vivo* was associated with a crosstalk, probably mediated by Epac, between urocortinergic canonic signaling pathway (cAMP/PKA/CREB) and insulin pathway (Akt/mTOR/S6; Akt/Foxo) in SM of normal mice. The objective

of this work is to investigate the effects of Ucn2 in SM in a model of insulin resistance induced by diet and also in an atrophic model induced by motor denervation.
Methods: C57Bl/6J male mice (8 weeks) received hyperlipidic diet (HL; 35% of lipids) for 3 months and to induce muscle atrophy, male mice (8 weeks) were surgically denervated (DEN). Using electroporation technique, empty vector (pcDNA3.1+) or Ucn2 plasmid was transfected *in vivo* into tibialis anterior (TA) muscles of obese (14 days before euthanasia) and 14-days-DEN mice (the transfection occurred in the same day of the denervation surgery). Then, TA were excised and processed to determine the expression of genes and proteins of interest. Protein synthesis was analyzed by the SUnSET method. Student's t-test was used to analyze data. Ethic committee approval: 063/2014.
Results: HL diet induces body gain mass, hyperglycemia, hyperinsulinemia and a tendency in decrease muscle mass indirectly measured by total protein content associated with a propensity in increase protein synthesis. HL diet reduces the phosphorylation levels of Akt (Ser473; Thr308), S6 (Ser235/236; Ser240/244) and FoxO1 (Ser256) and these effects were completed reverted by Ucn2 overexpression in TA of obese mice. Ucn2 in vivo reduced the protein expression of E3-ligases (atrogin and MuRF-1) in TA muscles of obese mice. In addition, HL diet decreases the protein content of LC3-II, an autophagy marker, and this effect were completed reverted by Ucn2 overexpression suggesting inhibition of lysosomal-autophagic proteolytic system. Ucn2 *in vivo* increased the protein expression of slow myosin heavy chain associated with an augmented in PGC1-α protein content in TA of obese mice. Unc2 partially reverted the atrophy induced by denervation measured by TA weight in DEN mice.
Conclusions: Ucn2 exerts its effects in SM of insulin resistant and atrophic models probably through insulin/IGF-1 signaling pathway stimulation. This research rises up new perspectives for the development of therapeutic strategies to protect muscle mass and also to cope with insulin resistance induced by HL diet.

4-07

Cyp27b1 ablation in skeletal muscle impairs muscle regeneration

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Introduction: Muscle regeneration involves various cellular and molecular mechanisms. Vitamin D is important in muscle function and repair. Cyp27b1 activates vitamin D into 1,25-dihydroxyvitamin-D3 inside mitochondrial inner membrane, which promotes muscle contraction velocity and strength. (Girgis, Clifton-Bligh, Hamrick, Holick, & Gunton, 2013). The local effects of cyp27b1 in muscle and extra-renal activation of vitamin D are not well understood. Global knockout cyp27b1 mice results in decreased muscle mass due to increased oxidative stress (Yu et al., 2021). Understanding the relationship between cyp27b1 and mitochondrial function may provide insights into underlying mechanisms of muscle degeneration.
Method: In vivo cyp27b1 knockdown was induced in male cyp27b1 floxed mice (3.5 months old) via bilateral gastrocnemius (GAS) intra-muscular injection of AAV9-CMV-CRE-GFP virus (100 ul, 2 x 10^12 vg/ml). After 10 days, GAS was collected for fiber type analysis, ex vivo functional testing, and qPCR. (n=3). Muscle injury was induced via I.M. injection of BaCl2 (1.2% w/v, 50 µl) in bilateral gastrocnemius 10 days after virus injection and observed for 7 days to evaluate muscle regeneration by H&E staining and qPCR. C2C12 myoblasts was used in loss-of-function and gain-of-function studies (n=3). One-way ANOVA and two-way ANOVA were used for the animal and cellular studies, respectively. The level of significance was set at $P<0.05$.
Results: In vivo knockdown of cyp27b1 reach up to 90% efficiency by qPCR. The knockdown resulted in significant changes in muscle fiber type distribution, i.e., type I (WT: 0.36%; KD 11.9%) and type IIA (WT: 23.5 %; KD: 46.4%) /IIB (WT: 76%; KD: 41.6%) and decrease in muscle force, specifically reduction in specific twitch force (-16%) and specific tetanic force (-29%). KD group showed lower mitochondrial biogenesis marker expression than the control, as indicated by qPCR and western blot. Following injury, there was decreased gene expression related to muscle regeneration and mitochondria biogenesis, delayed regeneration and increased immune cell infiltration were also observed. Cyp27b1 knockdown in C2C12 suppressed myogenic and mitochondrial biogenesis marker expression and proliferation, while overexpression had the opposite effect.
Discussion: Our findings suggest cyp27b1 plays a critical role in muscle regeneration after injury, likely due to its extra-renal effect on vitamin D metabolism in muscle tissues. The findings suggest potential for developing new therapeutic strategies for treating muscle damage, including the discovery of novel Cyp27b1 activators that could extend to other muscular disorders.

Reference:
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4-08

Role of mechanosensitive components in the regulation of myogenic differentiation

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Introduction: Mechanosensors are a class of proteins, capable of sensing mechanical forces and transmitting signals

to the cytosol and nucleus, initiating changes in gene expression and other cellular processes. In muscle cells, these mechanosensors are potentially not only important in response to mechanical loading/unloading but also during differentiation and regeneration. A critical role is attributed to the mechanosensitive integrins, a family of transmembrane receptors that provide the interaction between the extracellular matrix and the cytoskeleton. Processes of integrin activity, clustering and signaling are regulated by various cytoplasmic proteins including integrin-linked-kinase-1 (*Ilk1* gene) and kindlin2 (*Fermt2* gene). This study aims to enhance understanding of the role of Ilk1 and Kindlin2/Fermt2 during mouse muscle cell differentiation.
Methods: Mouse myoblast C2C12 cells were transduced by lentiviral vectors expressing microRNA-based shRNA (miR) targeting *Ilk1* or *Fermt2.* miR-*fLuc* was used as control. Differentiation medium (DMEM, 2% horse serum, 1% Pen-Strep) was added to transduced cells at 90% confluency in 6-well plates. At start and 1, 3, 5, and 7 days after differentiation initiation, cells were stained for DAPI and MyHC to determine myoblast fusion index (number of nuclei inside myotubes divided by total number of nuclei). Knockdown efficiency and mRNA expression of differentiation markers (*Pax7*, *MyoD*, *MyoG*, *Myh1, Acta1*) and mechanosensory components (*Ilk1*, *Fermt2*, *Itgb1*, *Itga7*) were evaluated by qPCR. All measurements were done in triplicates.
Results: Lentiviral delivery of *Ilk1* miR caused a stable 10-fold knockdown ($p<0.0001$) of *Ilk1* expression and reduced myotube differentiation with a 3-fold-lower fusion-index at day 7 ($p<0.001$) relative to miR-*fLuc*. *Ilk1* knockdown elevated expression of myogenic differentiation markers *Pax7*, *MyoD*, *MyoG, and Acta1* at D0 ($p\leq0.0001$), but the differentiation-induced further increase was blunted ($p\leq0.0001$ at D7). Increased expression of *Itga7* was similarly blunted throughout differentiation ($p\leq0.01$), whereas *Itgb1* or *Fermt2* were not affected by differentiation or *Ilk1* knockdown. In contrast, in *Fermt2*-KD cells, *Fermt2* expression rapidly increased from a 1.45-fold reduction ($p<0.0001$) at differentiation initiation reaching similar expression levels as controls from D1 onwards. Differentiation markers were not affected, but both *Ilk1* and *Itga7* expression increased with *Fermt2* knockdown.
Conclusions: The mechanosensing components *Ilk1* and *Itga7* are affected in myogenic differentiation in C2C12 cells. Whether the lack of effect of *Fermt2* knockdown on myogenic differentiation was due to its upregulation during differentiation or to compensatory upregulation of *Ilk1* and *Itga7* has to be further investigated.

4-09

MRI-based characterization of muscles in ageing mice fed on high-energy diet and sedentary lifestyle

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Introduction: The investigation of age-induced alterations in humans is time consuming and resource intensive. *One important* question for the evaluation of ageing is how similar changes over a lifetime are between humans and mice. Our primary goal was to assess leg muscle's trophicity and structure based on Magnetic Resonance Imaging (MRI) and function in a cohort of mice exposed to a high-energy diet and a sedentary lifestyle.
Methods: In this preliminary longitudinal study, C57Bl/6JRj male mice were used, fed ad libidum with high-energy diet (Safe®; EM Pig 3237 kcal/kg). 10 mice were scanned on a 7T MRI Bruker system with a surface cryoprobe positioned next to the Tibialis anterior (TA) muscle from 2.5 to 22 months of age (m). The MRI study included high-resolution anatomical images and T2 maps to evaluate muscle cross-sectional area (CSA) and muscle T2, respectively. Muscle strength was evaluated at 4.5, 12 and 19 m by a grip test. ANOVA and t-test were used to analyze MRI and functional data, respectively (p-value<0.05 for statistical significance).
Results: A Kaplan-Meier curve pointed out an increased mortality in our cohort with a survivorship of 50% around 20 m unlike data commonly reported for this strain. In parallel, mice body weight (g) increased in a normal range with age (2.5m: 26.9±2.1; 22m: 33.0 ± 2.5).
Grip tests emphasized a negative effect of age on force with a significant decrease of the maximal force normalized by BW (g/g) between 4.5 and 12 m (4.5m: 7.2±1.35; 12m: 5.2±1; $p<0.05$). Mean CSA (mm²) of TA tended to increase until 9 m then decreased with age (2.5m: 7.6±0.4; 9 m: 8±0.4; 12 m: 7.6±0.3; $p=0.069$). Finally, muscle T2 increased with age ($p<0.05$) mainly during growth.
Conclusions: High-energy diet and sedentary lifestyle have negative effects on life expectancy that could not be linked in our study to overweight as BW increased in a normal range with age. Additional individuals are necessary to investigate if the loss of muscle function after growth is due to muscle wasting and/or to changing in muscle tissue structure as T2, related to inflammation and muscle architecture, is increased with age. C57Bl/6 mice may represent a well-suited model to explore ageing and muscle wasting.

4-10

MR-based characterization of aging in human muscles

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Introduction: The typical adult will lose muscle mass with age; the loss varies according to sex and the level of muscle activity. Our primary goal was to assess leg muscle's trophicity, structure, function and biochemistry based on quantitative MR examination in a prospective open label study to benchmark various outcome measures.
Methods: Inclusion criteria were based on clinical screening, absence of any chronic disorder, age > 20 years. Physical activity assessment, grip test, gait speed were evaluated. 3T MRI scanner, homemade amagnetic ergometer and a standardized exercise protocol for plantar flexion were used. Cross sectional area, fat fraction and water T2 were measured. Interleaved MR sequences were developed to assess perfusion; BOLD-effect used deoxygenated hemoglobin as endogenous contrast; deoxymyoglobin (dMb) provided a means to monitor the oxygenation state of muscle. Descriptive statistics express results as mean ± SEM. Group comparison was based on T test and ANOVA.
Results: We present preliminary results on N = 61, aged 20 to 81 years, M/F ratio: 31:30. Volunteers were stratified as young (>35yo; N: 15), middle-aged (35-60yo; N: 25) and elderly (>60yo; N: 18). Of our cohort, 84% were either active or very active. Handgrip strength normalized by BMI changed only marginally over time. Gait speed normalized by height slightly decreased. Maximum plantar flexion force normalized by height did not change significantly.
Cross-sectional areas of *triceps surae* barely changed with age. Intramuscular fat fraction increased with age (0.11 ± 0.03; 0.16 ± 0.04; 0.19 ± 0.04, respectively). Intrinsic T2 values (ms) increased with age (36.5± 1.6; 37.3 ± 1.9; 38.8 ± 1.5, respectively).
Exercise induced most significant increase in the *gastrocnemius* muscles. Relative increase of perfusion was most important in mild-aged individuals. Increase in workload induced a raise in T2*, mostly in the gastrocnemius muscles, mainly in younger individuals. Whereas, dMb showed higher values at work in elderly people.
Conclusions: NMR provides interesting tools to assess not only structural aspects of the aging muscles, but our innovative

set-up allows to investigate functional and biochemical aspects also. Fatty infiltration of skeletal muscles appears to increase with age, as do T2 values. The dynamic range of blood perfusion rate in skeletal muscle is significantly higher than in any other organ. Adjustments occur as age progresses and can be monitored non-invasively. Regular activity seems to preserve muscle mass and function, but more subtle changes can be observed by MRI.

4-12

Long-term musculoskeletal consequences of chemotherapy in pediatric mice

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Introduction: Thanks to the recent progress in cancer research, nowadays most children treated for cancer survive into adulthood. Nevertheless, little is known about the long-term consequences of anticancer agents, especially in the pediatric population. We and others have shown that routinely administered chemotherapeutics can drive musculoskeletal alterations consistent with loss of muscle mass and strength, as well as bone decay, which altogether contribute to increased treatment-related toxicity and long-term morbidity and negatively impair cancer survival. Yet, the mechanisms responsible for enduring muscle and bone defects following anticancer treatments and whether these can potentially impact growth and quality of life in young individuals remain to be elucidated. Here, we aimed at investigating the late musculoskeletal effects of Folfiri, a chemotherapy regimen which we previously extensively characterized, in pediatric mice.
Methods: Three-week-old male C57BL6/J mice were administered Folfiri (5-FU, leucovorin, irinotecan; n=10) or vehicle (n=5) intraperitoneally for up to 5 weeks and followed up for up to 4 weeks after cessation of the treatment. Body composition, plantarflexion force and EMG were assessed at baseline and at regular intervals. At time of sacrifice, skeletal muscle, bones and other tissues were collected, processed and stored for further analyses.
Results: Body weight gain was significantly delayed in the mice receiving chemotherapy, resulting in progressively lower carcass weight at sacrifice, diminished lean and fat mass, as well as significantly smaller skeletal muscles. Consistently, muscle function was progressively impaired in the mice exposed to chemotherapy. BMC and BMD were also reduced upon 5 weeks of treatment with Folfiri, in line with loss of trabecular bone. Interestingly, 4 weeks after cessation of the treatment, the animals exposed to chemotherapy showed persistent musculoskeletal defects, consistent with lower bone mass, decreased lean and fat content and reduced muscle weights and function, in agreement with reduced levels of muscle mitochondrial proteins.
Conclusions: Our data supports the idea that anticancer treatments may lead to long-lasting musculoskeletal complications in actively growing pediatric mice. Further studies are needed to determine the mechanisms responsible for these complications, so that new therapies to prevent or diminish chemotherapy-related toxicities can be identified.

4-13

Extracellular vesicles are possible mediators of the liver-muscle axis in sarcopenia associated to liver disease

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Introduction: A loss of muscle mass and strength, referred as sarcopenia, is a condition highly prevalent in patients with chronic liver disease (CLD), in particular in alcoholic (ALD) patients. Although many factors contributing to skeletal muscle loss have been identified, mechanisms underlying sarcopenia in chronic liver diseases are still not completely understood as the mediators of the liver-muscle axis are not yet known.
As hepatic cells in pathological conditions, especially in ALD, release in circulation a large number of extracellular vesicles (EVs) and these have a key role in crosstalk between liver and other metabolic organs, including skeletal muscle, we aimed to investigate whether circulating EVs could induce muscle atrophy, mediating sarcopenia in liver disease.
Methods: C_2C_{12} cell culture were exposed to EVs isolated from serum of a mouse model of ALD, obtained feeding mice for 2 months with Lieber-De Carli *5*% (v/v) ethanol diet, and compared with cell culture exposed to EVs derived from control diet (CD)- mice. First, C_2C_{12} cells were examined for ability to uptake circulating EVs, exposing them with PK26-stained serum EVs; then, C_2C_{12} cell culture, treated with EVs isolated from ALD- and CD- mice, were analyzed on 2th and 6th day in differentiation medium for their capacity to fuse, differentiate and activate muscle synthetic or catabolic processes. Finally, to verify hepatic origin of circulating EVs, we isolated extracellular vesicles directly from liver tissue, investigating whether they affect C_2C_{12} cell culture similarly to serum-derived EVs.
Results: We demonstrated, by confocal fluorescence analysis, that circulating EVs were efficiently internalized by C_2C_{12} cells and myotubes. Moreover, ALD mice-derived EVs, in comparison with EVs isolated from CD mice, were able to cause *in vitro* muscle atrophy, inducing a decrease in muscle differentiation and in anabolic process accompanied by an increase in protein degradation: this was revealed by a reduced area and length of myotubes, downregulated expression of myogenin and myosin, decreased phosphorylation of Akt and mTOR, that are relevant markers of muscle protein synthesis, and upregulated mRNA expression of the muscle-specific atrophy-related markers MuRF1 and atrogin1. Similar effects were observed with EVs isolated from liver, suggesting a hepatic origin of the circulating EVs contributing to muscle atrophy.
Conclusions: Circulating and liver tissue-derived EVs in CLD could induce muscle atrophy, suggesting their role as mediators of the liver-muscle axis in sarcopenia associated to liver disease.

