

Abstract

1-16

Cancer cachexia induces iBAT thermogenesis in UCP1^{-/-} mice

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Background: Cancer cachexia (CC) is a multifactorial syndrome with an unknown aetiology. The main symptom is the progressive body weight loss. During the development of the syndrome, there is an increase in uncoupling protein 1 (UCP1) in white adipose tissue (WAT) and intrascapular brown adipose tissue (iBAT), resulting in increased energy expenditure and heat generation. Recently, it was proposed that energy expenditure in CC does not depend on UCP1 but on an independent thermogenic pathway. In this sense, this study aimed to evaluate the thermogenic activity of UCP1 knockout mice during CC.

Methods: Male C57BL/6 mice (8–10 week old) wild-type (WT) and knockout for UCP1 (UCP1^{-/-}) were subcutaneously inoculated with 200 μ L (3.5×10^5) of Lewis Lung Carcinoma Cell line (TB) and vehicle saline (CO). After 28 days, animals were submitted to thermal infrared measurements (T460, emissivity of 0.98, FLIR Systems). After analysing, animals were sacrificed, and the WAT subcutaneous (SC) and epididymal (EP), BAT, and gastrocnemius muscle (GA) were collected.

Results: UCP1^{-/-} TB presented higher maximum body temperature (10.4-fold, $P = 0.0500$) and tendency to increase the maximum temperature of BAT ($P = 0.0750$) when compared to UCP1^{-/-} CO. In addition, UCP1^{-/-} TB have preserved both the body weight loss (11.0-fold, $P = 0.0101$) and the values of the index of cachexia (45.4%, $P = 0.0305$) when compared to TB group. The adipose tissue atrophy (EP, 14.6-fold and BAT, 15.3-fold) was also attenuated in UCP1^{-/-} TB group when compared to TB group.

Conclusions: In general, the results showed that UCP1^{-/-} animals presented attenuation in the main markers of CC. In addition, the BAT of these animals showed an increase in their thermogenic capacity, suggesting that its activation, at least in part, may be activated by an UCP1-independent pathway.

1-17

Lack of synergy between β -agonist treatment and a blockage of sarcoplasmic calcium flow in a rat cancer cachexia model

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Background: Accelerated muscle and adipose tissue loss are two of the main aspects of cancer cachexia. The use of β 2-agonists, formoterol in particular, has proven to be very successful in the treatment of the syndrome in preclinical models. The aim of the present investigation was to study the effects on body weight loss in tumour-bearing animals of a combination of formoterol and dantrolene, an inhibitor of the ryanodine receptor 1 (RyR1) involved in the sarcoplasmic reticulum calcium flow.

Methods: Rats were divided into two groups, namely controls (C) and tumour-bearing (TB). TB group was further divided into four subgroups: untreated (saline as a vehicle), treated with formoterol (TF) (0.3 mg/kg body weight in saline, subcutaneous (s.c.), daily), treated with dantrolene (TD) (5 mg/kg body weight in saline, subcutaneous (s.c.), daily), and double-treated (TFD) with formoterol (0.3 mg/kg body weight, subcutaneous (s.c.), daily) and dantrolene (5 mg/kg body weight, subcutaneous (s.c.), daily). Seven days after tumour transplantation, muscle weights, grip force, and total physical activity were determined in all experimental groups.

Results: While formoterol has, as in previous studies, a very positive effect in reducing muscle weight loss, dantrolene had no effects, neither on skeletal muscle or any of the parameters studied. Finally, the combined treatment (formoterol and dantrolene) did not result in any significant benefit on the action of the β 2-agonist.

Conclusions: It is concluded that in the preclinical cachectic model used, no synergy exists between β 2-agonist treatment and the blockade of sarcoplasmic calcium flow.

1-18

Chronic kidney disease induces muscle wasting via soluble pro-cachectic factors

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Chronic kidney disease (CKD) represents the progressive and permanent loss of kidney function. While muscle wasting is a prominent feature of CKD and significantly increases morbidity and mortality, this interorgan signalling network remains poorly understood. Here, we identified muscle wasting in a mouse model of CKD (Klf3a deficiency), where we discovered an increased renal production of soluble pro-cachectic factors (i.e. Activin A) as shown by both transcriptional regulation and increases in plasma levels, an observation that was also confirmed in patients at different stages of CKD. Furthermore, pharmacological blockade of the identified pro-cachectic factor in mice prevented muscle wasting and progression to CKD by reducing its levels in the plasma—both a direct neutralization and recovery of kidney function. Together, this study uncovers a previously unrecognized crosstalk between kidney and muscle and provides a potential therapeutic strategy for muscle wasting in patients with CKD.

2-09

Interleukin-6 controls microRNA-regulated networks in skeletal muscle cells

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Systemic inflammation contributes to the development of cachexia, and the pro-inflammatory cytokine interleukin-6 (IL-6) has emerged as a critical factor related to muscle wasting during disease. Regulation of gene expression by microRNAs (miRNAs) in skeletal muscles integrates regulatory networks, which are predicted to involve thousands of transcripts through different mechanisms. Our objective was to analyse the global miRNA expression profile of skeletal muscle cells atrophy induced by IL-6 to uncover potential miRNAs involved with this catabolic condition. Genome-wide gene expression profiles of miRNAs were performed by using TaqMan Low-Density Arrays in C2C12 myotubes treated with IL-6, followed by *in silico* predictions for miRNA targets. High concentrations of IL-6 induced myotube atrophy and decreased the levels of *Myh7* and *e-MHC*. Moreover, we identified 20 differentially expressed miRNAs in C2C12 myotubes in response to IL-6 (five upregulated, and 15 downregulated). Gene Ontology analysis of the predicted targets of these miRNAs revealed potential posttranscriptional regulation of genes involved in cell differentiation, apoptosis, migration, and catabolic processes. Interestingly, the miR-497 was suppressed by the treatment with IL-6, and it was found in the literature to be downregulated in other muscle catabolic conditions. Thus, we used miR-497 mimics and inhibitors to explore the function of this miRNA. The miR-497 changed cell cycle target genes, such as *Ccnd2* and *Ccne1*, but did not alter myoblast proliferation, as assessed by the EdU assay. Also, miR-497 mimic induced myotubes atrophy. The miR-497 inhibitor did not change myotubes diameters but resulted in overexpression of the miR-497 target genes *Insr* and *Igf1r*. These genes are involved with the insulin-like growth factor pathway and are overexpressed in muscle samples of cachexia models (GSE48363, GSE63032, GSE24111, and GSE51931). Our miRNA analysis identified miRNA-regulated networks and suggests that miR-497 is involved in a compensatory mechanism to muscle atrophy in response to IL-6.

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2-11

Transcriptomic analysis reveals heme-related genes are downregulated in chronic obstructive pulmonary disease cachexia

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Background: Cachexia contributes to increased mortality and reduced quality of life in chronic obstructive pulmonary disease (COPD). COPD cachexia may be associated with underlying gene expression changes that could provide valuable insights for surveillance and drug development. Our goal was to identify differential gene expression signatures associated with COPD cachexia in current and former smokers.

Methods: We analysed gene expression data from a discovery cohort of COPD patients (COPDGene, $N = 400$) and assessed replication in ECLIPSE ($N = 140$). Whole blood expression data were generated using RNA-sequencing in COPDGene and Affymetrix in ECLIPSE. In COPDGene, cachexia was defined as weight loss $>5\%$ in the past 12 months or low body mass index (BMI) and 1/3 criteria: decreased muscle strength (6 min walk distance), anaemia, and low fat-free mass index (FFMI). In ECLIPSE, cachexia was defined as weight loss $>5\%$ in the past 12 months or low BMI and 3/5 criteria: low 6 min walk distance, anorexia, abnormal biochemistry (anaemia or high c-reactive protein), fatigue, and low FFMI. Differential gene expression was performed using regression models comparing cachectic and noncachectic subjects, adjusting for confounders including age and sex. Gene set enrichment analysis was performed using MSigDB.

Results: Cachexia prevalence was 13.7% in COPDGene and 7.9% in ECLIPSE. In COPDGene, 23 genes were significantly differentially expressed ($FDR-P < 0.05$) in cachectic versus noncachectic COPD patients. Replication analyses revealed 14/23 genes significantly replicated in ECLIPSE ($P < 0.05$) and were downregulated in each cohort. Several replicated genes are involved with heme metabolism (*ALAS2*, *ANK1*, *TNS1*, *SPTB*, *TRIM58*, *PPP2R5*) and biosynthesis (*ALAS2*,

SLC25A39). Remaining significant genes (*ASCC2*, *CDC34*, *GUCD1*, *PLEK2*, *RILP*, *SMIM24*, *UBXN6*) are involved with DNA damage repair, protein metabolism, and ubiquitination.

Conclusions: Several genes were downregulated among cachectic COPD patients, including genes regulating heme metabolism. Impaired heme biosynthesis may contribute to cachexia through free-iron buildup, oxidative tissue damage, and aberrant repair.

2-12

Pancreatic tumour organoid conditioned medium negatively affects the smooth muscle cell contractile phenotype

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Background: Patients with pancreatic cancer often suffer from gastrointestinal symptoms which may be the consequence of underlying gastrointestinal motility problems. Although muscle loss in cachectic pancreatic cancer patients is most obvious in skeletal muscle, these clinical symptoms as well as our recent analysis of smooth muscle characteristics in cachectic patients suggest that cachexia manifests itself also in smooth muscle, a tissue responsible for contraction of the gastrointestinal tract. We aimed to investigate whether tumour cells from cachectic pancreatic cancer patients directly affect the smooth muscle cell (SMC) contractile phenotype.

Methods: 3D organoids were established from pancreatic tumour tissue of eight patients with a variable degree of cachexia. Human visceral SMCs were grown to confluency on basement membrane matrix coated surfaces under reduced serum conditions to induce a contractile phenotype and subsequently exposed to organoid conditioned medium (CM) (50% v/v). Markers of muscle atrophy, contractile machinery, and proliferation were evaluated by qPCR and Western blot. SMC proliferation and migration was also monitored by real-time imaging.

Results: CM from pancreatic tumour organoids of cachectic patients did not affect expression of Atrogin-1, a key E3-ubiquitin ligase that is involved in skeletal muscle atrophy. Nevertheless, exposure to organoid CM caused reduced protein levels of α -smooth muscle actin (α -SMA) (1.4-fold, $P < 0.001$) and smooth muscle protein 22- α (SM22 α) (2-fold, $P < 0.001$), two key proteins involved in SMC contraction. Moreover, γ -smooth muscle actin expression was significantly reduced (1.4-fold, $P < 0.001$). Concurrently, expression of

S100A4, a key protein involved in SMC proliferation, was increased (1.4-fold, $P < 0.001$). In line, SMCs exposed to organoid CM showed a significantly reduced doubling time (control: 36.2 h vs. organoid CM: 29.9 h, $P < 0.001$).

Conclusions: Pancreatic tumour cells from cachectic patients secrete factors that diminish the contractile SMC phenotype, which may be the underlying cause of the frequently observed gastrointestinal motility problems in these patients.

2-13

In vitro chemotherapy response of pancreatic tumour organoids from cachectic and noncachectic patients

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Background: Pancreatic cancer is a devastating disease with poor clinical outcome due to a lack of adequate systemic therapies. Additionally, 80% of patients suffer from cachexia, a syndrome of severe weight and/or muscle loss that is associated with reduced chemotherapy efficacy. Organoids are 3D cell cultures that can be used to investigate drug responses *in vitro*. This study aimed to identify differences in responses to chemotherapy in tumour organoids derived from cachectic versus noncachectic patients.

Methods: Organoids were established from resected tumour tissue from patients with pancreatic ductal adenocarcinoma ($n = 9$). Three cell lines (two from cachectic donors and one from a noncachectic donor) were exposed to a concentration range of four chemotherapeutics that are frequently used for the treatment of pancreatic cancer: gemcitabine, paclitaxel, irinotecan, and 5-fluorouracil. After 5 days, cell viability was assessed using the CellTiter-Glo® ATP assay.

Results: Significant differences were observed between the IC50 values of the three patients for gemcitabine and paclitaxel that indicate resistance to these drugs. This resistance was not restricted to the organoid lines coming from cachectic donors. For gemcitabine, one of the cachectic patients showed significant resistance (IC50 $5.46 \times 10^{-2} \mu\text{M}$ versus $6.43 \times 10^{-3} \mu\text{M}$ and $9.09 \times 10^{-3} \mu\text{M}$, $P < 0.005$), whereas for paclitaxel, the noncachectic patient was significantly resistant (IC50 $9.18 \times 10^{-3} \mu\text{M}$ versus $2.22 \times 10^{-3} \mu\text{M}$ and $1.92 \times 10^{-3} \mu\text{M}$, $P < 0.01$). For irinotecan and 5-fluorouracil, the IC50 values were similar for all three patients.

Conclusions: Our present data show significant differences in chemotherapy sensitivity between organoid lines that are partly related to the cachexia status of the donor patient. Our aim is to relate the *in vitro* chemotherapy sensitivity to the cachexia status, patient treatment response, and survival. This can potentially lead to better selection of therapies for the treatment of cancer patients.

2-14

ZIP14 as a mediator of cachexia in metastatic cancers

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Category: Cachexia – Mechanisms, animal models

Metastasis contributes to the vast majority of cancer-related deaths. Metastatic tumours secrete factors that systemically affect various organs leading to metabolic dysfunction and accelerated death. More than 80% of metastatic cancer patients experience a progressive and debilitating loss of muscle mass and function by a process known as cachexia. Cachectic patients suffer deterioration of cardiac and diaphragm muscles and often die prematurely due to respiratory and cardiac failure. The prognosis for these patients is further diminished by the fact that they are often too weak to tolerate standard doses of antineoplastic treatments. Cachexia is therefore an important determinant of therapeutic response, outcome, and patient survival in metastatic cancer patients. Although systemic metabolic derangements and sustained inflammation predominate in cachexia, the underlying molecular mechanisms driving its development are not well understood. Therefore, insights into the specific interventions that could treat cachexia are expected to improve treatment outcome, survival, and quality of life in cancer patients. We identified a metal ion transporter, ZIP14 that is upregulated in cachectic muscles from metastatic colon, lung, breast, and pancreatic cancer. We find that TNF- α and TGF-beta cytokines upregulate ZIP14 in muscles, which in turn increases the accumulation of intracellular zinc in muscle cells. Increased zinc influx in muscle cells degrades myosin heavy chain protein and blocks normal muscle differentiation. Germline ablation or muscle-specific depletion of *Zip14* markedly inhibits cancer-associated cachexia. Our study demonstrates a novel function of ZIP14 in muscle cells as a mediator of cachexia in metastatic cancers. Insights from this study can be used to develop therapeutic strategies to prevent cachexia and to improve the survival and quality of life in metastatic cancer patients.