4-14

Skeletal muscle transcriptional dysregulation of genes involved in senescence is associated with prognosis in severe heart failure

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Introduction: The skeletal muscle hypothesis refers to a vicious cycle of successive deterioration of left ventricular function, skeletal muscle remodeling, and functional capacity in

patients with heart failure. The mechanisms involved in these processes in skeletal muscle are still largely unclear.
Methods: In the present study, a coexpression network was constructed based on RNA sequencing of muscle samples from 66 patients with severe symptomatic heart failure with reduced ejection fraction (NYHA III-IV, left ventricular ejection fraction ≤ 30%). A transcriptomic network was defined in skeletal muscle and validated in two independent cohorts.
Results: The final network consists of 14 communities with transcripts involved in well-established biological processes in human skeletal muscle. Compared with age-matched controls and consistent with the known skeletal muscle phenotype in heart failure, lower expression was observed for communities related to mitochondrial beta-oxidation, extracellular matrix remodeling, oxidative phosphorylation, and contractile elements. Several earlier suggested external stimuli and biological processes in the skeletal hypothesis was shown to influence network expression in the skeletal muscle hypothesis, but to different degrees, suggesting differential importance. By correlating with clinical features and prognosis, three network communities (extracellular matrix remodeling, fatty acid beta-oxidation, and p53 signaling) were identified as plausible key processes, with the latter two also having prognostic potential shown by a significant, independent association with mortality.
Discussion: The strongest association to mortality was the p53-signaling community. This community was, in contrast to the other network communities, upregulated in HF patients compared with controls, and higher expression was associated with worse prognosis. The p53 signaling community was enriched for genes associated with senescence but not physical activity, bed rest, or cancer cachexia. This indicates that altered cell-cycle control at the skeletal muscle level is a process of prognostic relevance and that is not primarily influenced by physical inactivity, general deconditioning or negative energy balance. The significant enrichment of genes associated with cellular senescence, together with the strong correlation with mortality in the current study, seem to indicate that cell senescence in skeletal muscle is involved in the pathophysiology of HF and that this dysregulation is also of significant prognostic importance.

4-15

Cachexia, sarcopenia and bone markers in patients with heart failure and hyperkalemia: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Introduction: Comorbidities in heart failure (HF) have a major impact on prognosis. Hyperkalemia (usually defined as serum potassium >5 mmol/L) is most prevalent in patients with diabetes mellitus, chronic kidney disease and in those taking inhibitors of the renin-angiotensin-aldosterone system. Patients with HF also present with cachexia, sarcopenia and have lower bone mineral density (BMD). The role of several regulators of bone remodeling, such as receptor activator of nuclear factor κB ligand (RANKL), osteoprotegerin and sclerostin in HF is not yet fully understood. We aimed to assess bone status, weight loss and muscle wasting in patients with HF and hyperkalemia.
Methods: A total of 266 patients from SICA-HF with available baseline potassium measurements were retrospectively included in this analysis. Study subjects were divided into two groups according to potassium levels < or ≥5 mmol/L. Dual energy X-ray absorptiometry was used to evaluate BMD and body composition. Cachexia was defined as weight loss ≥5% over a 1-year period. Sarcopenia was defined as appendicular skeletal muscle mass index <7.26 kg/m^2 in males and <5.45 kg/m^2 in females.
Results: Patients with hyperkalemia were more symptomatic (54 *vs*. 37% with NYHA class III-IV, p=0.037) and were more likely to have diabetes (58 *vs*. 38%, p=0.016) and an estimated glomerular filtration rate <60 mL/min/1.73m^2 (73 *vs*. 30%, p<0.001). No differences could be seen regarding cachexia and sarcopenia between the two groups. Interestingly, patients with HF and hyperkalemia had increased levels of osteoprotegerin (5.8 *vs.* 4.7 pmol/L, p=0.009) and sclerostin (92 *vs*. 74 pmol/L p=0.022), lower levels of RANKL (5920 *vs*. 20200 pg/mL, p=0.006) and higher total body BMD (1.25±0.11 *vs*. 1.21±0.12 g/cm^2, p=0.027) and Z-score (the number of standard deviations away from the mean total body BMD of a healthy person of same age and sex, 0.79±1.41 *vs*. 0.36±1.27, p=0.045). Using univariate logistic regression, osteoprotegerin (OR 1.218 95% CI [1.036-1.433], p=0.017), sclerostin (OR 1.014 95% CI [1.003-1.025], p=0.014), RANKL (OR 0.6 95% CI [0.388-0.928], p=0.022) and total body BMD (OR 1.455 95% CI [1.039-2.036], p=0.029) were all associated with hyperkalemia. In the multivariate model, osteoprotegerin and total body BMD remained as independent predictors of hyperkalemia (adjusted OR 1.305, 95% CI [1.058-1.610], p=0.013; adjusted OR 1.792, 95% CI [1.105-2.905], p=0.018, respectively).
Conclusions: We found an association between higher total body BMD and hyperkalemia in patients with HF. More data on the link between bone status and potassium levels are needed.

4-16

Low serum creatinine to cystatin C ratio predicts injurious falls in older men – the prospective STRAMBO study

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Introduction: Low muscle mass assessed by D3-creatine dilution predicts falls in men *(Cawthon, J Gerontol, 2019)*, but this method is poorly available. Appendicular lean mass (ALM) measured by dual energy X-ray absorptiometry is more available, but low ALM does not predict falls *(Harvey, J Bone Miner Res, 2021)*. We assessed the value of the serum creatinine/cystatin C (Cr/CysC) ratio, easily available surrogate of muscle mass, for the prediction of injurious falls in older men.
Methods: A cohort of 825 men aged 60-87 yr was followed prospectively for 12 years. Among them, 796 men had assays of baseline serum creatinine and cystatin C and at least one year of follow-up. Injurious falls were defined as falls (unintentionally coming to rest on a lower surface) requiring hospitalisation (one night or more). Extrinsic falls (vehicle accident) and falls from the height (>1m) were excluded. Physical function was assessed using a score combining chair stands and tests of static and dynamic balance *(Szulc, J Bone Miner Res, 2009)*.
Results: During the follow-up, 103 men had injurious falls. After adjustment for age, BMI, leisure physical activity, prior fractures and falls, diabetes mellitus, blood pressure, and C-reactive protein, low Cr/CysC ratio predicted injurious falls (HR=1.59/SD, 95%CI: 1.24–1.98, p<0.001). The link persisted after further adjustment for the physical function score (HR=1.53/SD, 95%CI: 1.21–1.94, p<0.001). In the multivariable model, the risk of injurious fall increased with decreasing Cr/CysC quartiles (trend p<0.005) and was higher in the lowest (<1.21) vs. the highest (>1.54) quartile (HR=2.35, 95%CI: 1.27–

4.33, p<0.01). The link persisted after further adjustment for the physical function score (HR=2.27, 95%CI: 1.23–4.20, p<0.01). Low Cr/CysC ratio (<1.37, median) and poor physical function (score<9) contributed to the higher risk of injurious fall (HR=4.20 vs. men with Cr/CysC>=1.37 and the score>8, 95%CI: 2.16–8.16, p<0.001). Low ALM and low grip strength were not associated with the risk of injurious fall.
Conclusions: Low Cr/CysC ratio predicted injurious falls in older men. Our results support previous data suggesting that the Cr/CysC ratio may be an easily available surrogate of muscle mass, of possible value in the clinical practice

4-17

Myeloid-Derived Growth Factor protects skeletal muscle from damage and is required for its repair and regeneration

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Introduction: Skeletal muscle, accounting for approximately 40-45% of body weight, plays vital roles in movement, respiration, and thermoregulation. Skeletal muscle has strong regenerative capabilities through muscle satellite cells. However, a decline in satellite cell regenerative potential can lead to impaired muscle repair, causing chronic inflammation, continuous tissue damage, fibrosis, and potentially lifelong disabilities. The cellular and molecular mechanisms of skeletal muscle regeneration are under investigation. This study aims to explore the role and related mechanisms of myeloid-derived growth factor (MYDGF) in skeletal muscle injury repair and regeneration.
Methods: An acute skeletal muscle injury model was established using cardiotoxin injection, with muscle injury repair assessed through HE staining, Sirius red staining, immunofluorescence staining, and mouse limb strength tests. MYDGF knockout mice were used to study MYDGF's role in muscle injury repair. Recombinant MYDGF protein was employed to investigate MYDGF's effects on myoblast differentiation, with downstream targets and signaling pathways explored through transcriptome sequencing. siATP7A transfection and pathway inhibitors were used for further validation of downstream targets and signaling pathways.
Results: MYDGF expression significantly increased after muscle injury and gradually declined during the repair process. MYDGF gene knockout inhibited mouse muscle regeneration and functional recovery, while suppressing new blood vessel formation and exacerbating muscle fibrosis. Immunofluorescence revealed co-localization of MYDGF with monocytes/macrophages in injured muscles. In vitro studies using recombinant MYDGF protein promoted myoblast differentiation and increased the expression of myogenic regulatory factors MyoG and MyoD. Conditioned medium from wild-type mouse-derived monocytes/macrophages promoted myoblast differentiation, but this effect was suppressed when MYDGF was knocked out. Transcriptome sequencing, RT-qPCR, and Western-Blot analysis revealed that Mydgf intervention significantly promoted ATP7A expression during myoblast differentiation. Using siATP7A transfection further confirmed MYDGF 's regulatory role on myoblasts through ATP7A. KEGG enrichment analysis and pathway inhibitor applications revealed that MYDGF modulates ATP7A through the PI3k/AKT pathway.
Conclusions: MYDGF participates in skeletal muscle injury repair, and MYDGF gene knockout hinders muscle injury repair. MYDGF intervention enhances myoblast differentiation, with monocyte/macrophage-derived MYDGF promoting myoblast differentiation. MYDGF regulates myoblast differentiation by upregulating ATP7A expression and modulates myoblast differentiation through the PI3k/AKT-ATP7A axis.

4-18

Metabolic remodeling during skeletal Muscle hypertrophy: role of glycolysis-derived intermediates in anabolic pathways

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Introduction: Proliferating cancer cells shift their metabolism toward glycolysis even in the presence of oxygen to generate glycolytic intermediates as substrates for anabolic reactions. However, whether and how a controlled growing muscle reprograms its metabolism in a similar manner is poorly researched. We hypothesise that a similar metabolic remodelling occurs during skeletal muscle hypertrophy.
Methods: We used mass spectrometry in hypertrophying muscles both in C2C12 muscle cells *in vitro* and plantaris mice muscle *in vivo* and assessed metabolomic changes and the incorporation of stable isotope [U-$^{13}C_6$]glucose tracer. We performed enzyme inhibition for further mechanistic analysis and a systematic review to align any changes in metabolomics during muscle growth with previous findings.
Results: The metabolomics analysis in C2C12 muscle cells revealed altered metabolite concentrations in anabolic pathways such as in the pentose phosphate (ribose-5-phosphate/ribulose-5-phosphate: +40%; p=0.01) and serine synthesis pathway (serine: -36.8%; p=0.009) to build up biomass, as well as in the hexosamine biosynthetic pathway that serves as a basis for the post-translational so-called *O*-linked glycosylation modification. L-carnosine and UDP-N-acetylgalactosamine metabolites were decreased and increased in both hypertrophied muscles in mice *in vivo (*-25.9% and +252%) as well as in C2C12 myotubes *in vitro* (-44.1% and +75.6%), respectively (all p<0.042). The systematic review showed that 12 of 20 identified metabolites associated with muscle hypertrophy were directly related to glycolysis and to its linked anabolic pathways. We demonstrated that labelled carbon from [U-$^{13}C_6$]glucose is increasingly incorporated by ~13% (p=0.001) into the non-essential amino acids in hypertrophying myotubes. The inhibition of the key enzyme phosphoglycerate dehydrogenase (Phgdh) supressed muscle protein synthesis by 74.9% (p=0.008) highlighting the importance of the serine pathway for maintaining muscle size.
Conclusion: Understanding the mechanisms that regulates skeletal muscle mass will help in developing effective treatments against muscle weakness. Our results provide evidence for metabolic rewiring of glycolytic intermediates into anabolic pathways during muscle growth, such as in the serine synthesis and hexosamine biosynthetic pathways.

4-19

Vitamin D signaling plays an inhibitory role in intramuscular adipogenesis of FAPs

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Introduction: Recent studies indicate an importance of muscle quality in Sarcopenia pathophysiology in addition to muscle quantity. Intramuscular adipose tissue (IMAT), which is known to be originated from fibro/adipogenic progenitors (FAPs) in adult skeletal muscle, is one of the key factors affecting muscle quality in elderlies, suggesting that to control IMAT formation is promising therapeutics for Sarcopenia. However, the molecular mechanism underlying IMAT formation in elderlies has not been clarified so far. We recently found that vitamin D receptor (VDR) is highly expressed in FAPs in comparison to myogenic cells, indicating a potential role of vitamin D signaling in FAPs. In this study, we aimed to clarify the role of vitamin D signaling in FAP's kinetics particularly focusing on adipogenesis.
Methods: FAPs isolated from mouse skeletal muscles were applied to adipogenic differentiation condition with or without vitamin D (1α,25(OH)2D3), and then adipogenicity was evaluated by expression of adipogenic markers. For *in vivo* analysis, tamoxifen-inducible FAP-specific *Vdr*-deficient (Vdr^{FAPcKO}) mice were newly developed to investigate whether lack of vitamin D signaling in FAPs was involved in IMAT formation.
Results: Vitamin D treatment almost completely inhibited adipogenesis of FAPs through direct transcriptional control of adipogenic genes, whereas *Vdr*-deficient FAPs differentiated into adipocytes in the presence of vitamin D. In consistent with *in vitro* studies, Vdr^{FAPcKO} mice exhibited fat deposition in atrophied-skeletal muscle.
Conclusion: Vitamin D signaling is important to prevent fate decision of FAP toward adipogenic lineage. Because of age-related decline of vitamin D level, our results indicate the possibility that decreased vitamin D is one of causes of IMAT formation in elderlies and vitamin D signaling becomes a novel therapeutic target for Sarcopenia.

4-20

To investigate the mechanism of adipose-derived stem cells in an in vitro model of dexamethasone-induced myotubes atrophy

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Introduction: Sarcopenia is a cause of muscle atrophy. The prevalence of sarcopenia increases with age, ranging from 5-13% in 60-70 years old to 11-50% in people over 80 years old. The literature confirms that sarcopenia is associated with adverse clinical outcomes. Therefore, how to treat patients with sarcopenia in later stages or those who fall into sarcopenia because of medical treatment, develop drug therapy to increase muscle mass and strength, improve patients' quality of life and survival rate, is an urgent but not yet received met medical needs.
Materials / method: In this study, we assessed the effect of ADSC on muscle differentiation and muscle atrophy in vitro through undifferentiated C2C12 muscle cells, by observing cell morphology, immunofluorescence staining and using qPCR. To evaluate whether ADSCs has the ability to promote the differentiation of mouse skeletal muscle cells, and to use Dexamethasone to induce atrophy of differentiated C2C12 myotube cells, so as to establish a cell model of muscle atrophy. By observing the morphology of muscle cells and using qPCR to detect and analyze the changes in muscle.
Results: According to past research, stem cells have the function of tissue regeneration, and stem cell transplantation is an important way to improve muscle atrophy caused by sarcopenia.
Conclusion: Stem cell therapy technology is gradually moving from basic research to clinical application. This project presents the impact of ADSCs in sarcopenia causing muscle atrophy.

4-22

Inhibiting serine synthesis pathway by PHGDH inhibition reprograms skeletal muscle cell metabolism and impairs anabolic processes

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Introduction: Skeletal muscle mass maintenance and growth require amino acids, nucleotides, and lipids for macromolecule and cell organelle synthesis. Some of these essential building blocks can be de novo synthesized from intermediates of the glycolysis in serine synthesis and pentose phosphate pathways. However, the knowledge of the importance of these metabolic pathways in muscle size regulation is poorly understood. The aim of this study was to identify enzymes from these metabolic pathways that limit myotube size, growth, and proliferation in cultured muscle cells.
Methods: We first tested the effect of inhibition of key enzymes of glycolysis, pentose phosphate pathway, and serine synthesis pathway on muscle cell protein synthesis. This small-scale screen led us to focus on studying the importance and mechanisms of the serine synthesis pathway using two different inhibitors of an essential enzyme phosphoglycerate dehydrogenase (PHGDH). We investigated murine C2C12 and human primary skeletal muscle cells by using a wide variety of analysis methods including EdU and radiolabelling, western blotting, confocal microscopy, qPCR, and nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography-mass spectrometry (LC-MS) metabolomics. In addition, we screened several potential exogenous compounds that could reverse the effects of PHGDH inhibition.
Results: We found that the inhibition of the serine synthesis pathway through PHGDH inhibition decreased protein synthesis in a dose-responsive manner and decreased myoblast proliferation and myotube size without affecting cell viability. The inhibition of PHGDH decreased glucose-derived carbon incorporation into proteins, RNA, and lipids in myotubes and myoblasts. Further, we found that PHGDH inhibition accelerated glycolysis and altered amino acid, nucleotide, and lipid metabolism without a major effect on mitochondrial parameters. In addition, PHGDH inhibition increased adenosine monophosphate (AMP) content and AMPK signalling, and unfolded protein response accompanied by decreased mTORC1 signalling in myotubes, which was associated with decreased muscle protein synthesis. Lastly, we

found that antioxidant/redox modulator N-acetylcysteine supplementation partially rescued the decreased protein synthesis and mTORC1 signalling induced by PHGDH inhibition.
Conclusions: The results suggest that the serine synthesis pathway and especially its first enzyme PHGDH is essential for the maintenance of biomass in skeletal muscle cells and that this is connected to mTORC1 signalling and changes in oxidative stress and redox balance. In further studies, the role of the serine synthesis pathway and its mechanisms in vivo should be studied in sarcopenia and muscle-wasting diseases.

4-23

Antisense oligonucleotides as a potential therapy in muscle wasting disorders

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Introduction: Muscle atrophy, or muscle wasting, is characterized by a significant shortening or thinning of muscle fibers and loss of overall muscle mass. It is a common symptom of several disorders. It can appear due to illnesses such as cancer, cardiac dysfunction, sarcopenia, or genetic muscular dystrophies. The role of microRNAs (miRNAs) in skeletal muscle is under study. MyomiRs, muscle-rich miRNAs, are essential for proper myocyte differentiation, protein turnover and skeletal muscle development and differentiation. Specifically, miR-23b is a myomiR belonging to the miR-23b/27b/24-1 cluster and the effects of its missregulation has been studied in myotonic dystrophy type I (DM1), a neuromuscular disorder characterized by loss of strength, muscle wastage and atrophy. Arthex Biotech is developing an antimiR (ATX-01) to inhibit the activity of miR-23b as treatment of DM1 patients. This ASO has been chemically modified to increase its specificity and bio-distribution to muscle. ATX-01 therapeutic activity on muscle wasting-related phenotypes has been tested in human DM1 myotubes and in adult DM1 mouse model HSALR
Methods: Primary and immortalised myotubes from DM1 patients were treated with ATX-01 at 50 nM. Rescue of the differentiation defects that characterized these cellular models, was determined by measuring area of fibers, their fusion index, and quantifying the splicing pattern of BIN1, which has been linked to muscle weakness phenotype in DM1 patients. HSALR mice were injected intravenously with ATX-01 at 12mg/kg and sacrificed at day 14. The therapeutic potential of ATX-01 in skeletal muscle was measured by grip strength, body weight and mass muscles of animals. Myopathy was determined by quantifying central nuclei in muscle fibers and the amount of compound in muscles were determined by ELISA.
Results: Inhibition of miR-23b with ATX-01 increases the area and fusion index of myotubes after differentiation. Treated HSALR mice showed an increase in muscle mass and strength and decreased central nuclei in muscle fibers suggesting an improvement of muscle structure. Treatment with ATX-01 rescues the alternative splicing of BIN1 in both mice and cells. Finally, the quantification of ATX-01 in muscle confirms that our delivery strategy importantly increase the amount of antimiRs in muscle.
Conclusions: ATX-01 is a lead compound for DM1, able to improve muscle wasting phenotypes in vitro and in vivo models. The PK/Pd data obtained with ATX-01 in the in vivo model supports its further development into clinics and validates our delivery strategy to target muscle tissue with antimir molecules.

4-24

Sex-specific molecular features of clear cell renal cell carcinoma are associated with muscle loss

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Introduction. Renal cell carcinoma (RCC) is the most common type of kidney cancer. Clear cell renal cell carcinoma (ccRCC) is the most common variant, with about 100,000 deaths annually. In RCC, low muscle mass (sarcopenia), with a prevalence in about 40 – 60% of patients, is associated with shorter survival. However, the underlying molecular mechanism is unknown. The hypothesis is that the changes in the molecular features of the tumor drive the phenotype. The aim is to characterize these features.
Methods. RNA-Seq and clinical data for ccRCC patients annotated by The Cancer Genome Atlas (TCGA; N = 539) and the Clinical Proteomic Tumor Analysis Consortium (CPTAC; N = 185) were accessed. Preoperative CT scans for 200 of the TCGA cases were accessed for body composition analysis from The Cancer Imaging Archive (TCIA). Muscularity was assessed at the level of L3 using SliceOmatic. Because height information was unavailable, sarcopenia was defined as the lowest tertile of skeletal muscle area. Sarcopenia-associated genes were identified by comparing gene expressions in the highest and lowest tertile. Due to sexual dimorphism in the molecular features of RCC, differentially expressed genes (DEGs) associated with sarcopenia were separately identified in males and females. Since sarcopenia is associated with advanced stages of ccRCC, DEGs associated with advanced T and M stages were excluded.
Results. Sarcopenia was associated with worse survival (HR = 2.546; p-value < 0.0001). In males, 231 DEGs comprised the molecular signature of the sarcopenia-associated variant of ccRCC. In females, 60 sarcopenia-specific DEGs were identified. Using these genes, classifiers were generated for the male and female sarcopenia-associated variants. As in patients with CT scans, in TCGA patients without a CT scan, and in CPTAC patients, survivals were significantly worse in individuals with the sarcopenia-associated variant. We performed gene set enrichment analysis (GSEA) to determine the biological features of sarcopenia-associated variants. In males, there was a positive enrichment of epithelial-mesenchymal transition (EMT), proliferative pathways, inflammatory pathways, and glycosaminoglycan metabolism. In females, there was an enrichment of TGF-β signaling, EMT, bile acid metabolism, and steroid metabolism. Interestingly, there was a negative enrichment in the inflammatory gene sets in females.
Conclusions. Sarcopenia is associated with worse survival in ccRCC. We have identified molecular features in ccRCC that are associated with sarcopenia. There is sexual dimorphism in these features. Future work will focus on other RCC subtypes

to see if the same features appear and how they are related to sarcopenia.

4-25

Influence of IGF-I serum concentration on muscular regeneration capacity in patients with sarcopenia

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Introduction: Previous research has described a neuroprotective effect of IGF-I, supporting neuronal survival, axon growth and proliferation of muscle cells. Therefore, the association between IGF-I concentration, muscle histology and electrophysiological markers in a cohort of patients with sarcopenia dares investigation.
Methods: Measurement of serum concentrations of IGF-I and binding partners, electromyographic measurements with the MUNIX (Motor Unit Number Index) method and muscle biopsies were performed in 31 patients with acute hip fracture older age 60 years. Molecular markers for denervation (neural cell adhesion molecule NCAM) and proliferation markers (Ki67) were assessed by immunofluorescence staining of muscle biopsy tissue. Skeletal muscle mass by bioelectrical impedance analysis and hand-grip strength were measured to assess sarcopenia status according to EWGSOP2 criteria.
Results: Thirty-one patients (20 women) with a mean age of 80.6 ± 7.4 years were included. Concentrations of IGF-I and its binding partners were significantly associated with sarcopenia (ß = − 0.360; p = 0.047) and MUNIX (ß = 0.512; p = 0.005). Further, expression of NCAM (ß = 0.380; p = 0.039) and Ki67 (ß = 0.424; p = 0.022) showed significant associations to IGF-I concentrations.
Conclusions: The findings suggest a pathogenetic role of IGF-I in sarcopenia based on muscle denervation.

4-26

Dynapenic abdominal obesity as a risk factor for the incidence of metabolic syndrome in individual 50 years of age or older: evidence from the English Longitudinal Study of Ageing

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Introduction: The reduction in neuromuscular strength (dynapenia) can coexist with obesity among older people. Adipose tissue and muscle are endocrine organs, and the co-occurrence of the two conditions in the same individual may increase the likelihood of the incidence of metabolic syndrome (MetS). The objective was to analyse whether dynapenic abdominal obesity is a risk factor for the incidence of MetS in individuals 50 years of age or older.
Methods: A longitudinal study was conducted with an eight-year follow-up involving 3,952 individuals from the English Longitudinal Study of Ageing (ELSA) who were free of MetS at baseline. Dynapenic abdominal obesity was defined based on waist circumference (> 102 cm for men and > 88 cm for women) and grip strength (< 26 kg for men and < 16 kg for women). The participants were classified as non-dynapenic/non-abdominal obesity (ND/NAO), non-dynapenic/abdominal obesity (ND/AO), dynapenic/non-abdominal obesity (D/NAO) and dynapenic/abdominal obesity(D/AO). The outcome was the incidence of MetS, the development of three or more components of MetS during follow-up: hypertriglyceridemia, hyperglycemia, low HDL cholesterol, arterial hypertension, and obesity. Poisson regression models were run and controlled for sociodemographic and behavioural variables.
Results: The adjusted model demonstrated that although abdominal obesity was a risk factor for the incidence of MetS (IRR: 2.73; 95% CI: 2.28 – 3.27), the effect size of the association was greater in AO/D individuals (IRR: 4.09; 95% CI: 2.51 – 6.66).
Conclusions: Dynapenic abdominal obesity increases the risk of the incidence of MetS with a higher effect size compared to obesity alone. The understanding of this synergic action could guide specific clinical strategies in order to prevent cardiovascular disease, disability and death.

Keywords: Dynapenia, abdominal obesity, metabolic syndrome, incidence.

4-27

Type II myofiber atrophy is not underpinned by deficits in acute anabolic signaling after resistance exercise and amino acid intake in healthy, lean older adults

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Introduction: Ageing is associated with progressive loss of muscle mass and function. Muscle mass below a certain threshold (sarcopenia) represents a risk-factor for several adverse outcomes, i.e., disability, reduced life quality and mortality. Muscle loss across the lifespan is however not equally distributed among different myofiber types, with specific atrophy of type II myofibers accounting for most of the atrophy. Leaving the muscle with an impaired capacity for fast contractions, this represents an important contributing factor in the development of muscle weakness and may predispose older adults to falls and fall-related injuries. Several mechanisms have been put forward as causal for sarcopenia, one of which is diminished responsiveness to anabolic cues, i.e., exercise and amino acids. Here we investigated whether "anabolic resistance" specific to the type II myofibers may explain their selective atrophy during ageing.
Methods: Ten young (22 ± 1 years) and 10 older (70 ± 1 years) healthy, lean men performed 10 sets of unilateral resistance exercise (RE). Muscle biopsies were obtained before and immediately after RE, and 60 and 180 min after intake of essential amino acids (EAA) in both the rested and the exercised leg. Myofiber characteristics were determined on muscle-cross sections using immunohistochemistry. Individual myofibers were dissected from freeze-dried muscle samples, fiber typed using the THRIFTY protocol, and pooled together according to their myofiber type. Phosphorylation of proteins downstream of mTORC1 were measured using immunoblotting. Statistics were performed using mixed-effect analysis with Bonferroni correction.

Results: At baseline, older adults had fewer and smaller type II myofibers and less satellite cells and capillaries associated with type II myofibers compared to young adults ($p<0.05$). In the rested leg, EAA induced phosphorylation of S6K1^{Thr389} and 4EBP1^{Ser65} similarly in both myofiber types ($p<0.05$), an effect that was greater in old than young adults ($p<0.05$). In the exercised leg, phosphorylation of S6K1^{Thr389} and 4EBP1^{Ser65} was increased compared to baseline in both myofiber types ($p<0.05$), however, this effect was similar in young and older adults. Phosphorylation of 4EBP1^{Ser65} was consistently higher in type I than type II myofibers across conditions and timepoints ($p<0.05$).
Conclusions: Type II myofiber atrophy during ageing is not associated with diminished mTORC1-signaling in healthy, lean older adults in response to high-dose EAA and high-volume RE. Other factors such as decreased satellite cell content and/or impaired blood flow to these myofibers may instead contribute to this selective atrophy.

4-28

Autophagosomes and protein aggregates accumulation in the skeletal muscle of septic patients, a pilot study

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Introduction: We have previously shown, in a model of human primary myotubes incubated with serum from intensive care patients, that serum from only 15% of the patients were able to block autophagy (1). This blockade was associated with an accumulation of autophagosomes, indicating a defect in the autophagy fusion step (1). Like neuronal cells, skeletal muscle is a postmitotic tissue that is highly dependent on autophagy. Blockade of autophagy has been well studied in neurodegenerative diseases and is associated with the accumulation of protein aggregates. In this pilot study, we aimed to investigate whether accumulation of autophagosomes and protein aggregates can be detected in skeletal muscle from critically ill septic patients treated in the ICU.
Methods: We analyzed cryosections from the vastus lateralis of 15 septic ICU patients and 8 age-matched control patients from a previous study (2). These cryosections were processed to measure colocalization of LC3 and p62 by proximal ligation assay (PLA) staining as a measure of autophagosomal vesicles. In addition, we measured the accumulation of phosphorylated Tau proteins by immunofluorescent staining.
Results: As expected, we observed a significantly lower fiber size area in the septic ICU patients compared to the control group (3530 ± 672 *vs* 2703 ± 756 μm^2; Control *vs* ICU, p = 0.0085). The septic ICU patients had a higher fraction of their fibers covered by autophagosomes in comparison with the controls (0.04 ± 0.01% *vs* 0.07 ± 0.02%; Control *vs* ICU, p = 0.0144). We did not detect a higher number of phosphorylated tau per fiber between control and septic ICU patients. However, as with autophagosomes, the percentage of fiber surface covered by phosphorylated tau aggregates was significantly higher in the septic ICU group (0.20 ± 0.17% vs. 0.44 ± 0.33%; Control vs. ICU, p = 0.046).
Conclusion: In this pilot study, we observed a higher accumulation of autophagosomes, replicating our previous in vitro observations. We also observed a higher accumulation of phosphorylated TAU, indicating a defect in proteostasis in skeletal muscle of septic ICU patients. Morover, phosphorylated TAU and autophagosomes were already present in muscle of some of the age-matched controls, indicating a potential age-related impairment of autophagy and pathways associated with proteostasis.

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4-29

Hand grip strength as a prognostic factor for mortality among COVID-19 patients admitted to the intensive care unit (ICU)

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Introduction: During the COVID-19 pandemic, older people and elderly seem to be particularly vulnerable to developing severe infections, with a higher risk of morbidity and mortality due to acute sarcopenia and muscle mass and strength reduction. Therefore, this study aimed to investigate the role of hand grip strength, as an assessment measure for physical frailty and muscle wasting, in predicting the mortality of patients hospitalized with COVID-19 in the intensive care unit (ICU).
Methods: The present study and its findings are part of a prospective observational cross-sectional study conducted between June and September 2021, with 472 COVID-19 patients (222 F and 250 M) aged 65-85 years admitted to ICU. Demographic data, hypertension, cardiovascular disease (CVD), obesity, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), smoking status, COVID-19-related symptoms, and laboratory and computed tomography (CT) findings were obtained from the patient's medical records. According to clinical and CT findings, patients admitted to the ICU had pneumonia with a respiratory rate > 30/min, oxygen saturation ≤ 80%, or extensive lung involvement in CT (CT score > 11). For quantifying radiological findings, we applied a semi-quantitative CT severity scoring system (0= no anatomical involvement, 1(<5%), 2(5-25%), 3(26-50%), 4(51-75%), and 5(>75%)). Using a JAMAR® hydraulic dynamometer, the average grip strength value (kg) after three measurements on the dominant side was recorded as the outcome for analysis. Low grip strength was defined as two standard deviations below the gender-specific peak mean value of the healthy young adults i.e. <33 kg in males and <21 kg in females.
Results: The distribution of deceased and non-deceased patients was 280 (59.3%) and 192 (40.7%), respectively. Patients who passed away in the ICU had the most frequent clinical symptoms including fever, hypertension, obesity, CVD, and COPD, as well as higher C-reactive protein (CRP), ferritin, D-dimer, and neutrophil levels ($p<0.05$). After entering the demographic and clinical variables into the binary logistic regression analysis, the results showed that COPD (odds ratio [OR]: 6.125 [95% confidence interval (CI): 1.425-25.330]), low grip strength (OR: 4.805 [95% CI: 1.624-10.776]), CRP (OR: 2.625 [95% CI: 1.256-7.356]), and obesity (OR: 1.358 [95% CI: 1.112-1.586]) are the most important independent predictors for the mortality of COVID-19 patients hospitalized in ICU, respectively ($p<0.05$).
Conclusions: Along with the well-known risk factors (i.e. COPD, CRP, and obesity), grip strength can be a quick and low-cost prognostic tool in the mortality rate of older adults affected by COVID-19.