3-20

Effect of human cancer cachexia on the partition of lipids and inflammation in the liver

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Background: Cancer cachexia is a paraneoplastic wasting syndrome present in 50% of all patients and is up to 80% of those with advanced disease. Recent studies have suggested that the liver plays a key regulatory role in the pathogenesis of cancer cachexia, even though the exact underlying mechanisms remain to be elucidated. We investigated inflammation and partition of lipids in the liver of colorectal cancer weight stable (WSC) and colorectal cancer cachectic patients (CC) (Evans, 2008).

Methods: Nine WSC and nine CC participated in the study and seven patients with coledochitis as a control groups (C). Liver biopsies were obtained during surgery. Liver samples were fixed in paraformaldehyde and embedded into paraffin. The sections were stained with haematoxylin and eosin, PAS, and Mallory. Biopsies were evaluated in terms of histopathology, adopting the NASH activity score (Kleiner's score). After osmium impregnation, nine liver biopsies were studied under light and electron microscopy. Protein expression of inflammatory and chemotactic factors, and liver proteins were measured with Multiplex Magpix (®) system. Gene expression of liver lipid metabolism proteins was measured by qRT-PCR. Student's *t*-test or Mann–Whitney test with multiple comparisons was employed for parametric and non-parametric data, respectively. The significance level was set at $P < 0.05$.

Results: Light histology and electron microscopy showed abundance of lipid droplets, indicating liver TAG accumulation in cachectic patients, as well as fibrosis, but NAFLD score yielded no differences among groups, despite increased portal activity in CC. Liver FABP mRNA was higher in WSC, compared with other groups ($P = 0.0021$). Protein expression of IL-1 α and IL-8 were higher in CC ($P < 0.05$), compared with control and WSC.

Conclusions: Liver inflammation is associated with cachexia and contributes to hepatic steatosis. CC liver expressed higher inflammatory cytokine and increased lipids inclusion content compared to WSC and control groups.

3-22

Transcriptome analysis reveals potential cancer cachexia biomarkers in head and neck squamous cell cancer patients with low muscularity

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Background: Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that leads to increased morbidity and poor prognosis. The incidence of cachexia in patients with head and neck squamous cell carcinoma (HNSC) is unknown, but more than 50% of patients with advanced head and neck cancer have significant weight loss and possible cachexia. The molecular mechanism of cachexia in HNSC is incompletely understood, and there is no biomarker to predict which patients will develop the syndrome.

Methods: Here, we reanalysed computed tomography (CT) images—available on The Cancer Imaging Archive database—and tumour transcriptome data from The Cancer Genome Atlas (TCGA) aiming to identify new potentially secreted molecules by the tumours of patients with low muscularity. Sternocleidomastoid muscle area from CT of 66 HNSC patients (training set) was analysed to identify patients with high or low muscularity. Next, we studied the relationship of muscularity to overall survival and disease-free survival. Moreover, to verify the biomarkers prognostic value in HNSC, we also used tumour gene expression data to predict survival using additional validation sets (four cohorts, 721 patients) available in SurvExpress database.

Results: Muscularity successfully discriminated HNSC patients into high-risk and low-risk groups, based on overall survival ($P = 0.0120$). Using tumour gene expression data from our training set, we identified 413 deregulated transcripts in patients with low muscularity. Genes encoding predicted secreted proteins such as *IL-6*, *IL-8*, *IL-24*, *CCL24*, *FGA*, *FGB*, and *FGG* were found upregulated genes and are new potential cachexia biomarkers in HNSC secretome. Noteworthy, these tumour biomarkers were capable of distinguishing HNSC patients with poor prognosis.

Conclusions: Our integrative analysis of muscularity CT-based data and transcriptome profiles identified cancer patients with low muscularity, from which the tumours expressed a set of cachexia-related transcripts capable of predicting poor prognosis.

3-23

Lipocalin 2 is a driver of sickness response during pancreatic cancer cachexia

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Background: Cancer cachexia is a devastating condition that occurs in up to 80% of patients with pancreatic ductal adenocarcinoma (PDAC), where it significantly contributes to reduced survival, accelerated disease progression, and limits patients' ability to tolerate therapy. Effective therapies are lacking for cachexia, and its mechanisms remain elusive. Lipocalin 2 (LCN2) is an acute phase protein that mediates inflammation in several pathologic conditions and appetite during normal physiology but is unexplored in cancer cachexia. In this study, we assessed the role of LCN2 in driving sickness responses during the development of pancreatic cancer cachexia.

Methods: A pancreatic tumor cell line from a syngeneic C57BL/6 KRAS^{G12D/+} P53^{R172/+} Pdx-Cre (KPC) mouse was orthotopically implanted into sex, age, and body weight-matched wild-type (WT) and LCN2 knockout (LCN2KO) mice. We monitored the effects of LCN2 deletion on PDAC cachexia through behavioural, molecular, and histologic analysis.

Results: LCN2 was robustly upregulated in the serum and cerebrospinal fluid of WT mice during PDAC cachexia, and brain endothelium amplify the expression of LCN2 when challenged with KPC conditioned medium *in vitro*. Central administration of LCN2 is sufficient to induce cachexia features of anorexia and weight loss. Finally, genetic deletion of LCN2 significantly ameliorated PDAC-associated anorexia, fatigue, and muscle catabolism in both skeletal and cardiac muscles.

Conclusions: LCN2 is robustly induced in the periphery and brain during PDAC cachexia and is a critical driver of anorexia, muscle catabolism, and fatigue. Our findings implicate LCN2 as a pathologic mediator of cachexia symptoms and demonstrate its promise as a novel therapeutic target for this crippling condition.

3-24

Colorectal cancer-released exosomes are enriched in Hsp70 in cachectic patients

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Background: Cachexia is an inflammatory syndrome characterized by muscle wasting that leads to an increased cancer

mortality due to weight loss, low quality of life, anorexia, and systemic inflammation. The mechanism about cancer-induced weight loss remains unclear. Emerging evidence support that tumour-released heat shock proteins, such as Hsp70 and Hsp90, are responsible for the tumour capacity to cause muscle loss. The aim of this study is to investigate levels of Hsp70 and Hsp90 released by tumour-derived exosomes from colorectal cachectic patients.

Methods: Colorectal cancer patients were divided into weight stable cancer (WSC $n = 10$) and cachectic cancer (CC $n = 10$) groups, after signature of the informed consent form. Samples were collected during surgery. Exosomes were isolated from tumour tissue explants culture and characterized based on size and morphology by transmission electron microscope (TEM). Western blot employing typical exosome markers (CD63) was performed. Hsp70 and Hsp90 levels in tumour-derived exosomes and plasma were analysed by ELISA following the manufacturer's instruction.

Results: Particles were confirmed to be exosomes by TEM; Exosomes presented typically cup-shaped extracellular vesicles morphology with 30–100 nm diameter. In addition, we found expression of CD63+ exosomes detectable in a dose-dependent assay (50, 12.5, and 3.1 μg). We detected high level of Hsp70 in tumour-derived exosomes from cachectic patients ($P = 0.022$), although we did not find difference in Hsp90 expression in the exosomes between the groups ($P = 0.955$). Finally, we observed a tendency of Hsp90 content to be increased in the circulation of cachectic cancer patients ($P = 0.075$).

Conclusions: In summary, the higher levels of tumour-released heat shock proteins in cachectic patients suggest a new role of Hsp70 and Hsp90 as cachexins contributing to muscle wasting, as previously found for animal models. These findings may be related to the increased tumour secretion of inflammatory factors and the unbalance redox response mediated by hypoxic conditions in the tumour microenvironment of cachectic patients described by our group in a previous study.

3-25

Biologically distinct body composition features in colorectal cancer

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Background: Cancer cachexia leads to marked alterations in body composition which can be captured using computed tomography (CT) imaging. Low muscle mass (sarcopenia), low muscle radiodensity (myosteotosis) and, more recently,

high-fat radiodensity have all been described in patients with cancer cachexia. However, it is not clear whether these represent different phenotypes driven by different biological phenomena.

Methods: In 340 patients with colorectal cancer (CRC) (stages 1–4), body composition features were evaluated on CT scans at L3 using Slice-O-Matic image analysis. Associations with overall survival (OS) were explored, using Cut-off Finder. Blood sera from these patients were analysed for 20 proteins implicated in cancer-associated alterations in metabolism and inflammation.

Results: We determined the skeletal muscle index, muscle radiodensity, and subcutaneous fat density associated with a decreased OS in this cohort. Specifically, we defined sarcopenia, myosteatorsis, and high-fat density by dichotomizing patients with optimal cut-off values associated with significantly decreased OS using log-rank testing ($P = 0.010$, $P = 0.048$, and $P = 0.001$, respectively). Using population-specific cut-offs, 44% had sarcopenia; 16% had myosteatorsis; and 33% had high-fat density. These features appeared mutually exclusive; 57% of patients had only one of these features. OS was even more truncated when more than one of these body composition features coexisted ($P < 0.001$). Patterns of circulating mediators were significantly different in individuals with each body composition feature. Briefly, sarcopenia was associated with low levels of IGF-1 ($P = 0.001$), myosteatorsis was associated with high levels of leptin ($P = 0.001$), and high-fat density was associated with high levels of adiponectin ($P = 0.005$).

Conclusions: Three body composition features associated with reduced OS were observed in CRC patients. These appeared to be mutually exclusive, biologically distinct, and have synergistic effects on survival. Currently, we are evaluating the serum lipidome and metabolome as well as broad-spectrum proteomics of this cohort to identify additional correlates that will inform underlying biological associations.

3-26

Risk factors for surgery-related muscle loss after liver resection for colorectal liver metastasis

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Background: Preoperative sarcopenia and surgery-related muscle loss (SML) negatively affect postoperative outcome. Although the impact of preoperative sarcopenia has been well described, limited literature is available about SML and its risk factors after liver resection. By identifying these risk factors,

perioperative intervention might prevent or reduce SML and subsequently improve postoperative outcome. This study investigated risk factors for (clinically relevant) SML and outcome after liver resection for colorectal liver metastasis.

Methods: We retrospectively analysed data of patients diagnosed with CRLM who underwent liver resection from 2006 to 2016. Total psoas area (TPA) muscle index was measured using computed tomography images at L3 level, obtained within 6 weeks before and 6 weeks after surgery. Change in TPA after surgery was calculated. Muscle loss $\geq 5\%$ was defined as clinically relevant SML.

Results: A total of 121 patients were analysed. Fifty-five (45%) patients had SML of whom 32 (58%) had clinically relevant SML. Multivariate analysis demonstrated that diabetes ($P = 0.027$) and a preoperative high TPA muscle mass index ($P = 0.039$) were associated with SML. However, a preoperative low muscle mass index ($P = 0.003$), diabetes ($P = 0.019$), pulmonary disease ($P = 0.002$), and male gender ($P = 0.026$) were associated with clinically relevant SML. Clinically relevant SML was associated with a decreased overall survival ($P = 0.029$).

Conclusions: Almost half of patients had SML within 6 weeks after liver resection for CRLM. Among them, nearly 60% had clinically relevant SML. A preoperative low muscle mass index, diabetes, pulmonary disease, and male gender were found to be independently associated with clinically relevant SML. Clinically relevant SML had a negative effect on overall survival.

3-28

Role of mTOR in skeletal muscle during cancer cachexia

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Cancer cachexia is a multiorgan syndrome which is characterized by a major loss in body weight, particularly in muscle and adipose tissue. It has been shown that if this cancer-related muscle wasting is reserved or prevented, lifespan is significantly improved. A critical mediator of adult muscle mass and function in skeletal muscle is the kinase mTOR; however, its role during cancer cachexia is unknown yet.

To assess the function of mTOR during cancer cachexia, we used two mouse models in which we have deleted mTOR or Raptor only in adult skeletal muscle; in the first one, both mTOR complexes are absent, instead, in the Raptor model, only mTORC1 result deleted. We performed two models of cancer cachexia: Lewis Lung Carcinoma (LLC) that leads to chronic cachexia and C26 Colon Carcinoma that leads to acute atrophy.

3-29

Investigation of the direct role of tumour secretions in the development of cachexia in head and neck cancer patients

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Background: Head and neck cancer (HNC) patients present a high prevalence of cachexia and malnutrition at diagnosis. Contributions of malnutrition versus the direct role of tumour secretions in the development of cachexia are still unclear in HNC patients. We have investigated the role of tumour-secreted factors in loss of skeletal muscle in HNC patients.

Methods: At 7 days of differentiation, human primary myotubes were incubated for 48 h with serum from HNC patients ($n = 25$) and controls ($n = 14$) or with conditioned media (CM) from two HPV human squamous cell carcinoma (HPV group) or a control CM (CMC group). At inclusion, HNC patients muscle mass was assessed by CT scan. Except for mitochondria respiration assays, due to limited volume, patients' serum were mixed in three groups: mix of controls (C, $n = 14$), mix of patient with low degree of sarcopenia (LS, $n = 10$), and mix of patient with severe sarcopenia (SS, $n = 10$).

Results: Basal mitochondrial respiration was 28% lower in myotubes incubated with serum from HNC patients ($P = 0.008$ vs. C). Mitochondrial biogenesis markers were unchanged in HPV group and patients' groups. MnSOD gene expression was significantly higher in SS and HPV groups compared to their respective controls. MyHC protein level was 50% lower in HPV-treated myotubes ($P = 0.0005$). MyHC level was unaltered in SS-incubated myotubes and 43% higher in LS-incubated myotubes ($P = 0.003$; C vs. LS). A 26S proteasome activity was unchanged in all tested conditions. A 31% higher phosphorylation of p70S6K (Thr-389) was measured in LS-incubated myotubes ($P = 0.008$; C vs. LS). We are currently assessing the protein synthesis rate (SUNSET method).

Conclusions: In our model, HNC patients' serum are able to decrease basal mitochondrial respiration without inducing atrophy. In this model, we cannot conclude yet if mitochondrial

impairments are an early event in atrophy development or if atrophy and mitochondrial impairment are independently regulated.