4-30

Validation of a bedside ergometer dedicated to longitudinal evaluation of neuromuscular function in intensive care unit patients

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*equally contributed

Introduction: Around 30% of intensive care unit (ICU) patients develop ICU-acquired weakness (ICUAW). To date, ICUAW diagnosis is delayed because it relies on the Medical Research Council score based on voluntary force evaluation which can only been performed in awaked patients. An early diagnosis of ICUAW using evoked force measurements could be a promising approach.
Methods: An innovative bedside adjustable ergometer, encompassing a force transducer on a movable and gradable platform to fit the patient's morphology, was designed for the study (Figure 1).

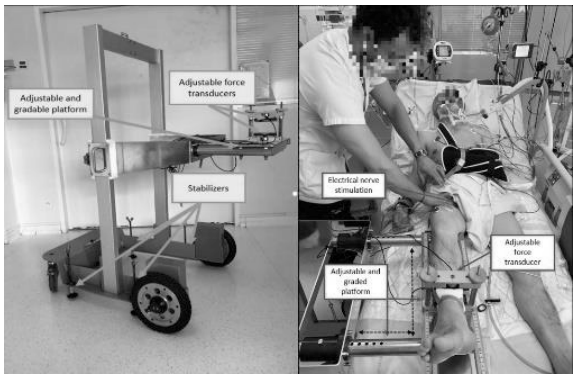

Figure 1: Experimental setup of bedside ergometer allowing for characterization of quadriceps neuromuscular function

Thirty-seven sedated patients with an expected duration of mechanical ventilation ≥ 3 day (SOFA: 8±3; SAPSII: 54±15) were evaluated in the early phase (i.e. at day 2-4), the late phase (i.e. > day 4) of ICU admission and at awakening. For each evaluation, measurements were initially performed (H0) and then repeated 1 hour (H1) later by a first experienced investigator. For the early evaluation, a second novice investigator completed the protocol 2 hours (H2) after the initial measurements). Force was recorded in response to stimulation of the femoral nerve using single (Tw) and paired (Db100) electrical and magnetic stimulations (ES and MS, respectively)(Figure 2). Reliability was assessed using the intra-class correlation coefficients (ICC) and coefficients of variation (CV).

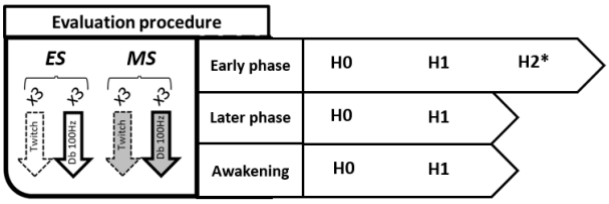

Figure 2: Study design. *Db100: doublet at 100 Hz; ES: electrical stimulation; MS: magnetic stimulation; Tw: twitch. *performed by novice investigator*

Results: Reliability measurements of electrically-evoked force production was comparable whatever phase, investigator or number of stimuli (Table1). Out of the 37 patients included, only 2 were tested during the 3 phases. No mechanical response was observed in response to MS in 6 patients. This is likely due to high body fat and/or generalized gross edema.

Table 1 : Reliability measurements of electrically-evoked force production in ICU patients

		Early phase (n=20)				Late phase (n=23)		Awake phase (n=7)	
		Intra-investigator		Inter-investigator		Intra-investigator		Intra-investigator	
		CV(%)	*ICC*	*CV(%)*	*ICC*	*CV(%)*	*ICC*	*CV(%)*	*ICC*
Force	*Twitch*	11.2%	0.948	7.8%	0.971	8.7%	0.958	11.8%	0.873
	Db100	8.8%	0.967	6.4%	0.963	8.1%	0.949	5.9%	0.924

Conclusions: The present study shows that measuring force at bedside in sedated patients using an innovative ergometer provided good-to-excellent reliability whatever the timing of testing or the experience of the investigator. These promising results should allow reliable measurements to track deconditioning and quantify early neuromuscular function alterations during ICU stay. This should provide early, quantitative and longitudinal force measurements in sedated patients that would be of utmost importance to refine the diagnosis of ICUAW.

4-31

Electrical stimulation (ES) exhibits a local and systemic restoring effect on muscular disarrangements associated with critical illness myopathy (CIM)

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Introduction: Critical illness myopathy (CIM) negatively influences the prognosis, morbidity, mortality, and health care costs in intensive care unit (ICU) patients. CIM has prevalence of 30% in the general ICU population and 100% in some ICU subpopulations, but there is currently no effective therapy available targeting the pathogenesis mechanism of CIM. Electrical stimulation (ES) has emerged as a safe and efficient substitute for physical exercise and has been applied to clinical settings to mitigate muscle wasting in patients with limited mobility and prolonged bed rest. In the present study, we aim to explore the therapeutic effect of ES against CIM.
Methods: A unique experimental ICU (ExICU) allowing for the study of CIM pathophysiology was employed in the present study. ExICU rats were exposed to 8-day ICU conditions (i.e., deep sedation, postsynaptic neuromuscular blockade, and mechanical ventilation) with or without unilateral direct ES of the soleus muscle. RNAseq-based transcriptomics (soleus) and Olink-based plasma proteomics were conducted to evaluate the therapeutic effects of ES in animals exposed to the ICU conditions.
Results: Transcriptomics analysis demonstrated dramatic muscular disarrangements in the soleus muscle, some of which were partially restored by ES, such as genes involved in "muscle system process", "fatty acid metabolic process", "extracellular matrix organization", etc. An unexpected

observation was a similar restoring effect in the unstimulated contralateral soleus muscle, referred to as the crossover effect. Based on plasma proteomic analysis, we identified several differentially expressed proteins in plasma after 8-day ICU conditions (Erbb4, Notch3, Il17a, etc.) and ES intervention (Yes1, Tgfb1, Ccl3, etc.), respectively. These circulating factors are forwarded as playing a significant role in CIM pathophysiology and in the crossover effect.
Conclusions: Results from this study demonstrate dramatic muscular disarrangements and plasma protein profile alterations of importance for our understanding of CIM pathophysiology. A local and systemic restoring effect was observed of ES which has the potentials to maintain muscle function in immobilized and unconscious mechanically ventilated ICU patients. Further, the circulating factors identified in plasma after 8-day ICU conditions and ES intervention may provide important biomarkers for CIM and potential targets for pharmacological interventions against CIM.
Keywords: critical illness myopathy; electrical stimulation intervention; local and systemic restoring effect; soleus muscle; Multiomics approach

4-32

The effect of awakening on leg muscle size in patients with critical illness who received early functional rehabilitation

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Introduction: Time to awakening is a variable timepoint for patients who are intubated and ventilated in the ICU. It remains a confounder to the implementation of active early mobilization in clinical trials. Non-volitional exercise such as neuromuscular electrical stimulation may address this gap however it is unknown whether this treatment effects muscle wasting prior to awakening. Therefore, we aimed to examine the effect of awakening on the rate of change of rectus femoris cross-sectional area in patients with critical illness receiving early functional electrical stimulation-cycling, recumbent cycling, or usual care.
Methods: This was an exploratory analysis of data not previously reported from a randomised controlled trial. Adults with critical illness who required >48 hours of mechanical ventilation, diagnosed with sepsis and/or systemic inflammatory response syndrome, expected to remain in intensive care for more than 4 days and safe to commence exercise were included. The intervention group received up to 60 minutes of recumbent cycle ergometry with functional electrical stimulation (FES) in one leg, the other receiving cycling alone. The control group received usual care rehabilitation. The primary outcome was rate of change in rectus femoris cross-sectional area (mm^2/day) measured using skeletal muscle ultrasound in the intensive care unit prior to awakening, post awakening and post intensive care unit discharge.
Results: Seventy-two participants were included (35 intervention; 37 control). Rectus femoris cross-sectional area declined prior to awakening (-14 mm^2/day [95% CI, -19 to -9]), increased post-awakening (6mm^2/day [95% CI, 0 to 12]) with mean difference 20 mm^2/day [95% CI, 12 to 29]; p<0.0001) and decreased post intensive care unit discharge (-4 mm^2/day [95% CI, -10 to 1]. There was no statistically significant difference in rate of change of muscle size between groups (p=0.864).
Conclusions: Awakening is an important and under-explored timepoint in recovery from critical illness when the rate of muscle decline could be arrested. The rate of muscle decline was not modified with early recumbent cycling, including FES-cycling, compared with usual care alone. These results indicate that timing of awakening may be pivotal in arresting muscle loss during critical illness and challenges the effectiveness of rehabilitation interventions in sedated patients.

4-33

Non-acidotic hypercapnia limits the loss of force of diaphragm muscle fibers in mechanically ventilated rats for 5 days

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Introduction: The diaphragm loss of function resulting from Mechanical Ventilation (MV) in Intensive Care Unit (ICU) patients has been termed "Ventilator Induced Diaphragmatic Dysfunction" (VIDD) and is characterized by a rapid and progressive loss of diaphragm muscle mass and function. Hypercapnia is a frequent condition in mechanically ventilated ICU patients and accepted as "permissive hypercapnia", typically in Acute Respiratory Distress Syndrome (ARDS). There are numerous negative effects of hypercapnia on different tissues, positive effects especially on cardiovascular system are known, but many other effects are still poorly understood. Acute hypercapnic exposure has shown benefit to *in vivo* diaphragm function in a porcine and rat ICU models, however our understanding of the effects of longer-term ventilation than 72 hour and the downstream signaling are less known. Here, we hypothesize that normoxic and non-acidotic hypercapnia would preserve diaphragm muscle function during MV.
Methods: Adult female Sprague-Dawley rats were deeply sedated, pharmacologically paralyzed, hydrated, nourished and mechanically ventilated in volume controlled mode for 5 days in normoxic-normocapnic compared with normoxic-hypercapnic conditions. Hypercapnic conditions (HC) ($EtCO_2$ between 60 and 80 mmHg) for the duration of the experiment ensuring normal arterial blood pH (7.37 – 7.43). This unique experimental rat model is more representative of the prolonged nature and effects of VIDD and thus provides clinically relevant assessment of hypercapnia efficacy. Diaphragm muscles were dissected and prepared for contractile function assessment and downstream signalling assessed at the gene and protein level.
Results: 1) cross sectional area (CSA) was decreased by 40% following normocapnic CMV when compared with CTR (p< 0.001), which was unaltered by hypercapnia treatment. 2) Specific force (SF; force normalised to CSA) was decreased to 58% of CTR following normocapnic CMV (p< 0.001). Hypercapnia increased SF by 15% when compared with normocapnic rats (p< 0.05); 3) Muscle E3 ligases MurF-1 and Atrogin-1 protein expression is unchanged following 5 days of CMV, irrespective of $C0_2$ conditions. 3) HC however, increased TNFα and Interleukin-1β transcript expression in the diaphragm when compared with normocapnic CMV and CTR groups; 4) HC decreased significantly the daily mean of respiratory peak pressure, improved the peripheral oxygenation and perfusion, the hemodynamic conditions. 5) Under HC the gene expression of indexes of mitochondrial dynamics, quality control and autophagy (mitophagy) improved.
Conclusion: non-acidotic hypercapnic conditions have beneficial effects on single fibre diaphragm function mediated

by improved mitochondrial function, irrespective of significant increase in muscle inflammation in non-septic animals.

4-34

Long Covid: a combination of self-reported symptoms, lower muscle function and disrupted inflammation

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Introduction: Long COVID may be defined as a condition in which persistent alterations occur after SARS-CoV 2 infection not explicated by other diagnosis. Fatigue appears as the most frequently symptom. Increased and sustained systemic inflammation seems to be involved in the pathogenesis of Long COVID. Objectives: We evaluated several circulating cytokines together with physical performance tests in 228 participants, who were hospitalised in 2020 due to acute COVID-19 and came back for a follow-up assessment 5-12 months after hospitalization.
Methods: The participants were separated in three groups: a Control group (n=77), who reported low frequency of self-reported symptoms in the follow-up assessment; a Self-Reported Symptoms group (SR, n=97), in which participants presented several symptoms, such as fatigue and muscle weakness; and the Self-Reported Symptoms with Lung Lesions group (SRLL, n=54), comprised by patients declaring self-reported symptoms concomitant with diagnosed pulmonary lesions. In the follow-up assessment, participants answered questionaries, performed physical tests, and blood was collected, for serum cytokine assessment. The variation in follow-up interval assessment was considered in the statistical analysis.
Results: In relation to Control, SRLL presented lower IL-10 and IL-4 (q=0.0170 and q=0.0208, respectively); lower IFNa2 and G-CSF (q=0.0059 and q=0.0175, respectively) and higher MIP-1β compared with SR (q=0.0191). SR presented lower MCP-1 compared with Control (and q=0.0381) and lower CCL11 levels, compared with Control and SRLL (q=0.0109 and q=0.0007, respectively). Female participants in SR and SRLL showed lower handgrip strength (q=0.0623 and q=0.0015, respectively) than women in the control group. Male participants in SR and SRLL needed more time to complete the timed up-and-go test (q=0.0302 and q=0.0078, respectively) in relation to controls.
Conclusions: Individuals with Long Covid presented lower muscle function in parallel with disrupted inflammatory markers and persistent self-reported symptoms, including fatigue. Heterogeneous long COVID symptom phenotypes are accompanied by distinct inflammatory markers in the circulation. The findings pointing to lower muscle function may have long-lasting consequences for health and quality of life and must be considered as an important sequela.

5-01

The association between protein intake and skeletal muscle parameters in patients with localized renal cell cancer

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Introduction: Low skeletal muscle index (SMI) and low skeletal muscle density (SMD) have been associated with worse survival in several cancer types, including renal cell cancer (RCC). Increasing dietary protein intake may increase skeletal muscle mass, but findings from studies are inconsistent. This study is first to investigate the association of total, animal and plant protein intake with SMI and SMD in patients with localized RCC.
Methods: We included patients treated with a (partial) nephrectomy for stage I-III RCC who were enrolled in the population-based cohort ReLife between January 2018 and March 2020. Dietary intake was assessed with a 163-item food frequency questionnaire (FFQ). Body composition was assessed using diagnostic Computed Tomography (CT) images at the level of the third lumbar vertebra. Nutrient residual and multivariable nutrient density regression models were used to evaluate the independent associations of protein intake with SMI and SMD. All analyses were adjusted for age, sex, total energy, smoking, alcohol intake, moderate-to-vigorous physical activity, and tumour stage.
Results: In total, 199 patients with available dietary information and CT scans were included. Mean age was 61.7 ± 9.6 years, 73% of patients were male, and the majority of patients were overweight (46%) or obese (21%). Mean energy-adjusted protein intake was 0.92±0.17 g/kg body weight/day. An increase of 0.1 g energy-adjusted total protein, animal protein, and plant protein per kg body weight/day was associated with a decrease in SMI (β: -0.88, 95% CI:-1.42, -0.34; β:-0.65, 95% CI: -1.29, -0.02; and β: -1.41, 95% CI: -2.37, -0.45, respectively). In contrast, these measures were associated with an increase in SMD (β: 1.73, 95% CI: 1.09, 2.36; β: 1.06, 95% CI: 0.33, 1.79; β: 3.28, 95% CI: 2.19, 4.37, respectively). No statistically significant associations were found for protein intake in g/day or for protein intake expressed as energy percentage.
Conclusion: These results suggest an inverse association between protein intake and skeletal muscle mass, but a positive association with skeletal muscle quality. Confirmation of these findings in our total ReLife cohort and stratified analyses by sex are planned.

5-02

An evidence based protocol for early identification of nutritional risk patients with cancer

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Introduction: Nutritional and metabolic care in cancer still represents a largely unmet need. A practical protocol for nutritional risk in oncology to enable oncologists to identify patients with or at risk of malnutrition for further evaluation and follow-up is warranted. Such approach should be simple and quick to implement so to fit the oncologist's schedule.
Methods: A panel of nutrition specialists and practicing oncologists identified three factors as essential components to give a rapidly identify patients' nutritional and physical status: i) body weight, ii) appetite and food intake, and iii) strength and mobility, The experts met twice in October 2021, with additional discussions occurring via email, allowing the development of the PROtocol for NuTritional risk in Oncology (PRONTO).
Results: By exploring through three simple questions three different domains, the protocol may allow for the fast identification of patients with or at risk of malnutrition and/or muscle depletion and provides guidance on next steps and is adaptable to multiple settings and countries, making implementation feasible by oncologists, ultimately optimizing patient outcomes.
Conclusion: This protocol could be used in countries/clinical scenarios where a specialized approach to nutrition care is not available. It was devised to give oncologists a simple nutritional protocol for optimization of the patient care pathway, and not to replace the already existing tools for malnutrition screening and assessment. Dissemination, validation testing, and feedback of the protocol are warranted.

Keywords: Cancer, early identification, malnutrition risk, protocol

5-03

Preoperative supportive nutrition at major cancer surgery in weight-losing patients.
Effects on muscle transcriptome.

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Introduction: Recommendations of strict pre-operative fasting have later on become replaced by provision of carbohydrate rich nutrition drinks prior to surgery. Carbohydrate (cho) drinks are shown to reduce postoperative insulin resistance and thus assumed to improve post-surgical muscle protein metabolism with expectations to reduce morbidity and complication rate, though meta-analyses indicate few clinical benefits. However, such studies investigating skeletal muscle metabolism are lacking. Therefore, our study evaluates skeletal muscle transcriptome alterations with relevance to carbohydrate and protein metabolism, by two different nutrition interventions.
Method: Patients scheduled for major upper gastrointestinal cancer surgery were asked to participate. Mean weight loss in the patient group was 7%. Provision of either oral carbohydrate -rich nutrition drinks (804 kcal cho/96 kcal protein) or provision of peripheral total parenteral nutrition (TPN) (400 kcal cho/180 kcal protein/350 kcal fat) were administered in a 12-hours over-night period prior to surgery. The control group received infusion of clear fluids only. Arterial blood samples and abdominal muscle biopsies were collected at operation start (n=38). Blood amino acids were quantified by LC-MS/MS and muscle mRNA transcripts were analyzed with Agilent SurePrint G3 Human GE v3 8x60K Microarrays. Data evaluation was done in Genespring software v.14.9.1.
Results: Statistical analyses indicated ~1200 transcripts as altered among groups (Anova, $p<0.05$). Post-Hoc analyses indicated ~500 transcripts as altered by each nutrition protocol with most alterations specific to each treatment. The results indicate that both carbohydrate rich nutrition drinks and total parenteral nutrition influenced muscle glucose metabolism, while transcript alterations related to protein translation were induced by parenteral nutrition only.
Conclusion: Carbohydrate rich drinks were not sufficient to sustainably support muscle metabolism and should not be recommended in combination with major cancer surgery.

5-04

Cancer-associated anorexia: DNA methylation signatures in patients with lung cancer

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Introduction: Anorexia is an extremely disabling symptom in cancer and its pathogenesis is multifactorial. We aimed at evaluating the potential role of epigenetic regulation on those gene expression marks by analyzing changes in methylation on PBMCs DNA of lung cancer patients presenting with poor appetite.
Methods: Genome wide DNA methylation analysis was performed in lung cancer patients at their first diagnosis compared to healthy controls. Anorexia was assessed by FAACT questionnaire. Four groups of genes were identified: hypermethylated repressed, hypermethylated induced, hypomethylated repressed and hypomethylated induced.
Results: The analysis was conducted on 24 participants to compare the DNA methylation status of anorexic cancer patients versus non-anorexic cancer patients and non-cancer controls. In cancer patients, 382 genes were differentially methylated compared to control group. Patients with cancer anorexia presented 586 hypomethylated and 174 hypermethylated genes compared to controls. 211 genes were hypomethylated and 90 hypermethylated in anorexic versus non-anorexic cancer patients. When microarray methylation data were merged with RNA sequencing, we observed significant differences in anorexic cancer patients with respect to controls. In this comparison, 42 genes resulted hypomethylated induced, 5 hypermethylated repressed, 10 hypermethylated induced and 15 hypomethylated repressed. The CG sites analyzed by targeted bisulfite sequencing in four genes of interest (*FLNA, PGRMC1, GNL3L* and *FHL1)* that resulted hypomethylated induced in the anorexic patients compared to healthy controls, allowed to validate the data obtained from DNA methylation analysis. Moreover, the four genes resulted significantly hypomethylated in anorexic

patients with respect to non-anorexic patients and to controls ($p<0.0001$).
Conclusions: Our data support in humans for the first time that epigenetic mechanisms through DNA methylation are implicated in anorexia in lung cancer patients.

5-05

Combined nutritional and exercise interventions for cachexia in chronic diseases: a systematic review

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Introduction: Cachexia is a serious condition characterized by weight loss and decreased skeletal muscle mass, often observed in patients with chronic diseases such as cancer and chronic heart failure. As cachexia is associated with nutritional problems, nutritional and exercise interventions are expected to be effective. However, the combined effects of these interventions have not been thoroughly investigated. This systematic review aimed to examine the effects of combined nutritional and exercise interventions on cachexia in patients with chronic diseases.
Methods: We searched databases including MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane Library), Embase, CINAHL, PEDro, WHO-ICTRP, and ClinicalTrials.gov for studies up to March 13, 2023. We included studies that investigated the effects of combined nutritional and exercise interventions in patients with cachexia defined by criteria established by Evans et al. or Fearon et al. compared to control groups. We attempted to pool outcomes such as body weight, body composition, mortality, activities of daily living (ADL), physical function, exercise tolerance, and quality of life (QOL).
Results: We identified 1,579 records, and ultimately included only two studies investigating the effects of combined interventions on cachexia in patients with cancer (Solheim, 2017 and Rogers, 2020). Despite limited research, these two studies suggested that combined nutritional and exercise interventions may practically alleviate cachexia symptoms. However, conducting a meta-analysis was difficult as these studies had limited data reporting and did not investigate common outcomes. No studies examining the effects of combined interventions on cachexia in other chronic diseases such as chronic heart failure, chronic kidney disease, and chronic obstructive pulmonary disease were included in this review. In addition, through the comprehensive search of databases, we were able to identify several ongoing studies within this field.
Conclusions: Our systematic review included several studies, but drawing definitive conclusions through meta-analysis proved challenging. At the same time, it became clear that there is very limited evidence supporting the expected benefits of combined nutritional and exercise interventions for cachexia. Future research is urgently needed to investigate the effects of combined interventions on cachexia in various chronic diseases. The results of other ongoing investigations are eagerly anticipated, and our research team is currently planning to conduct such a study.

6-01

Exercise decreases catabolic protein signaling in rat skeletal muscle 40 days post-burn

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Introduction: During the hypermetabolic state after a burn injury skeletal muscle mass loss is caused by a negative protein balance. In muscle wasting diseases such as cancer, exercise has been found to counterbalance a negative protein balance by increasing anabolic and decreasing catabolic protein signaling. We examined, in a rat burn model, the effects of exercise on skeletal muscle protein synthesis and breakdown 40 days postburn.
Methods: 22 rats (6 weeks old) received a 40% TBSA burn according to the Walker-Mason model and were assigned to an exercise (E) or non-exercise (NE) group. Animals of the E group were subjected to progressive treadmill training of 60 minutes for four days a week. Fourty days postburn, all animals were sacrificed, weighed and m.soleus (SOL) and m.extensor digitorum longus (EDL) were collected. Protein expression of pAkt and eEF2 proteins and of MURF-1, Atrogin-1 and FOXO3a were measured by Western blotting for analysis of protein synthesis and proteolysis, respectively. Protein expressions were normalised for Total Protein content. A linear mixed model was used to test for significant differences ($p<0.05$(*)).
Results: NE burned rats showed significantly less body weight gain* 40 days postburn compared to E burned rats, characterized by lower muscle weight/body weight ratios for both SOL* and EDL*. In the E group, both SOL and EDL showed less proteolytic activity of MURF-1*, Atrogin-1* and FOXO3A* in comparison to NE rats. Protein synthesis signaling, Akt* and eEF2*, was lower in EDL of E rats, in SOL eEF2 was also lower while Akt* expression was higher in comparison with NE rats.

Conclusion: The most important finding is that exercise postburn increased muscle mass through a shift in protein signalling pathways towards less catabolic protein signalling, in comparison to non-exercising rats.

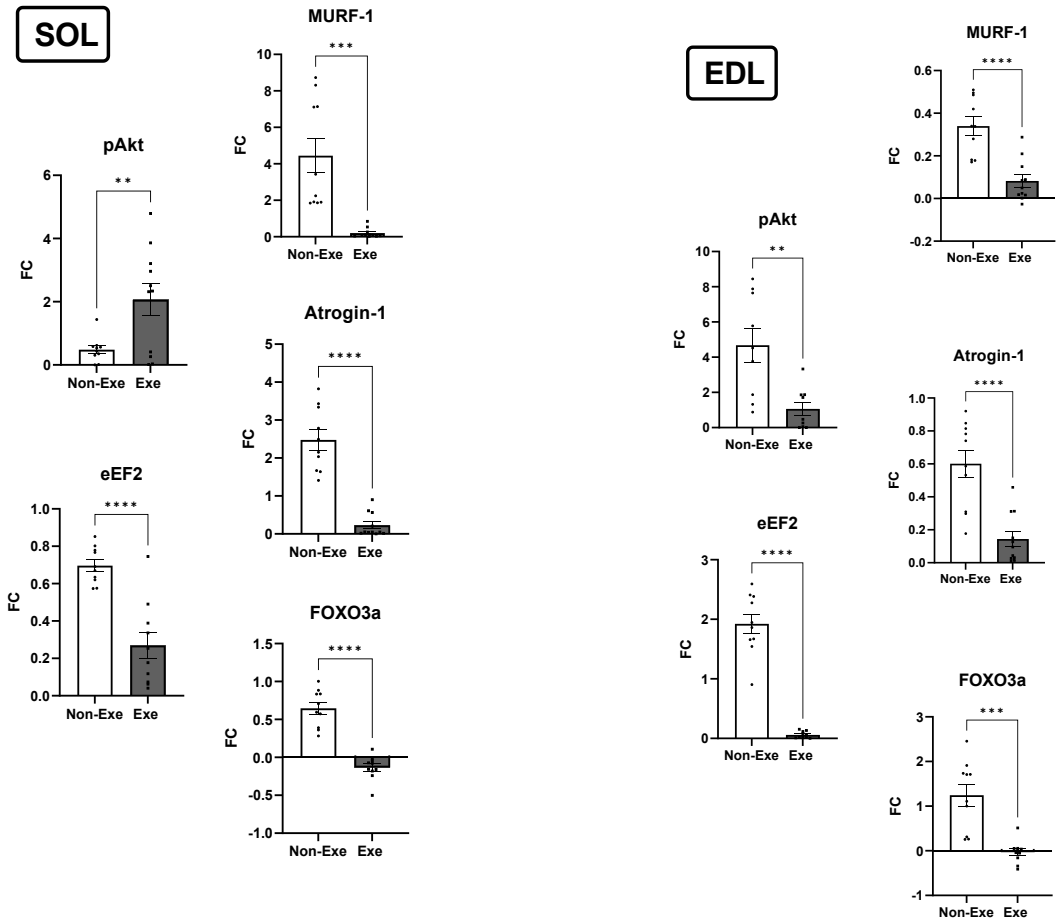

Figure 3: Fold changes of normalised signals (over Total protein stain) of Western blot analysis. eEF2 and pAkt for protein synthesis and MURF-1, Atrogin-1 and FOXO3a for protein breakdown of both Soleus (SOL) and Extensor Digitorum Longus (EDL) muscles at 40 days follow-up in burned non-exercise (Non-Exe) and exercise (Exe) groups. *= Significant difference p<0.05

6-02

Effect of exercise on sarcopenic obesity (SO) patients: research progress and perspectives

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Sarcopenic obesity (SO) is a prevalent and severely health-impairing geriatric syndrome characterized by the accumulation of body fat and a decrease in muscle mass and function. The prevalence of SO is reported to range from 5% to 10%. In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) published the first expert consensus on SO, which clarifies the definition, diagnosis and cut-off values. The pathogenesis of SO focuses on age-related changes in body composition, hormonal alterations, chronic inflammation, and poor lifestyle. The main adverse consequences of SO manifest as metabolic disorders, decreased physical function, increased risk of falls and disability, cognitive impairment, increased incidence of related complications and all-cause mortality. Exercise is well-proven to reduce body fat and increase muscle mass, suggesting it would be efficient for this population. However, guidelines for exercise prescription (ExRx) for SO have yet to be established. This paper aims to examine research on exercise training for SO, with regard to the components of ExRx, which are frequency, intensity, time, and type of exercise (FITT), and to evaluate the primary outcomes. The results show that exercise training improves body composition and function in SO patients. Resistance training is the primary type of exercise intervention, and its combination with aerobic exercise might be more effective in improving functional status in SO. The inadequacy of relevant research poses a challenge in determining the appropriate frequency and duration of exercise for SO. It is worth considering the ACSM ExRx guidelines for older adults, namely 3-5 days of aerobic exercise and at least 2 days of resistance exercise per week. Aerobic exercise needs to be guaranteed for 30-60 minutes (moderate intensity) or 20-30 minutes (higher intensity). There is no specific exercise duration recommendation for resistance exercise; however, it is crucial to engage in exercises that involve the major muscle groups during the workout. The intensity of aerobic exercise, mostly reported by rating of perceived exertion (RPE) scale(5-8 points,1-10 scale). While for resistance training, it recommended to start with a low intensity (e.g., 40%-50% of 1-RM) and gradually increase to moderate (e.g., 60%-80% of 1-RM). Due to limited evidence, ExRx and its components for SO require further investigation, and the underlying mechanisms by which exercise exerts its effects need further exploration.

6-03

Effect and Mechanism of Exercise on Diabetic Sarcopenia：a Systematic Review

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Introduction: The development of sarcopenia poses a significant threat to the well-being and quality of life of elderly individuals. Research interest is currently directed towards the coexistence of sarcopenia and diabetes as a comorbid condition, given that sarcopenia is regarded as a potential complication arising from diabetes. A reciprocal relationship exists between sarcopenia and diabetes, forming a vicious cycle. Numerous studies have confirmed that exercise interventions are effective in improving diabetes and sarcopenia, although the underlying mechanisms remain unclear. Therefore, this study analyzes studies related to exercise interventions in diabetic sarcopenia according to the FITT principle of exercise prescription and explores the possible mechanisms involved.
Methods: Searches of Pubmed, Web of Science, Embase, and Cochrane Library databases were performed for studies published in English from the earliest date available to April 2023. Randomized controlled trial (RCT) studies were reviewed to explore the effects of exercise interventions on individuals with diabetic sarcopenia. The study on exercise intervention was summarized with regard to the FITT principles, encompassing the frequency, intensity, time, and type of exercise. Mechanisms of exercise affecting diabetic sarcopenia study selected reliable experiments and papers for citation. Twelve RCT studies with a total of 652 patients were included in this study.
Results: Aerobic exercise is more effective than resistance exercise in increasing maximal oxygen uptake and improving glycemic control, and resistance exercise is more effective than aerobic exercise in maintaining and increasing the muscle mass. Aerobic combined resistance exercise combines the advantages of both types of exercise mode. The main possible mechanisms of exercise intervention for diabetic sarcopenia are the inhibition of inflammatory factor expression, increased insulin sensitivity, improved skeletal muscle microvascular function, and activation of mitochondrial autophagy.
Conclusion: This study found, through systematic evaluation, that patients who chose aerobic exercise at an intensity of 60%-80% of maximum heart rate or resistance exercise at an intensity of 50%-70% of 1RM for 8-12 weeks, at a frequency of 3 times a week for 30-45 minutes, improved muscle mass, muscle strength, and physical function in patients with diabetes. Sarcopenia and diabetes form a vicious circle, with the adverse effects of sarcopenia and diabetes interacting to exacerbate the patient's condition. Exercise can break this vicious circle by improving insulin sensitivity, blood glucose regulation, and reducing inflammation to treat diabetic sarcopenia.