4-07

A machine learning approach for cachexia diagnosis

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The diagnosis of cancer-associated cachexia before the manifestation of its most common symptoms, such as muscle wasting, is a major challenge nowadays. If feasible, this could greatly influence identification and management of the syndrome and the patient's prognosis and quality of life. Recently, artificial intelligence techniques, such as machine learning, have been used in health sciences to allow early and more precise diagnosis of several diseases. In this work, we explore a machine learning algorithm to evaluate clinical and biochemical data from patients with gastrointestinal cancer with clear symptoms of cachexia (CC group), weight stable cancer patients (WSC group), and healthy volunteers, that is, without being diagnosed with cancer (Control group). We employed the K-means algorithm to divide the data into two groups in an unsupervised approach, which means that the patients' previous group allocation was not known by the program. We created four different training models, ranging from models with a huge amount of features to simpler ones with only four biochemical parameters. In each model, the program was able to identify two distinct clusters: one allocated the majority of healthy patients and the other had the majority of patients with cancer cachexia. Then, patients with weight stable cancer were subjected to these classification tests; part of them were labelled by the computer as having biochemical alterations compatible with the cachexia group. Could this be indicative of very early stages of cachexia? In this work, we discuss the employed machine learning method and compare the proposed models regarding their accuracy, precision, and recall. Furthermore, the advantages of using a very small set of biochemical data will be approached as a way to identify patients with cancer in precachexia stages.

4-09

A multiple-plasma free amino acid signature predicts cachexia symptoms during first-line chemotherapy for advanced pancreatic cancer

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Background: The combining number of cancer cachexia symptoms (CACO) is an index of the severity of cancer cachexia (CAC). Circulating plasma levels of free amino acids (PFAAs) are known to be influenced by CAC and also by the presence of ductal adenocarcinoma of pancreas (PDAC) and could be a predictive biomarker of CACO. This study was aimed at building and validating a signature comprised of multiple PFAAs for discriminating severe CACO from nonsevere CACO during first-line chemotherapy for advanced PDAC.

Methods: A single-centre retrospective study on the diagnostic performance of multiple PFAAs was conducted. Patients (pts) with treatment-naïve PDAC whose frozen plasma samples were available were enrolled. The target population was divided into the training or validation cohort at an allocation ratio of 5:3. Symptom of CAC was defined as body weight loss $\geq 2\%$ in the previous 6 months, Karnofsky performance status (KPS) ≤ 80 , appetite interference score ≥ 4 according to the Japanese version of the MD Anderson symptom inventory, or serum C-reactive protein level ≥ 0.5 mg/dL, and was evaluated at 1 month after the start of first-line chemotherapy. Patients with three or more symptoms of CAC were classified as having severe CACO. A total of 19 PFAAs were measured using liquid chromatography–mass spectrometry. An index consisting of the PFAAs at the baseline was evaluated for its ability to predict severe CACO 1 month later.

Results: Data of a total of 160 pts with treatment-naïve advanced PDAC (100 in the training set and 60 in the validation set) were analysed in this study. Severe CACO at 1 month after the baseline was observed in 17% of the training cohort and 30% of the validation cohort. In the training set, 40 349 signatures consisting of two to six PFAAs were developed, and 322 multiple-PFAA combinations were identified as the diagnostic signature. For the best-performing PFAA signature, the area under the curve in the validation cohort was 0.807 (95% confidence interval, 0.685–0.930).

Conclusions: A multiple PFAA index is a promising biomarker for the prediction of CAC symptoms during first-line chemotherapy for advanced pancreatic cancer.

4-10

Low BMI obesity and increased myopenia in colorectal cancer patients with education and employment deprivation in the England: two sides of the same coin?

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Introduction: Adults living in the most deprived areas of England are 46% more likely to be obese than those in the least deprived areas. Little is known about the effect of deprivation on cancer cachexia. Patients with increased cachexia have a worse outcome from cancer, specifically in colorectal cancer (CRC) myopenia is associated with worse outcomes following surgery. We investigated the effect of employment and education deprivation on the body composition of patients with CRC.

Methods: A prospectively maintained database of primary CRC patients undergoing surgery at a UK specialist bowel hospital. Postal codes were used to determine the level of deprivation of each CRC case using England's index of multiple deprivation database. Preoperative computer tomographic body composition (CTBC) analysis was performed using SliceOmatic v5.0 and ABACS L3. Cut-off values for body composition variables were used from previous work by Prado *et al* (2008) and Doyle *et al* (2013).

Results: Myopenia was significantly associated with employment $P = 0.017$, OR 1.23, (95% CI 1.04–1.46) and education $P = 0.034$, OR 1.25, (95% CI 1.02–1.54) deprivation.

BMI Obesity (BMI > 30) was significantly associated with those with the least deprived in terms of employment $P = 0.004$, OR 1.18, (95% CI 1.05–1.33) and education $P = 0.001$, OR 1.17, (95% CI 1.05–1.29) deprivation. There was no significant relationship between visceral obesity and employment $P = 0.117$, OR 1.07, (95% CI 0.98–1.17) or education $P = 0.19$, OR 1.05, (95% CI 0.98–1.13) deprivation. A clinically significant neutrophil-to-lymphocyte ratio (NLR > 3) was associated with employment ($P = 0.009$) and education ($P = 0.038$) deprivation. Whilst a clinically significant raised platelet-to-lymphocyte ratio (PLR > 130) was associated with employment deprivation alone ($P = 0.008$).

Conclusions: Myopenia and systemic inflammation are associated with education and employment deprivation in CRC. BMI obesity is associated with CRC patients with the least education and employment deprivation. However, this is not reflected in visceral obesity where no significant difference exists between either group. BMI obesity fails to truly reflect the cachectic picture which appears markedly worse in the most deprived cancer patients.

4-11

Myosteatorsis is an independent predictor of distant metastatic disease in colorectal cancer: a potential biomarker to guide enhanced surveillance and earlier treatment

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Background: There are over 42,000 cases of colorectal cancer per year in the UK, with over 16,000 deaths from the disease per year. A total of 30% to 40% of the patients develop recurrent disease and most of these die from their disease. Early detection of recurrent disease at a presymptomatic stage may allow expedient treatment and increase survival. We aimed to determine whether body composition could be a used to predict recurrent disease.

Method: Analysis was performed on a prospectively maintained database of primary colorectal cancer patients undergoing surgery at a single UK specialist bowel hospital. Preoperative computer tomographic body composition analysis was performed using SliceOmatic v5.0 and ABACS L3. Cut-off values for body composition variables were used from previous work by Prado *et al* (2008) and Doyle *et al* (2013). Univariate and multivariate logistic regression analyses were performed on these data.

Results: A total of 1401 patients were included, median age 69 years [IQR 60–77] and 57% male. On univariate analysis, myosteatorsis ($P = 0.013$) and visceral obesity ($P = 0.006$) were found to be significantly associated with distant disease whilst myopenia ($P = 0.668$), sarcopenic obesity ($P = 0.675$), and BMI obesity ($P = 0.901$) were not. A total of 633 patients were included in the multivariate model; at the time of surgery, 10% (61) patients had poorly differentiated tumours; 69% (441) were T3/4; 41% (261) had positive nodes; and 23% (145) patients had or developed distant metastatic disease. Preoperatively, 59% (337) were viscerally obese and 74% (470) myosteatorsic. Myosteatorsis ($P = 0.001$), positive lymph nodes ($P = 0.0001$), and T3/4 tumours ($P = 0.004$) were independently associated on multivariate regression analysis with distant disease.

Conclusions: Myosteatorsis is an independent predictor of the presence of distant metastases and may even presage metastatic disease before it can be identified on imaging. This may allow clinicians to target surveillance and earlier intervention

towards those patients who are at risk of recurrent disease, potentially preventing or reducing the rate of disease progression.

4-12

Anaemia in children with end-stage chronic liver disease

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Background: Anaemia of chronic liver disease and therefore end-stage chronic liver disease (ESCLD) has been described in adults and has been associated with more severe liver disease. It has not been specifically studied in children.

Methods: Retrospective review of all children who had a liver transplant at our unit between 2013 and 2017 (inclusive). The aim was to identify the incidence of anaemia and its relationship with the disease severity in children receiving a liver transplant for ESCLD. A level of haemoglobin <10.5 g/L was considered as low.

Results: Our database identified 80 children (40 F: 40 M). Mean age was 5.2 years (range 0.3–15.88 years, median 2.9 years). Of those, 58 had ESCLD (mean age 5.48 years, range 0.31–15.88 years, and median 1.13 years). Forty-one out of 80 of the patients overall, where anaemic prior to liver transplant and in particular 27/58 of the ones with ESCLD, were anaemic. Of these, 19/27 had a normocytic anaemia, six a macrocytic, and two a microcytic. The anaemic children with ESCLD were significantly younger, had a higher bilirubin and were more coagulopathic, and had a higher PELD (paediatric end-stage liver disease) score than the nonanaemic ones. Anaemia did not correlate with white cell and platelet count (i.e. the presence of hypersplenism due to portal hypertension). The anaemic children had a significantly lower mean weight z-score than the nonanaemic ones (-1.7 versus -0.69 , $P < 0.05$). A total of 51.8% of the anaemic children had a weight z-score ≤ 1.96 , in comparison to 16.1% of the ones without anaemia. Anaemia did not correlate with length of stay in hospital after liver transplant.

Conclusions: The presence of anaemia in children with ESCLD is associated with the severity of the disease and the growth impairment.

4-13

Sarcopenia, myopenia, phase angle in cancer: a cut-off to optimize nutrition efficacy?

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Background: Poor nutritional status in cancer is mainly manifested by severe muscle mass depletion, that may happen at any stage of cancer treatments (curative, adjuvant, and palliative), independently of body weight. Evidence shows that sarcopenia/myopenia detrimentally impacts clinical outcomes; studies suggest a role of phase angle undernutrition diagnosis.

Methods: Ongoing study to include 400 cancer patients: gastrointestinal, lung, head–neck referred for radiotherapy. Parameters: PG-SGA, body composition + phase angle (PA) (BODYSTAT®), dietary intake, quality of life (QLQ-C30), symptoms/toxicity, physical function (Karnofsky, ECOG).

Results: In 63 patients (18F:45M), PA was below age/sex reference in 37/48 men and 13/18 women; PA fell 1 integer below lower limit in 27pts and fell 2 integers in 16pts. Coincidentally, 34/63pts with lowest PA had worse PG-SGA scores (>9points) and tended to have worse ECOG ($P = 0.06$). In men, PA and physical function were strongly correlated ($P < 0.001$). Lower FFMI was seen in patients with PA with two integers below lower limit and with worse ECOG ($P < 0.001$). Lower FFMI + PA correlated with nutrition impact symptoms ($P < 0.001$). Notably, protein intake was <1.5–1.4 g/kg/d in 3pts; ≤1.3–1.1 g/kg/d in 16pts; ≤1.0–0.6 in 24pts, ≤0.5 in 10pts; in 10pts intake ≈recent guidelines (≥1.5 g/kg/d). Most severe deficits (≤1.0–0.4 g/kg/d) were present in patients with lower PA (0.001) and FFMI (0.002).

Conclusions: In this cohort, significant impairments in body composition, PA, function, and symptom severity were present and interrelated already at diagnosis. The proposal of a cut-off for sarcopenia/myopenia/PA with an easy to use, cost-effective, globally available method could abbreviate a tailored intervention to prevent/reverse/treat further nutritional wasting. Conscious of the limitations intrinsic to sample size and BIA parameters, PA with 1–2 integers below lower limit combined with low FFMI, seemed effective in discriminating baseline wasting and in predicting function impairment and severe protein deficits. In the absence of CT scans to assess body composition, BIA may prove determinant and outperforms subjective methods. Given the role of body composition in oncological outcomes, strategies to optimize intervention are important for a successful cancer therapy.

5-05

Adverse muscle composition within obesity is associated with low functional performance and increased comorbidity: results from the large UK Biobank imaging study

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Background: Sarcopenia within obesity is not well described. Recent results based on the UK Biobank showed only 0.1% of participants with obesity had sarcopenia (EWGSOP2 criteria) while contradictory, they showed the highest prevalence of low functional performance¹. The main cause for under diagnosis of sarcopenia within obesity is the BMI-dependency of current sarcopenia definitions, where the correlation between body size and muscle mass has not been properly adjusted through division with, e.g., height², weight, or BMI¹.

Methods: A total of 9612 participants were included ($N = 4589$ with DXA). Fat-free muscle volume (FFMV) and muscle fat infiltration (MFI) were quantified using a 6 min MRI protocol and automated image analysis (AMRA® Researcher). For each participant, a sex-and-BMI matched virtual control group (VCG) was created. As a measure of deviating FFMV, the individual FFMV/height² z-score was extracted from each VCG-distribution (FFMV_{VCG})¹. Participants with obesity (BMI ≥ 30 kg/m²) and adverse muscle composition were stratified using sex-specific thresholds for MFI (above 75th percentile, whole cohort) and FFMV_{VCG} (below 25th percentile, whole cohort). The functional performance (hand grip strength, walking pace, stair climbing, and falls) and comorbidity (coronary heart disease and type 2 diabetes) in participants with obesity and adverse muscle composition were compared to those without adverse muscle composition. As reference, characteristics of the sarcopenia population (stratified through EWGSOP2 criteria using the DXA-subset) were also included.

Results: A total of 311 out of 1808 participants with obesity had adverse muscle composition (prevalence within obesity 17.2%). The prevalence of low functional performance was significantly higher in participants with adverse muscle composition for all variables (all $P < 0.05$, age-adjusted) except falls (non-significant) (Table 1). The prevalence of comorbidities was significantly higher in participants with adverse muscle composition (all $P < 0.01$, age-adjusted) (Table 1).

Conclusions: Adverse muscle composition within obesity, as identified using MRI, is commonly observed and associated with high prevalence of low functional performance and comorbidities.

Table 1 Characteristics of participants with obesity with (w/) and without (w/o) adverse muscle composition showing mean (SD) and prevalence including level of significance

	Groups for statistical comparison		Reference data	
	Obesity w/ adverse muscle composition	Obesity w/o adverse muscle composition	Sarcopenia (EWGSOP2) in DXA subset	Whole cohort
N participants	311	1497	102	9612
% females	50.5% ^a	51.9%	77.5%	52.5%
Age (years)	66.1 (6.7) ^{***}	61.2 (7.3)	65.6 (6.9)	62.6 (7.5)
Weight (kg)	92.8 (12.4) ^a	94.1 (13.4)	61.3 (8.9)	75.5 (14.8)
BMI (kg/m ²)	33.5 (3.1) ^a	33.5 (3.4)	23.1 (2.5)	26.6 (4.4)
Sarcopenia (EWGSOP2) in DXA subset	0.7% ^a	0.0%	100%	2.2%
Low hand grip strength	11.3%*	5.7%	100%	6.4%
Slow walking pace	23.8% ^{***}	9.2%	9.8%	4.4%
No stair climbing	16.4%*	8.7%	8.8%	7.9%
More than 1 fall last year	8.7% ^a	6.7%	8.8%	4.8%
Coronary heart disease	15.4% ^{**}	6.4%	7.8%	4.6%
Type 2 diabetes	19.3% ^{***}	9.0%	1.0%	4.5%

^anon-significant,* $P < 0.05$,** $P < 0.01$,*** $P < 0.001$, age-adjusted.