6-04

Higher fibroblast growth factor 23 levels are associated with low exercise capacity in patients with chronic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Introduction: Fibroblast growth factor 23 (FGF-23) is a key regulator of phosphate metabolism, inhibiting phosphate reabsorption and vitamin D activation in the proximal renal tubules. Meanwhile, several studies have shown that higher FGF-23 levels are associated with disease severity and adverse outcomes in heart failure (HF). However, the relationship between FGF-23 levels and exercise capacity in HF with reduced ejection fraction (HFrEF) patients remains unclear.
Methods: A total of 213 patients (67±11 years, 79% men) with HFrEF were evaluated for FGF-23 levels and exercise capacity from the Studies Investigating Co-morbidities Aggravating HF (SICA-HF). The Full-length intact FGF-23 level in the serum samples was detected using Human FGF-23 Enzyme Linked-Immuno-Sorbent Assay Kit (Merck KGaA, Darmstadt, Germany), and patients were divided into lower and higher FGF-23 groups based on the median value of 90 pg/mL. Exercise capacity was assessed by a treadmill cardiopulmonary exercise testing with a modified Bruce protocol for peak oxygen uptake (VO_2), with patients divided into low and high exercise capacity using the median value of 16.7 mL/kg/min.
Results: Patients with higher FGF-23 levels were significantly older, had higher New York Heart Association class, lower left ventricular ejection fraction, higher prevalence of sarcopenia, and higher levels of high-sensitivity C-reactive protein (2.4 [1.2-3.9] *vs.* 1.5 [0.7-3.1] mg/L, p=0.001), parathyroid hormone (55 [37-91] *vs.* 38 [31-48] pg/mL, p<0.0001), and N-terminal pro-B-type natriuretic peptide (926 [374-1936] *vs.* 315 [152-770] pg/mL, p<0.0001), and lower levels of haemoglobin (13.1 [12.1-14.4] *vs.* 13.7 [13.0-14.6] g/dL, p=0.01) and estimated glomerular filtration rate (57 [43-75] *vs.* 77 [64-87] mL/min/1.73m^2, p<0.0001) than those with lower FGF-23 levels. Muscle strength and exercise capacity were significantly lower in patients with higher than those with lower FGF-23 levels (handgrip strength: 36±11 *vs.* 41±12 kg, p=0.001; quadriceps strength: 37±11 *vs.* 44±14 kg, p<0.0001; peak VO_2: 15.2±4.2 *vs.* 18.8±4.6 ml/min/kg, p<0.0001). Multivariate logistic regression analysis revealed that higher FGF-23 levels were significantly associated with low exercise capacity (adjusted OR 2.62, 95% CI 1.06-6.44, p=0.04).
Conclusion: In patients with chronic stable HFrEF, higher FGF-23 levels are significantly associated with low exercise capacity.

6-05

Associations of Exercise Habits in Adolescence and Old age with Phase Angle in Older Adults: the Bunkyo Health Study

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Introduction: Phase angle (PhA) is a bioelectrical marker determined through bioelectrical impedance analysis, and higher PhA is associated with better cellular integrity, higher skeletal muscle mass, strength and quality (Silva et al., *Sport*

Sciences for Health, 2022). Earlier studies reported that exercise enhanced phase angle (Martins et al., *Arch Gerontol Geriatr*, 2022), and we recently showed that older adults with exercise habits in both adolescence and old age exhibited high muscle function (Tabata et al. *J. Cachexia Sarcopenia Muscle*, 2023). Thus, the present study investigated the associations between exercise habits in adolescence and older age, and their impact on PhA among older adults.
Methods: This study was conducted using data from the Bunkyo Health Study, a cohort study for 65-84 older adults. We included 676 men and 926 women who completed the full data of analysis necessary. In the current study, we defined the lower fifth of the PhA value as a PhA decline. We divided participants into four groups by combination of exercise habits: never exercised (NN), exercised only in adolescence (AN), exercised in old age (NA), and exercised both in adolescence and old age (AA). Logistic regression models adjusted for potential confounders were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the prevalence of PhA decline. As potential confounders, we adjusted age, years of education, smoking status, protein intake, and the presence of diabetes mellitus, cardiovascular diseases, and osteoporosis.
Results: The cutoff value of PhA decline is 4.6 in men and 4.1 in women. In men, the ORs (95%CI) for PhA decline were not significantly different among the groups {NA: 1.01(0.51-2.0), P=0.975, AN: 1.7(0.96-3.0), P=0.069, AA: 0.74(0.38-1.5), P=0.388}. In the women, the ORs of the AA group was lower than the NN group {0.51(0.29-0.88), P=0.015}, whereas the NA group and the AN group were not significantly different than the NN group {NA: 0.73(0.45-1.17), P=0.187, AN: 0.66(0.42-1.04), P=0.072}.
Conclusion: Older women, but not older men, with exercise habits in both adolescence and old age were at low risk of PhA decline.

6-06

Loss of hypoxia signalling-mediated PGC-1a expression underlies age-related loss of muscular adaptation to exercise

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Background: Exercise is necessary for the prophylaxis / treatment of aging-associated muscle loss or sarcopenia. However, muscular adaptation to exercise becomes increasingly diminished with aging, limiting the treatment efficacy. This likely reflects aging-related dysregulation of the required myogenic signaling pathways. Our previous studies uncovered loss of hypoxia signalling activation following exercise in aged muscle, accompanied by an elevation of prolyl hydroxylase domain enzyme (PHD)2 responsible for regulating HIF1A, the master transcriptional activator of the hypoxia sigianlling pathway.
Methods: Young (12-14 weeks old) and old (21 months old) mice were subjected to either 40 minutes of running training protocol at approximately 70% of VO^2 5 times per week for 8 weeks. The mice were tested for physiological performance, muscle functions, and gastrocnemius muscles were evaluated for histological, biochemical, and gene expression changes.
Results: Young, trained mice exhibited a significant increase in maximum distance running (250%, p<0.001), maximal running speed (23%, p=0.03), in comparison to age-matched untrained mice. In contrast, both trained and untrained old mice demonstrated similar endurance and maximal speed. Muscle fiber composition of gastrocnemius revealed a 2.5-fold increase (p=0.02) and 30% increase in the Type I and Type IIa fibers (p=0.03) in trained young mice, respectively, where these were absent in aged muscles. RNA seq analysis gastrocnemius muscles revealed 96 and 146 to be differentially regulated with exercise treatment in young and old mice, respectively, without any overlap, where 85% of the top 20 most upregulated genes in exercised young mice were the transcriptional targets of HIF1A. The exercise training led to a 50% decrease in PHD2 protein levels (p=0.006) with corollary increase in the HIF1A and PGC-1a protein levels in muscle of young mice, in contrast to old mice where neither change was present. Muscle-specific ablation of ARNT (transcriptional co-factor of HIF1A) or PHD2 elevation in vivo exhibited reduced response to exercise training, improvement in muscle fatigue, and fiber-type adaptation. Supplementation of old mice and these transgenic mice with ML228, HIF activator, partially reversed these parameters and improved overall physiological and muscular functions.
Conclusion: Age-related elevation of PHD2 hinders PGC-1a mediated fiber type adaptation and gain of muscle endurance by inhibition of HIF1A transcriptional activity in response to exercise. Pharmacological activation of HIF offers a promising method for improving exercise-based therapies for sarcopenia.

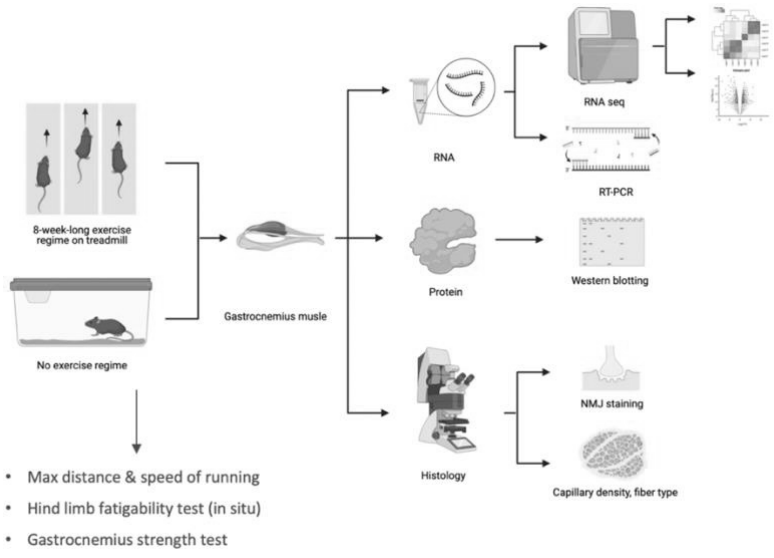

Figure 1: Method summary

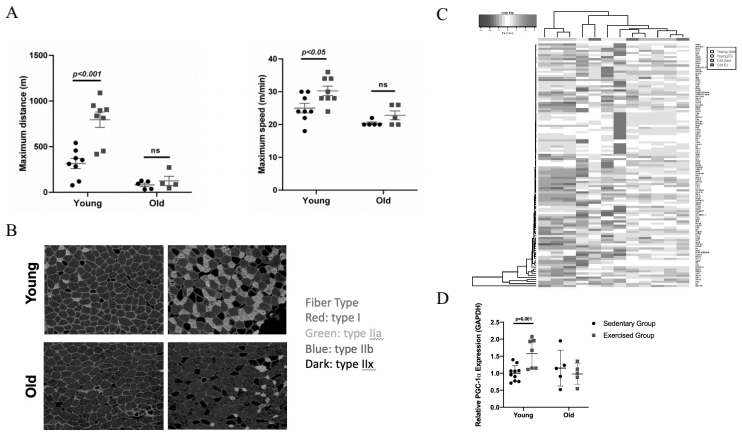

Figure 2: Young, trained mice exhibited a significant increase in maximum distance running (250%, p<0.001), maximal running speed (23%, p=0.03), in comparison to age-matched untrained mice (A). In contrast, both trained and untrained old mice demonstrated similar endurance and maximal speed. Muscle fiber composition of gastrocnemius revealed a 2.5-fold increase (p=0.02) and 30% increase in the Type I and Type IIa fibers (p=0.03) in trained young mice, respectively, where these were absent in aged muscles (B). RNA seq analysis gastrocnemius muscles revealed 96 and 146 to be differentially regulated with exercise treatment in young and old mice, respectively, without any overlap, where 85% of the top 20 most upregulated genes in exercised young mice were the transcriptional targets of HIF1A (C) . The exercise training led to a 50% decrease in PHD2 protein levels (p=0.006) with corollary increase in the HIF1A and PGC-1a protein levels in muscle of young mice (D)

6-07

Body cell mass to fat-free mass ratio and extra-to-intracellular water ratio are related to maximal oxygen uptake

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Fat-free mass (FFM) is a heterogeneous compartment comprising body cell mass (BCM), intracellular water (ICW), extracellular solids, and extracellular water (ECW). The BCM/FFM and ECW/ICW ratios vary among individuals and decrease with age. This study aimed to determine whether BCM/FFM and ECW/ICW ratios are predictors of maximal oxygen uptake ($\dot{V}O_2$peak) independently of age, sex, and objectively measured physical activity (PA). A total of 115 Japanese males and females, aged 55.3 ± 8.0 years (mean ± standard deviation), were included in the study. Anthropometry, explosive leg muscle power, and $\dot{V}O_2$peak were measured, and BCM, FFM, ICW, and ECW were estimated. Step count and PA were objectively measured using a triaxial accelerometer. Blood flow volume was assessed using ultrasonography. BCM and ICW were negatively correlated with age, whereas FFM and ECW were not significantly correlated with age. FFM, ICW/ECW, BCM/FFM, step counts, moderate and vigorous PA, and leg muscle power were positively correlated with $\dot{V}O_2$peak, even after adjusting for age and sex ($P<0.05$). Multiple regression analysis indicated that either BCM/FFM or ECW/ICW, leg power, and objectively measured PA were associated with $\dot{V}O_2$peak independent of age, sex, and FFM. Blood flow volume was significantly correlated with ECW ($P<0.05$), but not with BCM. The BCM/FFM and ECW/ICW ratios were significant predictors of VO_2peak, independent of age, sex, FFM, leg power, and objectively measured PA.

7-01

Anti-RANKL treatment attenuates mitochondria deterioration and suppresses macrophage infiltration during sarcopenia

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Introduction: Sarcopenia is an age-related geriatric syndrome which is associated with subsequent disability and morbidity. Currently there is no promising therapy approved for treatment. The receptor activator of nuclear factor NF-κB ligand (RANKL) is expressed in skeletal muscle and its activation mainly inhibits myogenic differentiation, which leads to skeletal muscle dysfunction. CD206 positive macrophage has been reported to be associated with progressive impairment of skeletal muscle function with aging. The study aims to investigate the effects of an anti-RANKL treatment on sarcopenic skeletal muscle and explore the related mechanisms in mitochondria modulation and the polarization status of macrophages.
Methods: Sarcopenic senescence-accelerated mouse P8 (SAMP8) mice at month 6 were treated intraperitoneally with 10mg/kg anti-RANKL (Bio X Cell) every 2 weeks and harvested at month 10 (Fig A). Senescence accelerated mouse resistant-1 (SAMR1) were collected at month 10 as age-matched non-sarcopenic group. *Ex-vivo* functional assessment, grip strength, oil red and immunostaining of CD45, F4/80, CD206, iNOS, C/EBPa, and Pax7 were performed. Mitochondria morphology was examined with a transmission electron microscope (Hitachi H7700, Tokyo, Japan). Data analysis was done with one-way ANOVA, and the significant level was set at $p \leq 0.05$.
Results: After anti-RANKL treatment, tetanic, twitch force and grip strength were significantly higher than CTL group ($p<0.01$, $p<0.01$ and $p<0.05$, Fig B). The SAMP8 mice at month 10 expressed significantly more C/EBPα (intramuscular adipose marker), CD206 (M2 marker) and LYVE1 (macrophage marker) positive area than in SAMR1 (Fig C). Anti-RANKL treatment could significantly decrease CD45 (general leukocyte marker), F4/80 (M1 marker), iNOS (M1 Marker), C/EBPα and CD206 positive area and oil red area, and significantly increase PAX7 (MDSC marker) positive cell numbers (Fig C and E). There was an increase in the number of intermyofibrillar mitochondria and restoration of mitochondria morphology in Anti-RANKL group. The structure of mitochondria and their cristae were more compact, compared with swollen mitochondria in the isotype group (Fig D).
Conclusion: These results indicated excessive inflammation and promoted the shift from M1 to M2 in macrophage phenotype during sarcopenia. The anti-RANKL treatment protected against sarcopenic skeletal muscle through suppressing muscle inflammation and modulating mitochondria which may represent a novel therapeutic approach for sarcopenia.
Acknowledgment: Collaborative Research Fund (CRF, Ref: C4032-21GF), CUHK Direct Grant (Ref: 4054690)

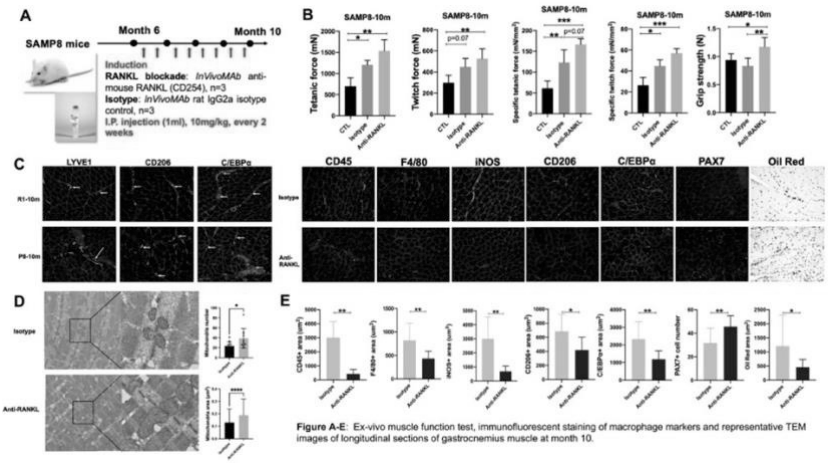

Figure A-E: Ex-vivo muscle function test, immunofluorescent staining of macrophage markers and representative TEM images of longitudinal sections of gastrocnemius muscle at month 10.