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5–24

Low-magnitude, high-frequency vibration treatment attenuates age-related neuromuscular junction degeneration

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Background: Sarcopenia is a phenomenon characterized by age-related decline in muscle mass and strength. There are multiple aetiological factors leading to sarcopenia, and neuromuscular junction (NMJ) degeneration is among one of the causes. According to our previous studies, whole-body low-magnitude high-frequency vibration (LMHFV) treatment could improve skeletal muscle function in sarcopenia, but the mechanisms are unclear, so this study aims to investigate the effects of LMHFV on NMJ degeneration in sarcopenia.

Methods: Senescence-accelerated mouse prone 8 (SAMP8) were previously characterized to exhibit sarcopenic phenotype. A total of 54 male mice aged 6 months were

randomized into control (Ctrl) and vibration treatment (VT) groups. The mice in the VT group were treated with LMHFV (35 Hz, 0.3 g, where g = gravitational acceleration) 20 min/day and 5 days/week. NMJ *ex vivo* function and structure were evaluated at months 0, 2, 3, 4, and 6 post-treatments with six mice in each time point. Student's *t*-test was used for treatment effect considered at $P < 0.05$.

Results: In NMJ *ex vivo* function tests, specific tetanic force in VT group at Month 3 post-treatment increased by 15% compared with Ctrl group. Morphologically, immunofluorescence of the whole-mount aged muscle specimens showed significant fragmentation of the characteristic pretzel structure. Quantitative results showed that discontinuity index of NMJ postsynaptic acetylcholine receptors in Ctrl group was higher than that in VT group at Month 4 post-treatment (10 in Ctrl versus 7.8 in VT group) with statistical difference.

Conclusions: LMHFV was previously shown to enhance muscle function in sarcopenic mice. Current results suggest that LMHFV treatment could achieve the enhancement through improving NMJ function and attenuate morphological degeneration of the NMJ in sarcopenic animal model during ageing suggesting that vibration is a promising treatment to tackle muscle denervation in aged muscles.

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5-25 Mid-arm muscle circumference is an anthropometric all-cause mortality's predictor for noninstitutionalized elderly: Cohort Elderly Project/Goiania

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Background: Mid-arm muscle circumference (MAMC) is an anthropometric indicator of muscle mass, which has been used in nutritional status assessment and risk prediction. However, its association with mortality in the elderly population remains unknown. We investigated the impact of low MAMC on mortality risk in noninstitutionalized elderly individuals.

Methods: Cohort study Elderly Project/Goiania, which evaluated 418 noninstitutionalized elderly (≥ 60 years old) living in Goiania's metropolitan area, capital of Goiás state, Brazil. MAMC was calculated using the standard formula: $MAMC = \text{mid-arm circumference} - (0.314 \times \text{triceps skinfold thickness})$. We categorized both male and female participants into tertiles based on their MAMC level. Low MAMC was defined as the lowest sex-specific tertile. Sociodemographic variables included age and gender. Data mortality was collected from the Brazilian Mortality Information System of the Health Ministry. We used Cox proportional hazards regression analyses to estimate the hazard ratios (HRs) for all-cause mortality. *P* values less than 0.05 were considered statistically significant.

Results: During a mean of 8.5 years of follow-up period, we observed 144 deaths from all-causes, 39.7% of the total cohort sample. We included 416 elderly being 66.0% female participants and an average age of 70.7 ± 7.1 years. The mean MAMC was 25.8 ± 2.7 cm in men and 23.6 ± 3.0 cm in women

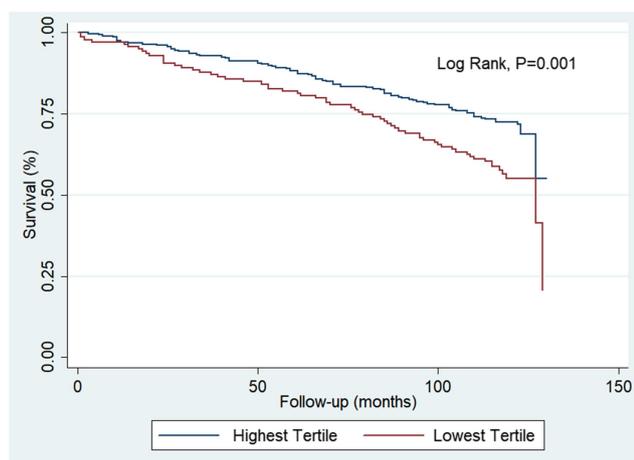


Figure 1 Kaplan–Meier survival curves stratified by mid-arm muscle circumference (MAMC) status (highest tertile vs. lowest tertile).

($P < 0.01$). Low MAMC was observed in 14.1% (95% CI: 8.29–19.87%) of men and 43.3% (95% CI: 37.38–49.16) of women ($P < 0.01$). Cox proportional hazards regression analyses showed that low MAMC was associated with all-cause mortality (HR = 1.70, 95% CI: 1.22–2.36) ($P < 0.01$) (Figure 1), with highest risk mortality among women (HR = 2.02, 95% CI: 1.32–3.09) ($P < 0.01$) than men (HR = 1.99, 95% CI: 1.02–3.86) ($P < 0.04$).

Conclusions: Our study showed that MAMC is inversely associated with all-cause mortality in Brazilian males and females noninstitutionalized elderly.

5-26 The sex difference of relationship between sarcopenia and chronic kidney disease in older Korean adults

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Background: Sarcopenia can affect the prognosis of patients with chronic kidney disease (CKD). CKD and sarcopenia increase with ageing. Males with CKD appear to be more prone to sarcopenia than females with CKD. However, few reports are available about the relationship between sex differences and sarcopenia and CKD stage in older people. The aim of this study was to examine the association between CKD and sarcopenia and sex differences in older adults.

Methods: This cross-sectional study is based on the Korean Frailty and Ageing Cohort study, which involved a population of 2403 people aged 70 years of age or over. Anthropometric, physical performance, and baseline laboratory data were collected. CKD was defined by an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² or proteinuria.

Results: The mean age of the participants was 76.0 ± 3.9 years old and 52.8% of them were female. The number of male and female CKD patients were 215 and 137, respectively (18.9 vs. 10.8%, $P < 0.001$). The eGFR was correlated with gait speed ($r = 0.137$, $P < 0.001$), sit to stand (STS) time ($r = -0.074$, $P = 0.001$), timed up and go (TUG) test ($r = -0.156$, $P < 0.001$). Appendicular skeletal muscle mass (ASM) index values were correlated with eGFR in male but not female participants. The share of participants with slow gait and STS and TUG increased according to CKD stage. Participants with low handgrip power were not different between men and women. The sex difference of relationship between physical performance and eGFR was the same after adjusting diabetes, weight, and laboratory data.

Conclusions: Declines in ASM Index and physical performance except handgrip power increase according to the CKD stage in older people. CKD was associated with an increased prevalence of sarcopenia in elderly men but not in elderly women. More detailed prospective studies are needed.

5-27

Comparison between the revised and the first version of the European Consensus for the diagnostic of sarcopenia in a follow-up study of Chilean older people

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Background: The care of older people requires early diagnosis of sarcopenia at primary care attention, therefore it is necessary to have the best diagnostic tool for its identification. The aim of this study is to compare the predicting validity of sarcopenia diagnosed with the first (EWGSOP1) and revised (EWGSOP2) versions of the European Consensus criteria, for functional limitations and falls in Chilean older people.

Methods: Follow-up (median = 4.8 years) of 430 community-dwelling participants (68.2 ± 4.8 years; 69.5% females) free of functional limitations, from 1006 subjects with measurements at baseline. The subjects were classified with sarcopenia by EWGSOP1 and EWGSOP2 criteria at baseline, to observe functional limitations and falls at the end of follow-up. The participants had measurements of muscle mass by dual-energy X-ray absorptiometry, gait speed, and handgrip strength. Self-reported and observed functional limitations, falls, and history of chronic diseases were also registered. χ^2 test and logistic models were used for the analysis.

Results: At baseline the prevalence of sarcopenia was higher with EWGSOP1 than EWGSOP2 (19.1% vs. 10.5%). EWGSOP1 criteria classified 40 subjects (9.3%; 29 females) as sarcopenic that EWGSOP2 classified as nonsarcopenic (no difference by sex). At the end of follow-up, after adjusting by age, sex, morbidity, nutritional state, and lean/fat ratio, sarcopenic subjects diagnosed by both criteria and sarcopenic subjects diagnosed by EWGSOP1 criteria and diagnosed as nonsarcopenic by EWGSOP2, presented risk of functional limitation (OR = 5.3; 95% CI: 1.4–19.4; OR = 3.2; 95% CI: 1.1–9.2) and of falling (OR = 3.8; 95% CI: 1.3–11.6; OR = 4.2; 95% CI: 1.8–10.0).

Conclusions: The prevalence of sarcopenia diagnosed by EWGSOP2 was significantly less than by EWGSOP1. The subjects that was classified as nonsarcopenic by EWGSOP2 but sarcopenic by EWGSOP1 showed a similar risk of functional limitation and of falling than sarcopenic subjects. The need to identify the majority of people at risk makes EWGSOP1 criterion very valuable yet.

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5-28

Prevalence of sarcopenia in elderly patients admitted to a university hospital: a pilot study

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Background: To assess the prevalence of sarcopenia and the associated factors is of great importance in order to describe and implement preventive actions in public hospitals. The objective was to estimate the prevalence of sarcopenia and its associated factors in hospitalized elderly patients.

Methods: Cross-sectional pilot study with 39 hospitalized elderly patients ($67,92 \pm 8,80$ years). Inclusion criteria were elderly patients of both sexes admitted to the surgical clinic of the Hospital of Federal University of Grande Dourados in the first 48 h. Patients with respiratory precaution, oedema or impossibility of hand evaluation, cognitive impairment, neurodegenerative diseases or severe psychiatric dysfunction, and the indigenous population were excluded. To assess the frequency of sarcopenia, the new criteria proposed by the European Working Group Sarcopenia in Older People (EWGSO). Calf circumference (CC) was used to assess muscle mass. This research is approved by the Research Ethics Committee/University (Protocol: 06426818.0.0000.5160). Descriptive statistics and the χ^2 test were performed. It was considered 5% of significance.

Results: Most were male (53.8%), married (74.4%), not working (71.8%), economic class C* (69.2%) and had one to three chronic diseases (CD) (74.4%). The patients had handgrip strengths (HS) equal to 26.43 ± 9.19 kg/f (right) and 25.69 ± 10.15 kg/f (left). The CC was 34.88 ± 4.04 cm with 18.4% loss muscle mass. The average gait speed was 7.84 ± 7.74 s (4 meters). We obtained 78.1% without risk of sarcopenia (HS = 27.4 ± 9.33 kg/f), 15.6% with risk for sarcopenia (HS = 25.5 ± 8.06 kg/f), and 6.3% with severe sarcopenia (HS = $17,0 \pm 7.07$ kg/f). The frequency of sarcopenia was not associated with gender ($P = .962$), work activity ($P = .568$), presence of CD ($P = .945$) but was significantly related to body mass index ($P = .021$), CC ($P = .003$), and right handgrip strength ($P = .030$).

Conclusions: Sarcopenia is associated with nutritional status and patients hospitalized for surgery are already identified at risk for sarcopenia or severe sarcopenia. We continue with data collection to improve the analysis.

*Economic class C: Average income (home) equal to 572 EUR (Central Bank converter on July 26, 2019)

5-31

Multiple biomarker approach to identify the patients with low muscle mass in heart failure

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Background: Identification of sarcopenia is still challenging in patients with heart failure (HF). Serum creatinine/serum cystatin C ratio (Cr/CyC) could reflect muscle mass, whereas B-type natriuretic peptide (BNP) might have an interaction with skeletal muscle metabolism. We sought to assess the validity of several biomarkers as a predictor of muscle mass.

Methods: We measured body components using the dual-energy X-ray absorptiometry (DXA) in 207 hospitalized patients with HF (70 ± 13 years, 63% male, ejection fraction 38 ± 16%). DXA and BNP were measured in a stable condition after decongestion therapy.

Results: The average appendicular skeletal mass index (ASMI) was 6.80 ± 1.20 kg/m² in men and 5.66 ± 1.05 kg/m² in women and the prevalence of the patients with low ASMI defined by Asian Working Group for Sarcopenia was 53%. Cr/CyC was associated with body mass index (BMI: $r = 0.20$, $P = 0.005$) and ASMI ($r = 0.39$, $P < 0.001$) but not fat mass index ($r = 0.02$, $P = 0.75$) whereas Ln BNP with BMI ($r = -0.32$, $P < 0.001$), ASMI ($r = -0.39$, $P < 0.001$), and fat mass index ($r = -0.23$, $P < 0.001$). Multivariable linear regression analysis revealed that BMI ($\beta = 0.64$, $P < 0.001$), male sex ($\beta = -0.34$, $P < 0.001$), sodium ($\beta = 0.08$, $P = 0.037$), and Cr/CyC ($\beta = 0.11$, $P = 0.011$), but not Ln BNP ($\beta = -0.06$, $P = 0.16$) was independently associated with ASMI. An optimal cut-off of BMI to identify those with low ASMI was 21.8 kg/m² for men and 20.0 for women, which had a sensitivity of 78%, specificity of 90%, and accuracy of 83%, respectively. To add BNP (cut-off: >400 pg/mL), but not Cr/CyC, after BMI raised sensitivity up to 90% without reducing accuracy (sensitivity 77% and accuracy 84%, respectively).

Conclusions: Cr/CyC was significantly associated with ASMI, independent of BMI. Using BNP after BMI, we could effectively identify patients with low ASMI in HF.

5-32

Evaluation of sarcopenia with bioimpedance variables and handgrip strength in middle-aged Italian obese women

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Background: Sarcopenic obesity (SO) is a condition where fat mass (FM) excess and muscle mass depletion coexist. A clear definition for SO is currently lacking, and there is therefore a need to develop a standardized approach of defining SO using body composition assessment. The aim of this study is to evaluate the prevalence of sarcopenic obesity in middle-aged adults with obesity (BMI > 30) using BIA and handgrip strength as screening tools according to EWGSOP criteria.

Methods: We studied 70 women [age 50 ± 8.2 years; weight 101.2 ± 19.1 kg, BMI 39.9 ± 7.27 kg/m², fat-free mass (FFM) 54.3 ± 8.9 kg, FAT 46.9 ± 12.9 kg, PFAT 45.8 ± 5.7%]. Anthropometric measurements and bioimpedance analysis (BIA) at 50 kHz (DS Medica) were performed early in the morning; skeletal mass was calculated according to Janssen equation $SM \text{ (kg)} = (h^2/BIA \text{ resistance} * 0.401) + (\text{sex} * 3.825) + (\text{age} * 0.071) + 5.102$; where height (h) is in cm, BIA resistance is in ohms; male sex = 1 and female = 0. The mean HGS was the average value of three handgrip measurements of the dominant hand. Sarcopenia was defined with two indexes: SMP INDEX = SM (kg)/body mass (kg) * 100 and SMI = SM/h².