7-02

Enhanced glutamine availability exerts different effects on protein and amino acid metabolism in muscles of healthy and septic rats

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Introduction: Glutamine (GLN) supply may affect the catabolism of branched-chain amino acids (BCAAs; valine, leucine, and isoleucine), which play a regulatory role in protein turnover. We examined the effects of enhanced GLN availability on leucine oxidation, amino acid concentrations, and protein metabolism in muscles from healthy and septic rats.
Methods: Cecal ligation and puncture was used as a model of sepsis. Twenty-four hours after surgery, the soleus (SOL, red muscle) and the extensor digitorum longus (EDL, white muscle) were incubated in medium containing 0.5 or 2.0 mM GLN, and L-[1-14C]leucine. Protein breakdown, protein synthesis, and leucine oxidation were determined via 3-methylhistidine release, L-[1-^{14}C]leucine radioactivity in muscle protein, and the radioactivity of released $^{14}CO_2$, respectively.
Results: In muscles from septic animals, increased proteolysis and leucine oxidation, and decreased protein synthesis were detected. These effects were more pronounced in the EDL. In septic muscles, the addition of GLN decreased leucine oxidation in both muscles and increased protein synthesis in the EDL. In muscles of untreated animals, decreased leucine oxidation after the addition of GLN to the medium was associated with decreased protein synthesis in the SOL and decreased concentrations of serine, glycine, histidine, alanine, arginine, proline, and lysine in both muscles.
Conclusions: White muscle fibers are more sensitive to septic stimuli than red fibers are. In sepsis may enhanced GLN intake ameliorate GLN deficiency, inhibit BCAA catabolism, and stimulate protein synthesis. In the healthy state, surplus of GLN may lead to marked alterations in the intramuscular concentration of several amino acids and impair protein synthesis.

Financial Support: Charles University, the Cooperatio Program, research area METD.

7-03

Exploring Lonafarnib's Potential for Sarcopenia Treatment in Dexamethasone-Induced Muscle Atrophy Models

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Introduction: Sarcopenia, characterized by age-related muscle weakness and a decline in muscle mass, is associated with increased falls, frailty, and mortality. This progressive and generalized skeletal muscle disorder affects the elderly population, leading to functional decline and a reduction in quality of life. Lonafarnib, an FDA-approved drug for Hutchinson-Gilford progeria syndrome and it has been shown to improve cardiovascular and skeletal abnormalities, which suggests that it may have beneficial effects on muscle tissue as well. This study investigated the potential of lonafarnib in treating sarcopenia using dexamethasone-induced muscle atrophy models in C2C12 myoblasts and rats.
Methods: We employed in vitro and in vivo dexamethasone-induced sarcopenia models. C2C12 myoblasts were treated with dexamethasone and lonafarnib, and myotube area, fusion index (FI), and muscle fiber diameter were assessed. Rats were divided into six groups: control without dexamethasone, control with 1μM or 5μM lonafarnib, dexamethasone-induced sarcopenia model without lonafarnib, and sarcopenia model with 1μM or 5μM lonafarnib. Body weight, grip strength, and electrophysiological studies were performed. After sacrifice, hind limb muscles were analyzed using immunohistochemistry for dystrophin and cytochrome C.
Results: In vitro sarcopenia models revealed that optimal concentrations of lonafarnib significantly increased myotube area and FI in dexamethasone-treated C2C12 myoblasts. Additionally, in vivo sarcopenia animal models showed that optimal concentrations of lonafarnib attenuated dexamethasone-induced body weight loss, grip strength reduction, and hindlimb muscle compound muscle action potential amplitude decrease. Lonafarnib also restored dexamethasone-induced cross-sectional area reduction and increased cytochrome C area, indicating its potential to promote functional restoration.
Conclusion: Lonafarnib effectively counteracted dexamethasone-induced muscle atrophy both in vitro and in vivo, demonstrating its potential as a promising therapeutic candidate for sarcopenia. Further research is needed to explore the molecular mechanisms underlying these effects and assess the drug's efficacy in clinical settings.

Acknowledgement
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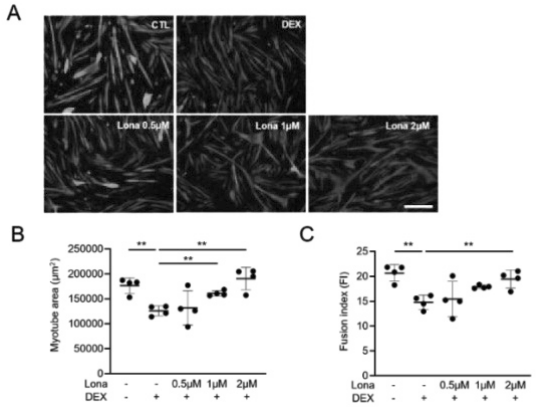

Figure 1. Lonafarnib reverses dexamethasone-induced muscle atrophy in cultured C2C12 myotubes.
Differentiated C2C12 myotubes showed reduced myotube area and fusion index (FI) with dexamethasone treatment, which were restored by lonafarnib treatment. (A) Immunofluorescence staining of MYH (green) and DAPI (blue) in C2C12 myotubes. (B) Quantification of C2C12 myotube area. (C) FI quantification. Magnification: x100; Scale bar: 275μm; **: p<.01. Data are presented as mean ± S.D. Statistical analysis was performed by one-way ANOVA followed by Games-Howell post hoc test.

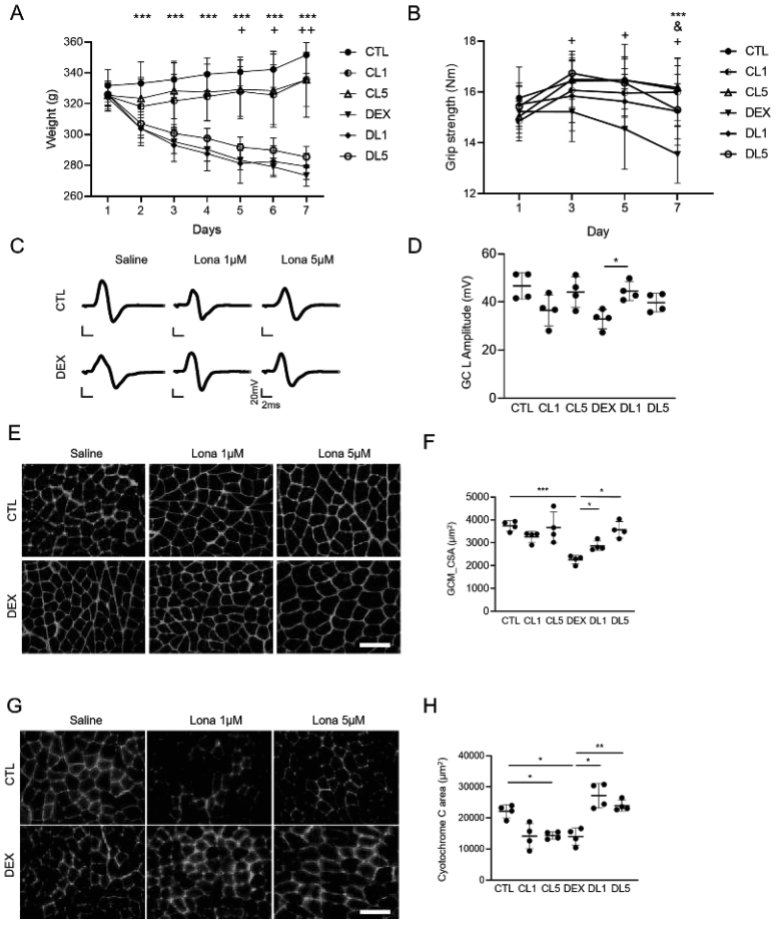

Figure 2. Lonafarnib protects against dexamethasone-induced muscle atrophy in S.D. rats.
Lonafarnib treatment protected body weight loss caused by dexamethasone treatment from Day 5-7 (A) [***: p<.001, CTL vs DEX groups; +: p<.05, DEX vs DL5] and grip strength (B) of S.D rats started to significantly decrease from Day 3 by dexamethasone treatment, whereas DL1 and DL5 groups grip strength were remains unchanged [***: p<.001, CTL vs DEX; &: p<.05, DEX vs DL1; +: p<.05 DEX vs DL5]. and CMAP amplitude (C, D) are restored in the DEX vs DL1 group [*: p<.05]. To determine changes in fiber cross-sectional area and fiber type, cross-sections of the GCM muscles of S.D rats were stained with immunofluorescence. Representative images of cross-sectioned muscles stained for dystrophin (green) and DAPI (blue) are shown in (E) and Representative images of mitochondria stained for Cytochrome C (Green) and DAPI (blue) are shown in (G). Fiber cross-sectional area (F) was quantified with total area and Cytochrome C area (H) was quantified with total stain area. Images magnification of 200x, scale bar: 125 μm. Data are mean ± S.D, statistical analysis was performed using one-way ANOVA followed by Games-Howell post-hoc test.

7-04

Muscle Protein Synthesis with a Hybrid Dairy and Plant-based Protein Blend (P4) is Equal to Whey Protein in a Murine Aging Model after Fasting

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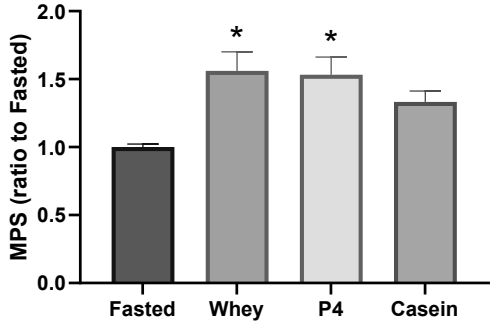
Introduction: P4, a specific combination of dairy proteins (whey and casein) and plant-based protein isolates (pea and soy) has been shown to provide a more balanced amino acid (AA) profile than its constituent single proteins [1]; however, less is known about how this translates to muscle protein synthesis (MPS). The aim of this study was to investigate the effect of P4 compared to whey or casein against fasted control on MPS.
Methods: C57/BL6Rj mice, aged 25 months, were fasted overnight, followed by an oral gavage of either whey, P4, casein, or water as a fasted control. 30-min after ingestion, puromycin (0.04 µmol·g^{-1} bodyweight) was subcutaneously injected; 30-min thereafter, mice were sacrificed. MPS, were measured by SUnSET-method, and signalling proteins were determined in the left-*tibialis anterior* (TA) muscle by WES-technique. AA-composition was determined in plasma and right-TA muscle. Dried blood spots (DBS) were analysed for postprandial AA-dynamics at 10-20-45-60-min.
Results: MPS was 1.6-fold increased with whey (p=0.006) and 1.5-fold with P4 compared to fasted (p=0.008), while no change was seen with casein (see Figure). This was confirmed by a significant increase of phosphorylated/total ratio of 4E-BP1 for both whey (p=0.004) and P4 (p=0.003). No changes were observed in p70S6K and mTOR phosphorylation/total ratio with whey or P4, however phosphorylation/total ratio was significantly lower in casein compared to fasted (p=0.027). Intramuscular leucine levels were lower for P4 (0.71 µmol·g dry weight^{-1}) compared to whey (0.97 µmol·g dry weight^{-1}) (p=0.0006). Ten minutes postprandial, DBS showed significantly increased blood AA-levels of BCAAs, histidine, lysine, threonine, arginine, and tyrosine for P4 versus fasted.
Conclusion: A mix of dairy and plant-based proteins (P4) resulted in a MPS response that was similar to whey protein in aged mice after fasting. This suggests that other anabolic triggers beyond leucine or the well-balanced amino acid profile and bioavailability of the blend benefit stimulation of MPS.



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7-05

A novel first-in-class USP19 inhibitor for the treatment of cancer-induced muscle atrophy

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Introduction: Cancer cachexia is a metabolic wasting syndrome characterised by weight loss, anorexia and anaemia as a result of tumour burden, and affects up to 80% of advanced cancer patients #1. Cachexia is particularly prevalent in pancreatic, lung, colorectal and gastro-intestinal cancers and can lead to reduced tolerance and responsiveness to chemotherapy, increased treatment-related toxicity and morbidity, and poor overall quality of life. There are currently no approved therapies for cancer cachexia. The development and maintenance of muscle tissue is dependent on the balance between protein synthesis and protein degradation, controlled through various anabolic and catabolic signalling pathways. Dysregulation of these pathways can result in muscle atrophy, which arises in many chronic illnesses. The ubiquitin proteasome system (UPS) has a central role in regulating skeletal muscle physiology. Previous work utilising USP19 knock out mouse models has demonstrated that USP19 plays an important role in muscle wasting and can protect against denervation-induced muscle atrophy #2. We have previously demonstrated that inhibition of USP19 enzymatic activity spares the muscle wasting observed in limb-casted and denervated mouse models of muscle wasting.
Method: Here, we report the discovery of a novel, highly potent and selective inhibitor of USP19 (ADC-846) and demonstrate its utility in an in vivo Lewis Lung Carcinoma-induced (LLC) cachexia model of muscle atrophy.
Result: Pharmacological inhibition of USP19 by ADC-846 increased lean muscle and fat mass following oral dosing in an LLC cachexia model and reduced the cachexic index by >60% compared to controls.
Conclusion: This data, in combination with our previous work detailing the effect of USP19 inhibition on muscle force and function, provides a much-needed novel pharmacological strategy for therapeutic intervention in muscle wasting conditions.

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7-06

Changes in CaCo-2 mRNA expression pathways affected by in vitro testosterone exposure

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Introduction: Cohort studies in male populations link reduced testosterone levels to increasing colorectal cancer incidence. Testosterone has been used in the ageing population to improve body composition, in different cancer types and in the perioperative timeframe to improve patient related outcomes. So far there is no clear evidence to link the use of perioperative testosterone in colorectal cancer patients, to improve their body composition is affecting the cancer progression. Our aim was to describe differences in mRNA expression patterns in a well-established colon adenocarcinoma cell line, treated with testosterone for 12 and 24-hours to identify pathways which could lead to cancer progression.
Methods: CaCo-2 cells (passages 12-20) were cultured in DMEM supplemented with 5% FBS, 2mM L-glutamine,100 U/ml penicillin, 100 µg/ml streptomycin, 1% NEAA, at 37^{O}C with 5% CO_2. Cells were sub cultured at 70-85% confluence. Evaluation of testosterone-related cytotoxicity was performed by the MTT colorimetric assay to identify the LD50 for the 12-hour and 24-hour treatment. The lower and higher physiological testosterone concentrations as well as the LD50 were added at 70-80% confluent cells. mRNA was isolated from the CaCo-2 cells using the RNAeasy kit (Qiagen). Sequencing was performed using the Illumina PE-150 platform. Following quality control (fastQC & cutadapt) and read mapping/ quantification (HISAT2 & featurecounts), the DESeq2 R/Bioconductor pipeline was used to identify differentially expressed genes. Pathway enrichment analysis was performed using overrepresentation (enrichR) and gene set enrichment analysis (GSEA), while the Hallmark, KEGG, Reactome, PID, Wikipathways, HumanCyc, and Biocarta databases were queried.
Results: Pathway enrichment analysis indicated upregulation of lipid metabolism pathways at 12 and 24-hours testosterone treatment windows. The inflammatory response remained similar for the physiological doses but was upregulated at LD50, enhancing expression of IL-2, IL-6, and TGFβ. mTORC1 and Wnt/ β-catenin signalling reduction at the LD50 for both groups. Genes upregulated by K-*ras* activation showed heterogeneous changes at the LD50 concentrations for both 12 and 24-hours treatments. *Hedgehog* signalling was significantly reduced at the 24-hour treatment. *Notch* signalling indicated changes at the LD50 concentration for both 12 and 24-hours.
Conclusion: Testosterone treatment alters pathways involved in progression, migration and growth in the CaCo-2 cell line. This has shown promising results for clinical utility but *ex vivo* and *in vivo* experiments are required to assess safety and efficacy.