Results: Mean SM was 23.8 ± 3.90 kg, mean SMP was 23.9 ± 3.09, mean SMI was 9.41 ± 1.41, mean HGS was 20.4 ± 4.93 kg (more than 50% of patients had mean HGS < 20 kg). According to Janseen cut-off of sarcopenia, we found that 31 subjects (44.3%) could be defined presarcopenic obese according to SMP index, whereas no one was defined sarcopenic according to SMI index. If we consider both SMP index and handgrip strength, 27.4% of the subjects were defined sarcopenic.

Conclusions: Sarcopenia rates vary widely based on different definitions. When SMP is used, we have observed the highest prevalence of Sarcopenia, whereas when we use also handgrip strength, we found lowest prevalence of sarcopenia. Further studies are required in a larger population to define SO.

5-33

Characterization of molecular profile of sarcopenia in osteoporotic and osteoarthritic patients

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Background: Sarcopenia represents an important risk factor for osteoporosis. Indeed, sarcopenia might decrease bone strength by reducing mechanical loading: less time the skeleton is loaded due to relative immobility, thus bone formation is reduced. The aim of this study was to identify the main molecular pathways involved in physio-pathogenesis of sarcopenia. In particular, we investigated the expression of BMP2, BMP4, BMP7, Myostatin, MDM2, and vitamin D receptor (VDR) and their relationship with muscle stem cells activity (PAX-7, myogenin, CD44).

Methods: We enrolled 32 patients that underwent hip arthroplasty for femoral fracture (OP), and 68 patients underwent hip arthroplasty for osteoarthritis. The main clinical/anamnestic data as well as haematochemical values and instrumental parameters were collected. Serial paraffin sections were used for morphometric and immunohistochemical analysis.

Results: Clinical and instrumental evaluation allowed us to characterize patients enrolled in this study. OP group included 25 patients with fragility hip fracture (T-score ≤ -2.5 SD); whereas OA group included 25 patients with positive radiogram for hip OA (T-score ≥ -2.5 SD). Morphometric investigations demonstrated the delay in the onset of sarcopenia in OA patients. Immunohistochemical analysis showed that BMPs and nuclear VDR were more expressed in OA patients than OP. As concern myostatin, we noted a strongly association between its expression and degenerative phenomena observed in muscle biopsies of OP patients. Also, for the first time, we correlated the expression of MDM-2 with muscle degeneration. Lastly, analysis of PAX-7, myogenin, and CD44 allowed us to observe an increase of satellite cells activity in OA patients compared to OP.

Conclusions: The identification of the molecular profile of sarcopenia can provide the rational for new therapies. In particular, our data allowed us to propose the use of human recombinant BMPs, VIT.D3 supplementation, and the anti-myostatin molecules as drugs capable to prevent or treat the sarcopenia of OP patients.

5-34

Predictor of sarcopenia and its association with disease activity status and physical function in rheumatoid arthritis

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Background: Rheumatoid arthritis (RA) is characterized by chronic inflammation, leading to joint damage. RA patients also present altered body composition, including loss of appendicular lean mass index (ALMI) with preservation or increase in fat mass index (FMI), but very little is known on the prevalence, progression, and impact on function of this complication. The adiposity is a confounder that may mask relationships between physical functioning and ALMI. This prospectively evaluate muscle mass relative to fat mass (ALMI_{FMI}) and its associations with disease activity status, physical function, and use of biologic therapies.

Methods: RA patients were recruited and followed for 12 months. ALMI and FMI were assessed by DEXA. RA patients were divided by remission or non-remission and use of biologic therapy. Physical function was assessed by HAQ-DI. Pearson correlations and GEE analyses were used ($P < 0.05$).

Results: Of the 90 patients analysed, most were women (86.7%), with mean age of 56.5 ± 7.3 and long disease duration. At baseline, the most patient showed remission disease activity, 30% of the patients were treated with biologic therapy, and after 12 months, these parameters were stable. twelve percent of RA patients showed low ALMI_{FMI} (z-score -1) at baseline and 16% after 12 months. After 12 months, ALMI_{FMI} was inversely associated with HAQ-DI ($r = -0.3$; $P < 0.05$). Women in remission showed higher ALMI_{FMI} in both times ($P < 0.05$). The use of biologic therapy was not related to changes in ALMI_{FMI}.

Conclusions: Changes in body composition were observed after only 12 months in RA patients with stable disease. Disease activity status was associated with changes on ALMI_{FMI}. Low ALMI_{FMI} was associated with decreased physical function in RA patients. Further long-term follow-up studies are necessary to elucidate the risk factors, impacts, and strategies to alleviate muscle loss in these patients.

5-35

Myopenia, myosteatosis, and systemic inflammation are dependent on ethnicity in patients undergoing surgery for colorectal cancer

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Background: Heterogeneity of body composition (BC) exists across ethnic groups. We know that in colorectal cancer (CRC) patients, myopenia and myosteatosis are related to a systemic inflammatory state and poorer outcomes. Despite this difference in BC between ethnic groups, no studies have examined the relationship between ethnicity, muscle mass, and inflammation in the presence of cancer. We aimed to examine this relationship with a view to elucidating a need to adjust existing cut-off values.

Method: A prospectively maintained database of primary CRC patients undergoing surgery at a single UK specialist bowel hospital was analysed. Patient self-declared ethnicity was coded using the NHS Data Dictionary codes from the Office of National Statistics 2001 UK census. These categories were further simplified for analysis into the broader categories listed within the NHS Data Dictionary. Preoperative computer tomographic BC analysis was performed using SliceOmatic v5.0 and ABACS L3. Cut-off values for BC variables were used from previous work by Prado *et al* (2008) and Doyle *et al* (2013).

Results: A total of 1401 patients were included in the analysis; ethnicity data was held for 1098 individuals. Sixty-eight percent of patients were white, 19% Asian/Asian British, and 8% Black/Black British, the remainder were of mixed race or "other ethnic group." Black patients were significantly less myopenic than white and Asian patients $P = 0.0005$. White patients were significantly more myosteatotic than Asian patients $P = 0.0005$. Ethnicity was associated with a clinically significant difference in preoperative neutrophil-to-lymphocyte ratio (NLR > 3) $P = 0.0005$ but no clinically significant relationship between platelet to lymphocyte ratio (PLR > 130) $P = 0.419$.

Conclusions: In myopenia and myosteatosis, there are significant differences that exist between ethnic groups; this is also reflected in a significant difference in systemic inflammation. This in turn may have a bearing on outcomes from colorectal cancer. Further investigation is warranted to define cut-off values further taking ethnicity into account.

5-36

Loss of skeletal muscle mass during neoadjuvant chemotherapy and the relation to survival in patients with ovarian cancer: a prospective analysis of the OVHIPEC-1 cohort

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Background: Skeletal muscle depletion in women with advanced ovarian cancer has been associated with adverse clinical outcome and survival. To validate earlier results in a homogenous population, we analysed whether a decrease in skeletal muscle index (SMI) during neoadjuvant chemotherapy (NACT) is associated with worse outcome in patients with stage III epithelial ovarian cancer, who were included in the OVHIPEC trial.

Methods: Within the phase III OVHIPEC trial, 245 patients with stage III ovarian cancer were randomized after three cycles of NACT with carboplatin and paclitaxel to receive interval cytoreductive surgery (CRS) with or without HIPEC. Randomization was performed after at least stable disease after two cycles of NACT and when complete or optimal CRS was achieved. CT scans performed at baseline (Timepoint 1), and after two cycles of NACT (Timepoint 2) were selected. A slide on the third lumbar level was selected from each CT scan, and the difference in SMI between both scans (Δ SMI) was calculated using SliceOMatic. Overall and recurrence-free survival of patients with a decrease or increase in Δ SMI were performed using Kaplan–Meier estimates and log-rank tests.

Results: Of the 245 patients randomized in the OVHIPEC trial, SMI and Δ SMI of scans at both timepoints were available for 212 patients (87%). After a median follow-up of 4.7 years, 116 of 212 patients (55%) had died. In survival analysis, 43 of 74 patients (58%) in the group with a decrease in Δ SMI,

and 73 of 138 of the patients (53%) in the group with stable/increase in Δ SMI had died. Median overall survival did not differ significantly ($P = 0.764$).

Conclusions: A decreasing skeletal muscle index during neoadjuvant chemotherapy was not associated with worse outcome in patients with stage III ovarian cancer, who were treated with complete/optimal interval CRS and six cycles of chemotherapy within the OVHIPEC trial.

5-38

Agreement between measurements of body composition by dual-energy X-ray absorptiometry and bioimpedance analysis

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Background: Sarcopenia is getting increased awareness as a relevant comorbidity in patients with chronic heart failure (HF). Its impact in quality of life and mortality increases the importance of having valid measurement methods available for all patients, despite their condition or device implantation. The aim of this study is to compare the measurements of body composition on patients and controls and to compare the classification of patients with and without sarcopenia with respect to the given methods.

Methods: A total of 130 ambulatory patients with stable chronic HF [age: 68 ± 10.13 years; NYHA(I/II/III/IV):13/73/39/1; BMI: 29.81 ± 5.3 kg/m²; Female: 39 (30%)] were enrolled as part of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Additionally, 42 healthy controls [age: 64 ± 10.8 years; BMI: 25.29 ± 3.32 kg/m²; Female: 20 (48%)] were enrolled. Body composition on both, patients and controls, was measured using dual-energy X-ray absorptiometry (DEXA) and bioimpedance analysis (BIA). Depending on the method to measure muscle mass, we defined sarcopenia as the appendicular muscle mass index (ASMI) <7.26 for males or <5.45 for females from the DEXA scan and as the skeletal muscle index (SMI) ≤ 8.50 for males or ≤ 5.75 for females from the BIA scan. The ASMI was defined as the lean mass (kg) of both arms and legs combined (ASM) and then normalized by height squared (m²). Accordingly, using the resistance from BIA, SMI was calculated as absolute skeletal muscle mass (kg) normalized by height squared (m²).

Results: Overall, patients and controls were similar in age ($P = 0.06$) and showed similar composition of appendicular

muscle mass (23.44 ± 5.19 vs. 22.59 ± 5.51 kg, $P = 0.37$). Patients, in contrast to controls, presented with higher BMI ($P < 0.001$), total fat mass, and total lean mass (30.72 ± 10.46 vs. 21.58 ± 7.64 kg, $P < 0.001$ and 54.87 ± 11.57 vs. 49.81 ± 10.78 kg, $P = 0.01$, respectively). In comparison to the DEXA measurements, we also obtained for fat mass (FM), fat-free mass (FFM), and skeletal muscle mass by BIA a difference between patients and controls (29.35 ± 9.92 vs. 22.08 ± 7.07 kg, $P < 0.001$; 58.89 ± 12.84 vs. 51.82 ± 11.73 kg, $P < 0.001$; 26.85 ± 6.4 vs. 24.35 ± 6.42 kg, $P = 0.04$, respectively).

In order to show the compatibility of the two methods, we calculated the limits of agreement based on the Bland–Altman plot. Comparing fat mass by DEXA with fat mass by BIA, we obtained a mean of the differences with limits of agreement lower and upper as $(1.36 [-7.86; 10.59])$ on patients and as $(-0.51 [-7.85; 6.83])$ on controls. The comparison of lean mass (DEXA) with fat-free mass (BIA) was given on patients by $(-2.02 [-9.83; 5.79])$ and on controls $(-4.02 [-12.7; 4.65])$. Comparing the definitions for sarcopenia as described above, we identified 13 (10%) patients with sarcopenia using the cut-off for ASMI by DEXA and 24 (19%) patients with sarcopenia using SMI by BIA. Restricted to these patients, we calculated the Bland–Altman plot, obtaining the following mean of differences with limits of agreement. For the patients with sarcopenia defined by DEXA cut-offs, the mean of differences for the fat-free mass was $(-6.5 [-15.56; 2.56])$. In comparison to this result, the patients with sarcopenia defined by BIA cut-offs, the means of the differences was $(-2.91 [-12.75; 6.92])$.

Conclusions: We have shown that the measurements of fat-free mass BIA and lean mass DEXA are comparable. The definitions for sarcopenia using the respective cut-offs deliver similar persistence on this population. Moreover, in order to increase the accordance in the persistence given by the different definitions, we encourage validating the comparison on a larger population.

6-21

Characterization of central and peripheral age-related changes in the neuromuscular system of C57BL/6J mice

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Ageing is associated with a reduction of muscle mass and strength, a process called sarcopenia. Structural and molecular changes in the cellular elements that shape the neuromuscular system could be causative factors of the age-related skeletal muscle involution. Therefore, interventions aimed at preventing these changes may have a great impact in the preservation of skeletal muscle function in elderly. To gain new insights in the alterations occurring in the neuromuscular system with age, motor behavioural and electrophysiological tests and histological and immunocytochemical analyses were performed in young adult and old C57BL/6J mice. We found that although old mice did not exhibit significant changes in the size of spinal cord motoneurons (MNs), these displayed a marked loss of cholinergic and proprioceptive inputs. Ageing also induced prominent astrogliosis and microgliosis around MNs, with spinal cord of old animals exhibiting a significant increase in the density of pro-inflammatory M1 microglia and A1 astroglia. Compared to muscles from young adult mice, those from old animals exhibited higher numbers of both denervated and polyinnervated neuromuscular junctions (NMJs), a higher proportion of myofibers showing increased size and central nuclei, and augmented expression of different molecules related to NMJ stabilization and plasticity including CGRP, GAP-43, FGBP1, and TGF- β 1. These changes were found to be more prominent in *soleus* and *gracilis* than in EDL and tibialis anterior muscles. In relation to young adult mice, old animals had a significant reduction in the nerve conduction velocity and a decline in the amplitude of the compound muscle action potential in distal plantar muscles. Further work is necessary to study the relevance of these structural and molecular changes and their impact on motor activity defects linked to ageing.

6-22

The evaluation of body composition and lifestyle habits in a healthy population

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Background: Changes in body composition (BC) mainly reduction in lean muscle mass affect functional capacity. The objective of this study is to evaluate BC and correlate it with anthropometric, laboratory, and clinical parameters [nutritional, comorbidities, bone mineral density (BMD)].