7-07

CaCo-2 intracellular calcium changes following testosterone treatment

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Introduction: Intracellular calcium (Ca_i) homeostasis is important for regulating cellular functions. Previous studies in various cancer cell lines have identified changes in the apoptosis, altered cellular responses to stimuli, altered oxidative response and promotion of cell invasion. Testosterone induces a spike on Ca_i in myocytes and induces apoptosis in neuronal cells. There is no current evidence on how supplementary testosterone for body composition improvement affects the adenocarcinoma progression in patients. The aim of this study is to identify dynamic and end point Ca_i changes in CaCo-2 when treated with both physiological and supraphysiological testosterone concentrations.
Methods: CaCo-2 cells (passages 12-20) were cultured in DMEM supplemented with 5% FBS, 2mM L-glutamine,100 U/ml penicillin, 100 µg/ml streptomycin, 1% NEAA, at 37^{O}C with 5% CO_2. Cells were sub cultured at 70-85% confluence. Testosterone-related cytotoxicity was performed by the MTT colorimetric assay kit (ab21109). CaCo-2 cells were grown in a 96-well plate, treated with growth media without FBS and with the addition of physiological and supraphysiological (LD_{50}) testosterone concentrations for 12-hours and 24-hours, in order to measure the end point calcium homeostasis. The cells were also grown in a 96-well plate in PBS, the physiological and supraphysiological testosterone concentrations were added in order to identify the acute dynamic changes in Ca_i for the first 2 minutes while colorimetric measurements were taken at 20sec intervals Ca_i concentration was measured using the Fluo- 4NW Calcium Assay Kit (Invitrogen) on a microplate reader (BMG Labtech).
Results: There was statistical significance between the treatment concentrations at 12-hours as determined by one-way *ANOVA* (F=6.971, *p=0.003*), Tukey *post hoc* test identified differences between the highest physiological testosterone concentration and LD50 at 12-hours (*p=0.002*) for the end point Ca_i levels. At 24-hours treatment the Ca_i results one-way *ANOVA* (F=9.027, *p=0.0007*), Tukey *post hoc* test showed a difference between the highest physiological concentration and LD50 (*p=0.0005*). For the dynamic Ca_i changes at 12-hour and 24-hour treatment results are illustrated in figure 1.

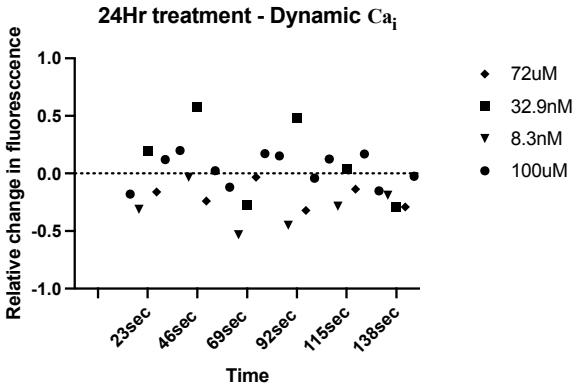

Figure 1: Ca_i changes in CaCo-2 cells using physiological, 12-hour & 24-hour LD_{50} testosterone treatment

Conclusion: Supraphysiological testosterone levels significantly reduce Ca_i compared to physiological levels and can induce cell death in CaCo-2 cells when Ca_i is measured at the end of the in vitro treatment. Dynamic Ca_i show the highest changes at the LD_{50} 12-hour treatment doses. Future studies should concentrate on pathway and membrane receptor expression and changes during the treatment.

7-08

Developing an evidence and theory based multimodal integrative intervention for the management of renal cachexia: a theory of change

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Introduction: Many health research advisory bodies have suggested that it is best practice to report on the Theory of Change (ToC) prior to piloting and evaluating an intervention to ensure the context and the effective elements of the intervention are understood. However, there are no previous ToC studies in relation to renal cachexia. Therefore, the aim of this study was use ToC to develop a theoretical framework for a multimodal, integrative, exercise, anti-inflammatory and dietary counselling (MMIEAD) for patients with renal cachexia, to better understand the causal pathways, anticipated outcomes and most suitable evaluation methods.
Methods: We used a Theory of Change (ToC) approach to guide six steps. Step 1 included inputs from a key stakeholder workshop, step 2 included the findings of our mixed-methods study and step 3 included the results from our systematic literature review. In step 4, we used wider research to identify the underlying causal pathways for renal cachexia. In steps 5 and 6 we developed and refined the ToC map in consultation with key stakeholders to illustrate how the intervention components of MMIEAD interact to achieve the intended long-term outcomes and anticipated impact.
Results: The ToC approach to this study provided a theoretical framework which allowed the context and effective elements of an intervention for renal cachexia patients to be better understood. We were able to develop a ToC map which not only allowed the design of a multi-modal intervention, but also delineation of the 'causal pathway', 'ceiling of accountability', 'preconditions' and identification of the 'ultimate impact' of the intervention (improved quality of life, optimal symptom management and reduced premature mortality). The ToC map will be used to form the basis of an evaluative cluster randomised controlled trial.
Conclusion: There have not been any previous studies that have used a ToC approach to develop an integrated multi-modal intervention for renal cachexia patients. Our ToC map will provide an evidence base for such integrated interventions aimed at improving quality of life, optimising symptom management and reducing premature mortality in patients with renal cachexia.

7-09

TERESA feasibility study (TEstosterone REplacement therapy (TRT) in SArcopenic male colorectal cancer patients) – Lessons from low recruitment numbers

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Background: Colorectal cancer is the third most common cancer worldwide (WHO data 2018), with rectum being the most commonly affected site. Cancer, via numerous complicated and not fully elucidated molecular pathways, results in sarcopenia and fatty infiltration of the muscle, known as myosteatosis. Colorectal cancer patients may experience sarcopenia with a prevalence of 25-60%, which increases further in metastatic cases. Sarcopenia and myosteatosis occur during chemotherapy, with sarcopenia occurring more in males compared to females.
Male cancer patients, experience either primary or secondary hypogonadism (prevalence 40-90%). Lower androgenicity has been associated with poor survival in the colorectal cancer population. The study's aim is to assess the recruitment and retention of the patients, the acceptability of the treatment (NCT 05367284).
Material and methods: This is a prospective single arm open label non randomised feasibility study. Recruitment takes place during the patient's diagnosis, if booked straight for an operation, or upon completion of chemoradiotherapy. The eligibility criteria, include colorectal cancer patients above the age of 45 years old, sarcopenic as assessed on their diagnostic or monitoring CT preoperatively, with low testosterone on two separate occasions (12nmol/L), while their surgery is planned 4-8 weeks from recruitment. The exclusion criteria ensure that the patient will not have any major complications from the use of testosterone treatment and included a PSA>3ng/ml, a haematocrit higher than 52%, metastatic disease, treatment for hypogonadism and morbid obesity among others. If patients fulfil the eligibility criteria, they are started on a topical testosterone gel (Testogel pump 16.2mg/g®), applied once daily for a total of 12 weeks. Patients are assessed at two further points during their treatment with regards to the testosterone levels and treatment acceptability, including quality of life, appetite and fatigue questionnaires.
Results: The study is currently open and recruiting at two UK sites, each with a high volume of rectal cancer patients being treated. Recruitment has been challenging due to the multiple visits from the patients and the multiple blood test to establish hypogonadism.
Conclusions: Our hypothesis is that by normalising the testosterone level, we are improving their post-surgical outcomes by increasing their muscle mass and optimising their physiological function. The main outcome of the study is to assess the feasibility of introducing testosterone replacement in the perioperative window. Similar future studies should take into consideration the patient visits during the study design.

7-10

Phase 2 study to assess the efficacy, safety, and tolerability of the GDF-15 inhibitor ponsegromab in patients with cancer cachexia

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Background: Cancer cachexia is a multifactorial metabolic syndrome of wasting characterized by anorexia, unintended weight loss, and decreased skeletal muscle mass, leading to progressive functional impairment, fatigue, diminished quality of life, poor response to anticancer therapy, and reduced survival. One of the biomarkers associated with cancer cachexia is cytokine growth differentiation factor 15 (GDF-15), which is secreted by tumor cells. Preliminary phase 1 data suggest that suppression of GDF-15 may lead to improvement in cachexia-related symptom burden. Ponsegromab is a potent and selective humanized monoclonal antibody that inhibits GDF-15-mediated signaling. The primary objective of this study (NCT05546476) is to assess the effect of ponsegromab on body weight in patients with cancer, cachexia, and elevated circulating GDF-15 concentrations. Secondary objectives include assessing physical activity, gait, anorexia/appetite, nausea and vomiting, fatigue, and safety. Exploratory objectives include evaluating pharmacokinetics, pharmacodynamics, and immunogenicity.
Trial Design: This phase 2 study will enroll approximately 168 adults with non–small cell lung, pancreatic, or colorectal cancers who have cachexia and elevated GDF-15 concentrations. The study will be conducted in 2 parts. The initial 12-week treatment period will be a randomized, double-blind, placebo-controlled study wherein participants who meet eligibility criteria will be randomized 1:1:1:1 to one of 3 dose groups of ponsegromab (administered subcutaneously [SC] every 4 weeks [Q4W]) or placebo. The double-blind period will be followed by optional open-label treatment (OLT) with ponsegromab Q4W SC for up to 1 year. Upon completion of the optional OLT period, there will be a follow-up visit at Week 72. Participants who do not proceed with the optional OLT period will complete the Week 12 visit and a follow-up visit at Week 16. The primary endpoint is the mean change from baseline in body weight at Week 12. A mixed model for repeated measures followed by a Bayesian E_{max} model will be used for the primary analysis. Secondary endpoints include physical activity and gait measured by remote digital sensors; patient-reported appetite-related symptoms assessed by Functional Assessment of Anorexia-Cachexia Therapy scores; anorexia/appetite, nausea, vomiting, and fatigue evaluated according to questions from the Cancer-related Cachexia Symptom Diary; and incidence of adverse events, safety laboratory tests, vital signs, and electrocardiogram abnormalities.
ClinicalTrials.gov identifier: NCT05546476

7-11

Ruxolitinib's Nutritional Effects In patients with Myelofibrosis: preliminary results

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Introduction: Myelofibrosis (MF) is a chronic myeloproliferative neoplasm that can cause cachexia by inducing systemic inflammatory state (IL-6 and TNF-a) and by reducing nutritional intake due to massive splenomegaly. We aimed at evaluating improvement and modifications of nutritional status in MF patients during Ruxolitinib therapy, the first JAK1/2-inhibitor available.
Methods: Before (baseline, T0) and during treatment (3 months, T1; 6 months, T2; 12 months, T3) Malnutrition (GLIM criteria), Anorexia (FAACT score), body composition (BIA) were assessed.
Results: We enrolled 23 MF patients (M:13, mean age 64.7±12.5). At baseline, anorexia, malnutrition and unintentional weight loss, were present in 22%, 50% and 70% of them, respectively. During treatment with Ruxolitinib, we observed improvement in body weight (BW, Kg) (T0 68.6±14.22; T3 77.3±12.4), fat mass (FM, Kg) (from T0 15.8±5.8; to T2 20.3±8.11 and to T3 23.4±7.6) (p=0.04, p=0.01 respectively) with preservation of lean body mass (LBM, Kg) (T0 52.8±12; T2 52.1±12.1; T3 54.3±12.4) (p>0.05) and increase of anorexia score for all patients (p=0.0005) and for anorexic ones (T0 26.2±6.3; T1 37.6±6; T2 39.2±6.2) (p=0.01), irrespective of disease response to therapy according to IWG criteria (11 patients with clinical improvement, 7 and 3 patients with stable and progressive disease respectively, 2 not evaluable for recent enrolment).
Conclusion: Our preliminary data show that Ruxolitinib is associated with improvement of anorexia score and BW in MF patients. The latter is mainly due to increased FM, and preservation of LBM. This data suggest that Ruxolitinib may be associated with benefit in nutritional status and body composition, regardless of clinical response in patients with MF.

7-12

Assessing the effect of intra-abdominal malignancy on the impact of a short-term homebased unsupervised exercise on skeletal muscle mitochondrial OXPHOS function

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Introduction: Exercise has long been viewed as a potential intervention to combat the declines seen with both sarcopenia and cachexia. Previous studies have shown that 4 weeks of high-intensity interval training improves cardiorespiratory fitness in patients with malignancy, but not all. The underlying physiological response to exercise is not fully understood, but alterations to mitochondrial respiration are thought to play a part. Animal models have demonstrated that mitochondrial function is as a potential causative component of sarcopenia and cachexia, with translational studies less clear.
We hypothesised that malignancy reduced the ability for skeletal muscle mitochondrial function to be altered by an exercise intervention.
Methods: This study was approved by an NHS research ethics committee (IRAS ID: 275264). Male patients awaiting surgery with curative intent for colorectal and prostate cancer, and healthy controls were recruited. Muscle biopsies of *vastus*

lateralis were taken before and after 4-weeks home-based exercise (3x/wk). Mitochondrial oxidative phosphorylation (OXPHOS) was analysed using high-resolution respirometry (Oroboros Instruments).
Results: To date there have been 7 healthy volunteers (Age: 68.8 (6.5)) and 12 cancer patients (Age: 65.6 (6.8)) completing the intervention.
Cancer patients had significantly lower maximal coupled (55.62pmol/(s*mg) *vs.* 81.38pmol/(s*mg), *p*=0.001) and uncoupled (57.96pmol/(s*mg) *vs.* 98.88pmol/(s*mg), *p*=0.006) OXPHOS capacity compared to healthy controls at baseline. Post exercise training there was no significant difference in maximal coupled (55.62pmol/(s*mg) vs. 75.02pmol/(s*mg), p> 0.05) and uncoupled (71.38pmol/(s*mg) vs. 95.26pmol/(s*mg), p=0.16) OXPHOS capacity between the two cohorts. Conclusions: Our study demonstrates that the OXPHOS capacity of skeletal muscle mitochondria is impaired within the cancer cohort studied, this supports the previous animal studies suggesting its role in cancer cachexia.
A short homebased unsupervised exercise program appears to attenuate the declines in OXPHOS function seen in the cancer cohort. Further work is needed to optimize an exercise intervention, and to assess the impact of varying malignancy type and stage upon mitochondrial function.

7-13
Association between sarcopenia and urinary dysfunction in patients with dysphagia

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Introduction: To investigate the association between sarcopenia and urinary dysfunction in patients with dysphagia.
Methods: A cross-sectional study was conducted on 460 patients registered in the Japanese Sarcopenic Dysphagia Database with no missing data on urinary dysfunction and sarcopenia. Urinary dysfunction was defined as either urinary incontinence or urethral catheter use. Sarcopenia was diagnosed according to the AWGS2019 criteria. The association between urinary dysfunction and sarcopenia, calf circumference, and handgrip strength was assessed in univariate and multivariate analyses. Logistic regression analyses were adjusted for age, sex, facility type (acute care or non-acute care), Charlson Comorbidity Index (CCI), and Barthel Index.
Results: The mean age was 80.8 ± 10.5 years, with 229 men and 231 women. 202 were in acute care hospitals and 258 in other settings. Sarcopenia was present in 404 (88%) patients. 54 (12%) patients had urinary incontinence and 83 (18%) patients had urethral catheters, resulting in 137 (30%) patients with urinary dysfunction. Median handgrip strength was 12 kg (interquartile range: 6 kg, 19 kg). Median calf circumference was 28 cm (25 cm, 31 cm). Median Food Intake Level Scale (FILS) score was 7 (3, 8). Median Barthel Index score was 25 (5, 50). Median CCI was 2 (1, 4). Univariate analysis showed no significant association between sarcopenia and urinary dysfunction (p=0.440). In contrast, calf circumference (with urinary dysfunction: 27.4 cm, without urinary dysfunction: 28.5 cm, p=0.006) and handgrip strength (with urinary dysfunction: 9.7 kg, without urinary dysfunction: 14.4 kg, p<0.001) were significantly associated with urinary dysfunction. Logistic regression analysis showed that sarcopenia (odds ratio: 0.921, 95% confidence interval: 0.435, 1.950) and calf circumference (odds ratio: 0.990, 95% confidence interval: 0.933, 1.050) were not independently associated with urinary dysfunction. On the other hand, handgrip strength was independently associated with urinary dysfunction (odds ratio: 0.968, 95% confidence interval: 0.938, 0.998), with a cut-off value of 10.85 kg (sensitivity 0.598, specificity 0.562, AUC 0.644) in the ROC curve.
Conclusions: Sarcopenia was not significantly associated with urinary dysfunction; however, handgrip strength was significantly associated with urinary dysfunction. The handgrip strength of the patients in this study was significantly lower than the cut-off value for the diagnosis of sarcopenia in the AWGS 2019 criteria. This suggests that lower handgrip strength in patients with sarcopenia may be associated with urinary dysfunction.

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A, B1-3

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J, M1, N

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Poster Session 1.1, E, Poster Session 2.1, P, T1

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