Methods: Observational, cross-sectional study that included healthy men and women ≥ 18 years old with body mass index (BMI) ≥ 18.5 – 29.9 kg/m². Athletes, smokers, those with disease, or in use of drugs that could affect BC were excluded. Patients answered questionnaires about socio-demographics,

food intake, and physical activity [“International Physical Activity Questionnaire” (IPAQ)] data. Short Physical Performance Battery (SPPB), total body densitometry exam by DXA, and laboratory test were performed.

Results: From 1100 individuals invited, 299 were included, 150 men (45.1 ± 20.4 years) and 149 women (47.1 ± 19.4 years), $P = 0.45$. There was a negative correlation between % total fat (TF) and age in men and women ($R = 0.5$, $P < 0.00$, for both) mainly in trunk, superior members, and android region. Men showed lower %TF accordingly to their physical activity ($P < 0.005$); however, women did not. Vitamin D and calcium ingestion were negatively correlated to android fat (AF). Multivariate analysis showed that %TF was dependent of age, BMI, abdominal circumference (AC), and gender (male); however, when the level of physical activity was included in the model, age lost significance when individuals were active ($R^2 = 0.75$, $P < 0.0001$). Lean body mass (LBM) was higher accordingly to the level of physical activity in men ($P < 0.002$), but in women, although high LBM was observed between the active individuals compared to the sedentary, no difference was seen between the active and insufficiently active. In multivariate analysis, LBM was dependent of BMI, AC, male gender, and active by IPAQ ($P < 0.005$). AF was higher in individuals with comorbidities ($P < 0.005$).

Conclusions: Physical activity is an independent factor influencing body composition in men and women, regardless of age.

6-24

Low muscle mass as a predictor of mortality risk among older adults: a systematic review

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Background: Sarcopenia is a geriatric syndrome, and it is associated with poor health outcomes such as death. We aimed to review the evidence of low muscle mass (LMM) as a predictor of mortality among older adults.

Methods: Systematic review of observational cohort studies was conducted according to the PRISMA guidelines. PubMed and Scielo databases were searched. The search strategy used was (elderly OR “older adults”) and (community OR non-institutionalized) and “low muscle mass” and mortality. Inclusion criteria were (i) prospective cohort studies; (ii) studies investigating whether sarcopenia according to LMM was a predictor of mortality; (iii) studies published in Spanish, Portuguese, and English languages; and (iv) studies published within the last 5 years. Exclusion criteria were (i) type of participants: hospitalized and (ii) article type: review articles, letters, dissertation, and thesis.

Results: Of 17 studies identified, three were included. Studies were conducted in Australia and Brazil. Follow-up periods varying from 4 to 10 years, and the relative risk (RR), odds ratio (OR), or hazard ratio (HR) were used. The participant's minimum age ranged from 50 to 70 years old. All studies used dual-energy X-ray absorptiometry (DXA) as diagnostic criteria for muscle mass. The prevalence of sarcopenia ranged from 20.73% to 26.63% among men and 21.33% to 21.51% among women. LMM was significantly associated with mortality risk (RR = 1.54, 95% CI: 1.14–2.08, $P < 0.05$). Analysis by sex demonstrated that the mortality risk was higher among women (OR = 62.88, 95% CI: 22.59–175.00, $P < 0.001$) than men (OR = 11.36, 95% CI: 2.21–58.37, $P = 0.004$). However, there was a study that not found mortality risk among men (HR = 0.88, 95% CI: 0.70–1.11, $P = 0.29$). Association between LMM and mortality risk was not found when predefined cut-offs were used to diagnosis muscle mass.

Conclusions: Sarcopenia according to LMM increases mortality risk among noninstitutionalized older adults. However, further researches are needed to explain gender discrepancies.

6-25

Correlation among sarcopenia stages and fear of falling in prefrail community-dwelling older women

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Background: Sarcopenia is characterized by a reduction in muscle mass, muscle strength, physical performance and can contribute to falls. This study's purpose is to correlate the stages of sarcopenia and fear of falling in prefrail community-dwelling older women.

Methods: Cross-sectional study with 70 prefrail elderly women (71.2 ± 4.5 years; BMI: 9.4 ± 4.1 kg/m), classified according to the Fried frailty phenotype. Handgrip strength (HGS) through dynamometer; muscle mass (MM) was estimated by calf circumference (CC) and Lee equation (MM-Lee); gait speed in 4 meters (GS 4 m); lower limb strength (chair-stand Test - CST5rep); fear of falling (*Falls efficacy Scale – Internacional FES-I* BRAZIL).

Results: The older women showed 20.0 ± 6.0 kgf (HGS), CC 36.4 ± 3.7 cm, and GS4m 1.02 ± 0.2 m/s. It was detected nonsarcopenia in 80% ($n = 59$) (CST5rep = 11.6 ± 3.3 s; MM - Lee = 7.9 ± 0.9 kg/m²; FES-I = 22.5 ± 5.6), probable sarcopenia in 15.7% ($n = 11$) (TSL5X = 11.9 ± 3.9 s; MM - Lee = 7.8 ± 1.7 kg/m²; FES-I = 28.3 ± 8, 3 cm), and sarcopenia in 4.3% ($n = 3$) (TSL5X = 11.9 ± 3.4 s; MM - Lee = 7.4 ± 0.7 kg/m²; FES-I = 28.4 ± 6.8 cm) of participants. It was found the following correlations: nonsarcopenia and fear of falling

($P = 0.357$; $P = 0.003$) and probable sarcopenia and fear of falling ($P = 0.309$; $P = 0.01$).

Conclusions: The prefrail community-dwelling older women in a probable sarcopenia stage and those with sarcopenia presented fear of falling indicating sporadic falls. However, even the nonsarcopenics showed association with fear of falling.

6-26

Body mass index and mortality among community-dwelling older adults from Southern Brazil

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Background: The objective of this study is to evaluate the association between body mass index (BMI) and mortality among community-dwelling older adults in Pelotas, Brazil, using two different criteria to classify the BMI and considering the myopenia.

Methods: It is a cohort study started in 2014 with older adults living in the city of Pelotas, Southern Brazil. BMI was classified according to the World Health Organization (WHO) and Lipschitz. Deaths were identified up to April 2017. Calf circumference ≤33 cm in women and ≤34 cm in men diagnosed myopenia. Cox proportional hazards regression investigated the associations adjusting for sociodemographic and behavioural characteristics in addition to the number of chronic diseases.

Results: We interviewed 1451 older adults in 2014. Around 10% ($N = 145$) of the participants died in almost 3 years. Relationship between BMI and risk of mortality was L-shaped. Participants with low weight had higher risk of mortality in comparison to those with adequate BMI in both criteria. According to WHO criterion, overweight individuals had lower risk of mortality (HR: 0.58; 95% CI: 0.38; 0.87) in relation to those with adequate BMI. There was no statistical significance in the risk of mortality in overweight older adults using the Lipschitz criterion. Among participants with myopenia, hazard ratio for risk of mortality was below the null value in the overweight group in both criteria, although not statistically significant, whereas those classified with low BMI according to Lipschitz had higher risk of mortality than participants with adequate BMI (HR: 2.09; 95% CI: 1.06; 4.14).

Conclusions: Low BMI increased the risk of mortality in up to a 3 year period among community-dwelling older adults. The Lipschitz criterion seemed to be more adequate to identify

high risk of mortality based on BMI in this sample. Higher BMI decreased the risk of mortality when myopenia was not taken into account.

6-27

Calf circumference as a predictor of all-cause mortality among noninstitutionalized elderly in Brazil

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Background: Calf circumference (CC) reflects muscle mass status in the elderly population. However, its effectiveness in predicting long-term mortality risk has not been fully elucidated. We aimed to evaluate the effectiveness of CC in predicting mortality risk in noninstitutionalized elderly.

Methods: This is a 10 year follow-up cohort study (Elderly Project/Goiania) with noninstitutionalized elderly individuals aged greater or equal 60 years. Trained nutritionists performed CC using a standardized procedure. Mortality data were collected from the Brazilian Mortality Information System of the Health Ministry. The association of mortality risk with low CC (<34 cm for men and <33 cm for women) was assessed by Cox regression. Statistical significance was set at P value < 0.05.

Results: We evaluated 416 elderly individuals with a mean age of 70.7 ± 7.1 years, and 66.1% were women. Mean CC was 34.7 ± 3.1 cm in men and 34.1 ± 3.6 cm in women, without statistical difference ($P = 0.14$). Prevalence of low CC was 36.3% (95% CI: 31.66–40.94), being 39.7% (95% CI: 31.54–47.89) in men and 34.6% (95% CI: 28.89–40.20%) in women,

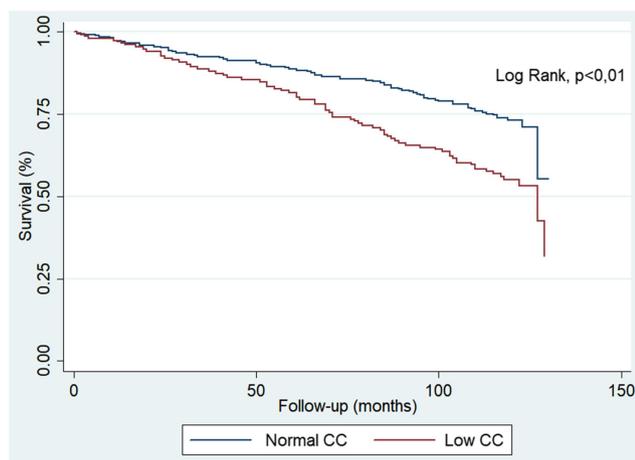


Figure 1 Survival curves of the study population according to calf circumference (CC). Low CC: <34 cm for men and < 33 cm for women.

without statistical difference ($P = 0.30$). There were 144 deaths within an 8.5 year follow-up period, representing 34.6% of the study sample. Cox regression analyses showed that mortality risk is greater in elderly with low CC (HR = 1.88 95% CI: 1.35–2.61) ($P < 0.01$) (Figure 1). Greater mortality risk was also observed among women (HR = 1.94 95% CI: 1.27–2.96) ($P < 0.01$) compared to men (HR = 1.74 95% CI: 1.03–2.96) ($P = 0.04$).

Conclusions: Low CC is an anthropometric indicator with relevant impact on all-cause mortality in both sexes of noninstitutionalized Brazilian elderly. Considering that CC is a non-invasive, low-cost, and easily standardized measure compared to gold standard methods, effort should be made to increase the use of this indicator in clinical practice.

6-28

Dysmobility syndrome is associated with cognitive and functional impairment in middle-aged and older adults of Mexico City

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Background: Dysmobility syndrome is a new concept in the literature that may have a role as predictor of adverse outcomes in older people. The results of this article are relevant for the geriatric and gerontological scientific communities as they call attention for the association of two frequent geriatric syndromes with dysmobility syndrome: disability and cognitive impairment. The objective of this study is to investigate the frequency of dysmobility syndrome (DS) and its association with geriatric syndromes in community-dwelling middle-aged and older adults of Mexico City.

Methods: In this cross-sectional analysis of the FraDySMex study, 534 participants aged 50 years and older were included. Body composition, gait speed, and grip strength were evaluated with DEXA, GAITRite instrumented walkway, and hand dynamometer, respectively. Sociodemographic characteristics, clinical history, falls, mental, nutritional, and functional status.

Results: Participants' mean age was 71.3 ± 9.5 years, 80.1% females. The frequency of DS was 28.1% ($n = 150$). After adjustment, geriatric syndromes associated with DS were cognitive impairment (OR = 2.38, 95% CI = 1.29–4.40, $P = 0.006$) and dependence in basic activities of daily living (OR = 2.21, 95% CI = 1.08–4.54, $P = 0.031$).

Conclusions: DS is independently associated with cognitive impairment and disability in community-dwelling middle-aged and older adults. Further studies are needed to better understand the role of DS as a geriatric syndrome predictor.

6-29

Impact and risk factors for clinically relevant surgery-related muscle loss in patients after major abdominal cancer surgery: study protocol and preliminary results from a prospective observational cohort study (MUSCLE POWER)

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Background: Surgery-related muscle loss (SRML) occurs in at least one out of three cancer patients within 1 week after major surgery. Though, this important phenomenon has hardly been investigated.

Methods: The MUSCLE POWER is a prospective, observational cohort study that investigates the presence, impact, and predictors for clinically relevant SRML in 178 cancer patients after major abdominal surgery using ultrasound measurements, squeeze and force measurements, and quality of life (QoL) questionnaires (Figure 1). Primary end point is the proportion of patients with clinically relevant SRML defined as $\geq 5\%$ muscle loss within 1 week after surgery, measured by the anterior–posterior diameter of three different muscles: m. biceps brachii, m. rectus femoris, and m. vastus intermedius. Possible correlation with QoL and fatigue up to 6 months after surgery will be explored. Physical activity and protein intake during hospital stay will be monitored with a motility tracker and a nutrition diary. Possible predictors for clinically relevant SRML—consisting of age ≥ 65 years, preoperative diabetes, preoperative sarcopenia, major postoperative complications (Clavien–Dindo \geq III), insufficient physical

activity, and insufficient protein intake—will be investigated with a multivariable logistic regression analyses with a backward stepwise approach. Variables with $P < 0.05$ will be retained in the final multivariable model.

Results: Preliminary results of the first 60 patients can be presented at the *Cachexia Conference 2019* in Berlin. We hypothesized that 50% of our patient population will have clinically relevant SRML which will lead to a reduced QoL and fatigue up to 6 months after surgery. We expect that the possible predictors investigated in this study can predict clinically relevant SRML prior to surgery.

Conclusions: The MUSCLE POWER study investigates the presence, impact, and predictors for clinically relevant SRML in cancer patients after major abdominal surgery. Crucial information to design future intervention studies to prevent postoperative muscle loss and improve postoperative outcome.

6-30

“Dry” appendicular muscle mass as measured by segmental impedance spectroscopy during the 12 channel routine electrocardiogram relates to aortic dysfunction in chronic heart failure

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Background: There are known relationships between sarcopenia, visceral fat, and arterial stiffness. We have thought to improve these relationships by correcting

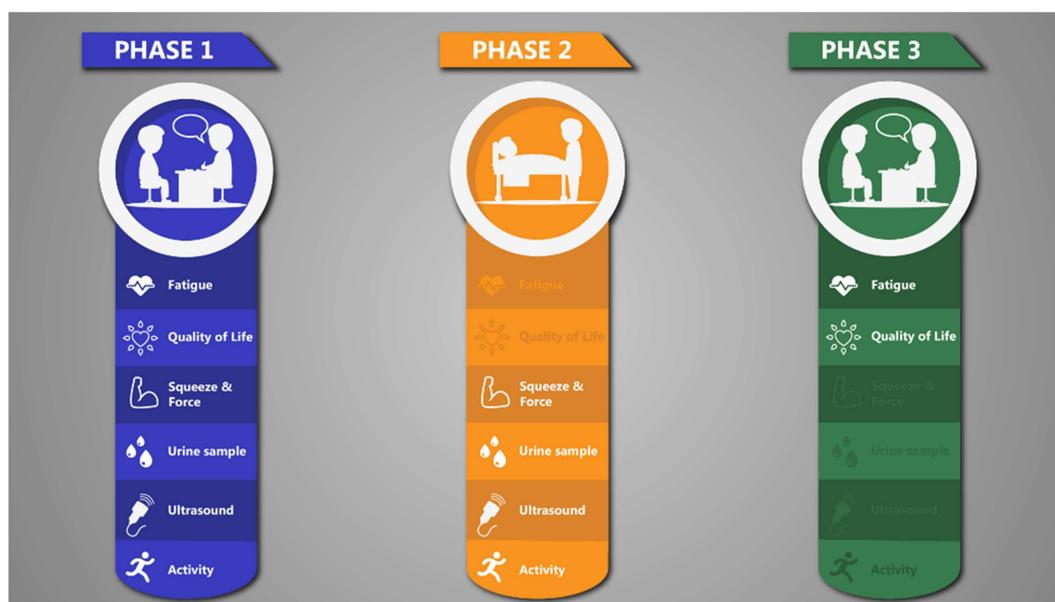


Figure 1 Study design. Phase 1: One day prior to surgery; Phase 2: Weeks after surgery till discharge; and Phase 3: Three and six months after surgery.

appendicular muscle mass measurements for excess extracellular water (“dry AppMM”) and to include all necessary measurements in the routine 12 channel ECG.

Methods: A 12 channel ECG supplies impedance measurements at multiple frequencies in six body segments (thorax, abdomen, and the extremities) and also impedance plethysmographic measurements at the four extremities [Medical Engineering & Physics 36 (2014) 896& 44(2017) 44]. All measurements are performed automatically without time delay during the routine ECG. AppMM, extracellular water (ECF), total body fat, and trunk fat were determined from segmental impedances at six body segments. DXA-derived AppMM was also measured. From the peripheral impedance plethysmographic measurements, aortic volume wave velocity (aoVWV) was derived in analogy to carotid femoral volume wave velocity measured by mechanical transducers. “Dry AppMM” corrected for ECF excess, body fat and aoVWV were measured in 158 normotensive, healthy participants (72 males) and in 98 patients with CHF (NYHA class 2 to 4) (56 males) during the routine ECG.

Results: In multiple backward stepwise regression analysis, aoVWV was related positively to age and negatively to dry AppMM index (males’ total $r = 0.73$, females’ total $r = 0.53$, both $P < 0.001$). In contrast, DXA-derived AppMM index uncorrected for ECF excess and body fat were excluded in the stepwise backward regression analysis.

Conclusions: DXA-derived AppMM that is not corrected for ECF excess overestimates AppMM by up to 30% in patients with CHF because of overhydration. In contrast, appendicular muscle mass measured by six-segment multifrequency impedance corrected for ECF excess can classify sarcopenia with greater precision. The inverse relation between dryAppMM index and aortic volume wave velocity, both derived during the routine 12 channel ECG, reemphasizes the importance of muscularity for vascular health in CHF.

6-32

The association between urine creatinine excretion and bone mineral density in CKD: from the KNOW-CKD study

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Background: Previous studies have shown that decreased lean body mass or muscle mass is associated with decreased bone mineral density in individuals with preserved renal function. However, this relationship is uncertain in chronic kidney disease (CKD), where more diverse factors such as decreased renal function and disordered mineral metabolism impact on

bone health. The aim of this study was to verify the relationship between muscle mass estimated from creatinine excretion and bone mineral density in a large Korean cohort of CKD.

Methods: This cross-sectional study analysed 1740 participants from the KNOW-CKD cohort. The bone mineral densities of the lumbar spine, total hip, and femur neck were assessed by dual-energy X-ray absorptiometry. Muscle mass was estimated from 24 h urine creatinine excretion (UCr). Participants were divided into three groups according to their UCr.

Results: The study participants’ mean eGFR was 53.7 ± 32.7 mL/min/1.73 m². Among them, 100 (5.8%) participants had osteoporosis. Osteoporosis was more prevalent among the lower UCr groups (12.2%, 4.7%, and 0.3% for the 1st to 3rd tertile, respectively, $P < 0.001$). For each 100 mg/day increase in UCr, BMD increased by 0.07 for lumbar spine, 0.06 for total hip, and 0.04 for femur neck in multivariate linear regression analysis. In multivariate logistic regression, the OR for osteoporosis compared to the 1st tertile was 0.55 (0.33–0.92, $P = 0.023$) in the 2nd tertile and 0.08 (0.02–0.37, $P = 0.001$) for the 3rd tertile.

Conclusions: Creatinine excretion was significantly and independently associated with low BMD and osteoporosis in CKD. Future research is warranted to determine if osteoporosis can be prevented through intervention to increase muscle mass.

6-33

Associations between body composition and prognosis of patients admitted because of acute pancreatitis: a retrospective study

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Background: We investigated associations of muscle and visceral fat mass with the prognosis of patients hospitalized with acute pancreatitis. Visceral adiposity was shown to be associated with improved prognosis in patients with acute calculous cholecystitis.

Methods: This is a retrospective analysis of patients admitted with acute pancreatitis during 2008–2014. Body composition analysis (Sliceomatic, Tomovision, CA) was performed on CT images at the L3 level. Regression analysis was used to examine associations of body composition with 1 year mortality and 1 year readmission rates.

Results: A total of 158 patients were included [mean age 63.7 ± 17.4 years, 91 (57.6%) were male]. Fat was the most

abundant tissue ($408 \pm 180 \text{ cm}^2$ surface area). None of the prognostic factors examined were associated with 1 year mortality. Values below compared to above the medians for muscle mass and visceral fat were associated with higher mean 1 year readmissions: 1.7 versus 1.0, $P = 0.02$ and 1.6 versus 1.1, $P = 0.09$, respectively. Logistic regression analysis showed an association of high visceral fat with reduced 1 year readmission (OR 0.995, 95% CI: 0.991–1.000, $P = 0.03$). Linear regression analysis showed an inverse correlation of visceral fat mass with the number of 1 year readmissions (HR -0.004 , 95% CI -0.008 – 0.000 , $P = 0.070$).

Conclusions: Higher amounts of visceral fat and muscle mass were positively associated with lower recurrent hospitalizations in patients admitted with acute pancreatitis. These results support the importance of nutritional rehabilitation in patients after admission due to acute pancreatitis.

6-34

Cut-off points of phase angle and its association with sarcopenic, frailty, and physical performance in community-dwelling Mexican older adults

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Background: The phase angle (PhA) is the parameter of the electrical bioimpedance (BIA) expresses changes in the amount and quality of soft tissue mass. PhA can be an important tool to evaluate the clinical outcome or to evaluate the progression of the geriatrics syndromes as sarcopenia, frailty, and low physical performance. The lack of reference values of PhA has limited its use in clinical situations and is unknown the relationship between AF and sarcopenia, frailty, and low physical performance.

Methods: It is a cohort of community-dwelling adults from Mexico City; PhA was measured by BIA[®]SECA (50 Hz). Muscle mass by dual-energy X-ray absorptiometry (DXA) (Hologic Discovery-WI; Hologic Inc, Bedford-MA). The appendicular lean mass index ratio (ALMBMI) was calculated dividing the appendicular skeletal muscle mass by the body mass index. A hand strength by dynamometer (JAMAR Hydraulic Hand Dynamometer, Lafayette, IN). In our study, sarcopenia was defined in accordance with the Foundation for the National Institutes of Health (FNIH) criteria, Fried's criteria to frailty, and short battery physical performance (SPPB) to low physical performance.

Results: A total of 498 adults of >50 years and older were included. The mean age was 71.1 ± 9.5 , the mean of PhA was 4.6 ± 0.70 . The cut-off point of PhA to frailty was ≤ 4.1 , sensitivity = 80.13%, specificity 68.89% LR (+) 2.57, LR (–) 0.28; AUC = 0.83 95% IC (0.8019–0.8686). The cut-off point of

PhA to sarcopenia was ≤ 4.1 , sensitivity = 80.44%, specificity 71.11% LR (+) 2.78, LR (–) 0.27; AUC = 0.84 95% IC (0.8387–0.9142). The cut-off point of PhA to low physical performance was ≤ 4.3 , sensitivity = 80.0%, specificity 44.91% LR (+) 1.45, LR (–) 0.44; AUC = 0.70 CI 95% (0.6667–0.7484).

Conclusions: The association between PhA, sarcopenia, and frailty has a good sensitivity and AUC, both low specificity. Low physical performance has low sensitivity, specificity, and AUC. PhA could be an early and accessible marker to evaluate future changes in body composition (sarcopenia) and frailty in community-dwelling older adults.

6-35

Myosteatosi is associated with increased oxidized lipid within dendritic cells in patients with colorectal cancer: dendritic cell dysfunctional: the missing key to unlocking the mystery of myosteatosi?

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Background: Myosteatosi is associated with the oncogenic systemic inflammatory response and poor prognosis and outcomes in patients with colorectal cancer (CRC). CT scan analysis can identify these changes in muscle quality. Dendritic cells (DC), the bodies primary antigen presenting cells, orchestrate the cellular immune response. DC have been shown to take up lipid becoming adipocyte-like. Oxidized lipid within DC is associated with DC dysfunction, interfering with antigen presentation. A significant association between expression of the fat-scavenger receptor CD36, which drives lipid uptake, on circulating DC and myosteatosi in CRC patients has been demonstrated. We assessed whether the lipid profile of these key immune cells was associated with myosteatosi in CRC.

Methods: Peripheral blood mononuclear cells were isolated from whole blood of preoperative CRC patients and labelled with antibodies to identify DC. Cells were permeabilized to examine intracellular total lipid (using Bodipy dye) and oxidized phospholipids (using the monoclonal antibody to E06). Positive staining was determined using fluorescence minus-one controls. Analysis of preoperative CT scans (SliceOmatic v5.0) identified the presence of myosteatosi using predefined cut-off values based on the mean muscle attenuation (Hounsfield units) and BMI.

Results: Fourteen CRC patients were included in this analysis, median age 64 (male $n = 11$), seven had myosteatosi. In patients with myosteatosi, the frequency of myeloid-DC (mDC) and plasmacytoid-DC (pDC) staining positively for E06

(oxidized lipid) was significantly greater than in patients without myosteatorsis, $P = 0.026$ and $P = 0.017$, respectively. There was no significant difference in total lipid content (Bodipy) between groups, mDC $P = 0.80$ and pDC $P = 0.19$.

Conclusions: DC dysfunction caused by increased intracellular oxidized lipid is significantly associated with myosteatorsis. There is no significant change in DC total lipid uptake in myosteatorsis. CD36 could be an immunotherapy target in CRC patients with myosteatorsis—preventing oxidized lipid uptake and allowing appropriate presentation of tumour-specific antigen to the immune downstream effectors.

6-36

Inflammation-induced skeletal muscle wasting: emerging role of the NLRP3 inflammasome

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Systemic low- and high-grade inflammation in various acute and chronic diseases is associated with loss of skeletal muscle mass and metabolic dysfunction. Complicating factors in understanding molecular mechanism underlying this loss is that muscle wasting is a multifactorial process, and human tissue under well-controlled wasting conditions is sparse. To mechanistically study how inflammation induces skeletal muscle atrophy and metabolic dysfunction, we differentiated C2C12 myoblasts into myotubes and treated them with lipopolysaccharide (LPS) to induce a low-grade (10 ng/mL) or high-grade (100 ng/mL) inflammation. Within 24 h, LPS reduced muscle fiber diameter by $12 \pm 9\%$ (10 ng/mL) and $42 \pm 6\%$ (100 ng/mL; both $n = 150$, $P < .001$). A higher concentration of LPS (200 ng/mL) severely disrupted normal fiber morphology. IL-6 concentrations within the supernatant dose-dependently increased upon LPS treatment. After 72 h, LPS-treated muscle fibers remained significantly smaller than vehicle-treated cells.

While the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is an integral component of the innate immune system, its role in the development of muscle wasting in skeletal muscle is poorly understood. NLRP3 and downstream caspase-1 mRNA gene expression levels were higher in LPS-treated myofibers after 24 h, but no IL-1 β was detected in supernatant. While the supplementation of an extracellular danger signal, 5 mM ATP, did not result in more muscle wasting, NLRP3, and (pro-)caspase-1 protein concentrations were marginally increased. Using immunofluorescence, we observed that this NLRP3 protein had a high

colocalization to mitochondria. These data suggest a primed, but not fully activated, NLRP3 inflammasome in skeletal muscle upon LPS treatment and a possible mechanistic link with mitochondrial dysfunction. Current studies are underway to fully understand the role of the NLRP3 inflammasome and metabolic alterations associated with inflammation-induced skeletal muscle dysfunction. This also allows compounds aimed to alleviate muscle wasting to be tested.

6-38

Fried frailty phenotype and hand grip strength in advanced cancer patients

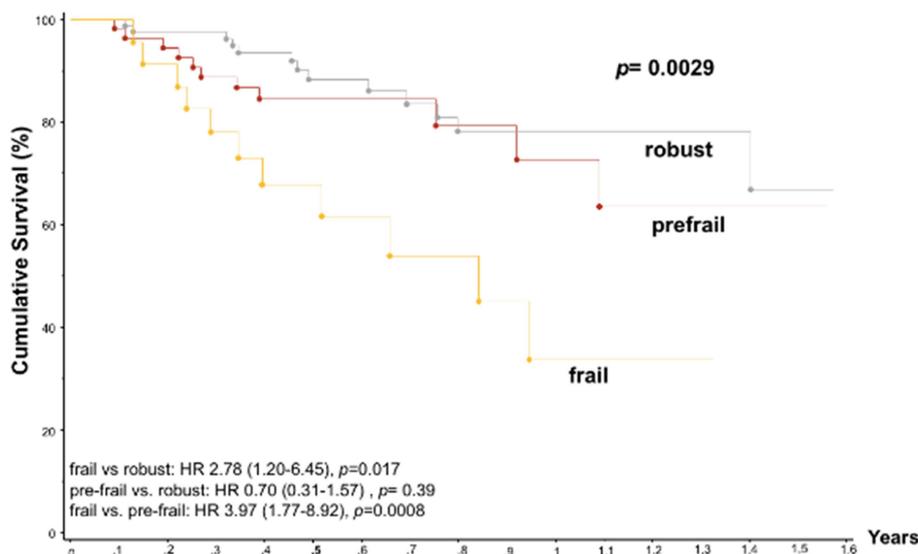
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Background: The most used questionnaire for frailty assessment in geriatric patients, the Fried frailty phenotype, has rarely been used in advanced cancer patients.

Methods: From November 2017 to July 2019, we prospectively enrolled 178 patients with cancer (61 ± 14 years, 57% men, BMI 25.4 ± 4.7 kg/m², 78% cancer stage ≥ 3) and 49 healthy controls of similar age and sex. We used the Fried frailty phenotype to assess frailty with 5 domains (each 1 point): shrinking (>10 pounds' unintentional weight loss), weakness (low hand grip strength), poor endurance and energy (self reported), slowness (slow 15-foot gait speed), and low physical activity level (low energy expenditure). 0 points $\hat{=}$ robust, 1–2 points $\hat{=}$ prefrail, 3–5 points $\hat{=}$ frail.

Results: Ninety-three (52%) patients with cancer were prefrail and 25 (14%) frail. Four (8%) healthy controls were prefrail. In patients with cancer, shrinking, poor endurance and energy, low physical activity level, slowness, and weakness were present in 77 (43%), 30 (17%), 28 (16%), 29 (16%), and 47 (26%), respectively, compared to healthy controls with 2 (4%), 0, 0, 0, 2 (4%). Between the cancer groups, robust, prefrail, and frail, we compared different modes of assessing hand grip strength (average or maximum, dominant



or non-dominant arm, stronger or weaker arm) and found the greatest difference in hand grip strength between the groups when the average of three tries was calculated for the strongest arm (37.0 ± 11.1 kg vs. 29.8 ± 8.9 kg vs. 23.3 ± 8.1 kg, P value < 0.0001), respectively. During a median follow-up time of 10 months (max. 21 months), 35 (20%) cancer patients died. The Fried frailty score was a predictor of survival in univariable (per 1 point, HR 1.38, 95% CI 1.08–1.76, $P = 0.009$) and multivariable analyses (per 1 point, HR 1.29, 95% CI 1.01–1.65, $P = 0.042$), adjusted for tumour type and stage, surgery, and chemotherapy.

Conclusions: Ninety-three (52%) patients with advanced cancer were prefrail and 25 (14%) frail. The Fried frailty score was independently associated with higher mortality.

6-39

Cross-sectional associations between sex hormones, IGF-1, fat-free mass, and vitamin D in men aged 50–78 years in the UK EPIC-Norfolk Study

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Background: Fat-free mass (FFM), an index of skeletal muscle mass, declines with age, contributing to the onset of sarcopenia. The age-related effects on circulating sex hormones and IGF-1 also contribute to sarcopenia, as do low concentrations of 25(OH)D. We therefore, investigated

associations between circulating concentrations of sex hormones, IGF-1, and 25(OH)D with FFM, in men aged 50–78 years in the UK EPIC-Norfolk Study. We further explored whether circulating concentrations of 25(OH)D modified associations between FFM%, sex hormones, and IGF-1.

Methods: Total fat-free mass (measured using bioelectrical impedance) was calculated as a percentage of body weight (FFM%). Circulating concentrations of testosterone (T), sex hormone-binding globulin (SHBG), free testosterone (FT), dehydroepiandrosterone sulphate (DHEAS), and IGF-1, in nmol/L, $N = 2368$, and 25(OH)D (nmol/L, $N = 1743$) were measured. Statistical analyses were performed in STATA (MP V16) with multivariable regression analyses adjusted for the covariates; age, self-reported physical activity, smoking habit, height, and protein as a percentage of total energy intake (calculated from 7 day food diaries). Concentrations of sex hormones and IGF-1 were log transformed.

Results: Significant correlations were only found between FFM% and T (R 0.14, $P < 0.001$) and SHBG (R 0.25, $P < 0.001$), FT (R -0.05 , $P = 0.01$) which remained after adjustment for covariates in multivariable analysis (T, 0.009% FFM/nmol, $P < 0.001$, and SHBG 0.014% FFM/nmol, $P < 0.001$). The association between 25(OH)D and FFM% was significant in multivariable analysis (0.11% FFM/nmol, $P < 0.001$) but when 25(OH)D was included in the multivariable models, the existing associations between T and SHBG and FFM% did not differ substantially.

Conclusions: Although circulating concentrations of testosterone and SHBG are significantly associated with FFM in middle and older aged men, the impact of 25(OH)D on this relationship appears to be small.

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6-40

Use of primary human skeletal muscle cell cultures for the study of chemotherapy-induced muscle wasting

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Background: Muscle wasting during cancer chemotherapy is a known but poorly understood phenomenon that contributes to reduced survival prognosis. In this study, we have established several primary human myoblast cultures to investigate the molecular mechanisms involved in chemotherapy-induced muscle wasting.

Methods: Biopsies from m. vastus lateralis were obtained from healthy donors after informed consent. Satellite cells were derived by a novel explant procedure and myoblasts with myogenic potential subsequently were expanded in growth medium containing 20% fetal bovine serum (FBS). Experiments were performed on differentiated myotubes induced at 80% confluence by complete FBS withdrawal. After initiation of myotube formation (2–3 days) substrate was exchanged to postfusion medium containing 2% FBS. Cisplatin (Pfizer) or Fluorouracil (Hospira Nordic AB) were applied to myotubes for 24 h, and after additional 4–5 days in postfusion medium myotubes were harvested for Western blotting and immunofluorescence analysis.

Results: Cells with myogenic potential proliferated and expressed Pax7 in the undifferentiated state. Multinucleated myotubes were found to form in differentiation medium, expressing myogenin as well as myosin heavy chain (MyHC) isoforms. Exposure to increasing concentrations of cisplatin leads to myotube atrophy concurrent with marked reduction in MyHC expression. As cisplatin concentrations approached levels experienced by chemotherapy patients (5 µg/mL and above), MyHC completely disappeared. Fluorouracil, on another hand, did not seem to affect either phenotype or MyHC expression to any significant extent.

Conclusions: In the present study, we have developed and validated a cell based *in vitro* assay to study the physiological effect of chemotherapeutic agents on muscle cells *in vitro*, using biopsy samples from human skeletal muscle. Our findings indicate that not all cancer drugs induce muscle loss to the same extent, cisplatin being markedly more muscle-toxic

than fluorouracil. The present assay system may help to study cellular mechanisms and pathways involved in chemotherapy-induced muscle wasting. Further, the present approach provides an important possibility to study muscle wasting induced by chemotherapy, allowing to distinguish this from cachexia induced by other factors such as cancer itself or age. Muscle wasting in cancer patients is a major prognostic factor. An improved understanding of the underlying mechanisms is imperative to improve therapy efficiency, to which ends the present *in vitro* assay system may serve as an important tool.

6-41

The influence of aetiology on body composition and muscle strength in male patients with heart failure

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Background: Ischaemic patients with heart failure (HF) have worse outcomes in comparison to their nonischaemic counterparts. Moreover, patients with HF and Chagas' disease have also shown to present a higher mortality rate compared to other aetiologies, including ischaemic patients. However, the impact of aetiology on body composition and muscle strength in patients with HF is still unknown. This aims to evaluate the influence of aetiology on body composition and muscle strength in patients with HF from dilated, ischaemic, and chagasic origin in two distinct cohort studies [Brazil (Testo-HF) and Germany (SICA-HF)].

Methods: We enrolled 64 male patients with HF matched by body mass index (BMI), 20 dilated and 22 ischaemic patients from SICA-HF (Göttingen, Germany), and 22 chagasic patients from TESTO-HF (São Paulo, Brazil). All patients were in New York Heart Association functional class II–III (NYHA) with left ventricular ejection fraction (LVEF) ≤40%. Dual-energy X-ray absorptiometry was used to assess lean body mass (LBM) and fat mass (FM). Muscle strength was measured by hand-grip strength. All patients underwent a maximal cardiopulmonary exercise testing on cycle ergometer (Brazil) or treadmill (Germany). Venous occlusion plethysmography was used to measure forearm blood flow (FBF). Blood samples were also drawn in the morning after an overnight fasting.

Results: Patients with dilated HF had higher FM (27.6 ± 9.4 vs. 19.3 ± 8.0 vs. 16.3 ± 8.1 kg; *P* < 0.05) and higher peak

absolute VO_2 (1.50 ± 0.45 vs. 1.15 ± 0.36 vs. 1.17 ± 0.36 L/min; $P < 0.05$) than ischaemic and chagasic patients, respectively. Chagasic patients showed a trend towards decreased LBM when compared with ischaemic patients (48.3 ± 7.6 vs. 54.2 ± 6.3 kg; $P = 0.094$). Moreover, patients with Chagas' disease showed lower handgrip strength (27 ± 8 vs. 37 ± 11 vs. 36 ± 14 kg; $P < 0.05$) and FBF (1.84 ± 0.54 vs. 2.75 ± 0.76 vs. 3.42 ± 1.21 ; $P < 0.01$) compared with ischaemic and dilated patients, respectively. In addition, FBF correlated positively with handgrip strength ($r = 0.36$; $P = 0.004$) and LBM ($r = 0.31$; $P = 0.012$). In a logistic regression, haemoglobin (hazard ratio, 1.560; 95% confidence interval, 1.043–2.177; $P = 0.029$) and appendicular skeletal muscle mass (hazard ratio, 1.179; 95% confidence interval, 1.011–1.374; $P = 0.035$) were independently associated with peak VO_2 (median value < 1.15) adjusted for age, LVEF, NYHA, creatinine, and FBF. There was no difference between the three groups for laboratory characteristics.

Conclusions: Muscle strength showed to be reduced in male patients with HF and Chagas' disease. In addition, reductions in muscle blood flow were also correlated with impaired function and lean body mass, whereas appendicular skeletal muscle mass was independently associated with reduced functional capacity in these patients.

6-42

A novel link between the ubiquitin proteasome system and mitochondrial function to control muscle metabolism

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Skeletal muscle metabolism of proteins, carbohydrates, and lipids is critical for systemic energy homeostasis. Muscle loss and metabolic alterations in obesity, diabetes, ageing sarcopenia, and cancer cachexia reduce the quality of life, increasing mortality. In these catabolic conditions, a failure in mitochondrial quality control pathways is deleterious for the maintenance of muscle function. However, how mitochondrial dysregulation in muscles contributes to these metabolic disorders is not clear. To address this issue, here we dissect the role of the novel circadian muscle-specific E3 ubiquitin ligase Asb2b. Asb2b is so far, the only E3 ubiquitin ligase sufficient to cause muscle atrophy when overexpressed in muscles. However, the mechanisms involved and which are its specific substrates are unexplored issues. To unravel its cellular function, we generated muscle-specific Asb2b knockout mice. Our data show fiber-type switching, oxidative stress, and several abnormalities in the mitochondrial distribution, turnover, and function in Asb2b-null mice. Under

catabolic conditions, fibers lacking Asb2b cannot cope with energy stress inducing alterations in the metabolism of glucose, suggesting that Asb2b is required for fiber function and integrity during an energy crisis. In addition, the expression levels of Asb2b are induced in diet-induced obesity, ageing sarcopenia, and cancer cachexia. Thus, Asb2b is central in mitochondrial homeostasis which impacts on both muscle mass and metabolism.

7-09

A nutritional supplementation with leucine improved the functional activity of Walker 256 tumour-bearing Wistar rats

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Background: Cancer cachexia is characterized mainly by anorexia and involuntary weight loss, with intense muscle and fat mass waste. These symptoms jeopardize patient's quality of life, reducing survival during treatment. A leucine-rich diet has been shown to increase muscle anabolism and minimize the catabolism. This study aimed to evaluate the effects of a leucine-rich diet in the functional activity in an experimental model of cachexia.

Methods: Wistar adult rats were distributed into four groups: control (C, $n = 5$) and Walker 256 tumour-bearing (W, $n = 7$), both groups fed a control diet (18% protein) and leucine (L, $n = 6$), and leucine tumour-bearing (LW, $n = 7$) groups fed a leucine-rich diet (18% protein +3% leucine). All rats were monitored, weighed, and the food intake measured three times/week. Their functional activity was assessed, during the night time, analysing the distance covered (cm), the average velocity (cm/s) and the time spent in movement (s) using the software *EthoVisionXT12*. After 21 days of tumour evolution and diet administration, all groups were euthanized, and their serum was collected to measure total protein, albumin, and glucose concentration. Moreover, tibialis anterior muscle and perirenal adipose tissue were collected, weighted, and then normalized by the tibia length.

Results: The tumour growth induced cachexia in rats, resulting in weight loss, decreased food intake, muscle and fat mass loss, and impaired the functional activity. Serum biochemical analyses were reduced in both tumour-bearing groups ($P < 0.05$). However, as a benefit of leucine-rich diet, LW group maintained the fat mass (LW = C; W < C, $P = 0.0375$), lose less body weight (LW > W, $P = 0.0252$),

and showed a better physical functional activity (speed and time moving, $LW > W$, $P < 0.05$).

Conclusions: Rats fed a leucine-rich diet have a better functional activity (faster, more mobile, and resilient) than rats with the same health status under a conventional diet.

7-10

Effects of garlic extract on cancer-induced muscle wasting

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Background: Cancer cachexia is characterized by weight loss mainly due to ongoing loss of skeletal muscle mass, leading to progressive functional impairment. Skeletal muscle atrophy is considered as the most important factor of cancer cachexia and is ineffectively reversed by nutritional support. Thus, in this study, we investigated whether garlic extract (GE) would alleviate muscle atrophy in a mouse model of colon cancer cachexia in order to provide evidence for candidates to prevent and/or treat cancer cachexia.

Methods: After inducing a xenograft model with CT26 cells in BALB/c mice, animals were treated with 0 (Tumor Control, TC), 5 mg/kg (GE5), 10 mg/kg (GE10) for a week. Muscle tissue weights, and the cross-sectional area were measured. The mRNA expression of markers related with inflammation and protein degradation was determined by RT-qPCR. Statistical analysis was conducted by one-way ANOVA followed by Duncan's post hoc test using SAS software version 9.4.

Results: GE administration effectively suppressed total muscle weight loss ($P = 0.01$) and muscle fiber atrophy ($P < 0.0001$). In the mice treated with GE, the mRNA expression of E3 ubiquitin ligases was significantly decreased compared with TC group. Similarly, the levels of pro-inflammatory cytokines and genes associated with JAK/STAT3 signalling pathway were significantly reduced in response to GE supplementation.

Conclusions: Our data indicate that GE improves skeletal muscle atrophy induced by cancer cachexia through down-regulating systemic inflammatory response and expression of muscle protein catabolic markers. Therefore, these findings suggest that GE has beneficial effects on the prevention and/or treatment of cancer cachexia.

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7-11

Prevalence of malnutrition-sarcopenia syndrome in Mexican older adults living in nursing homes

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Background: Sarcopenia is a geriatric syndrome involving multiple factors among which malnutrition is present. The co-existence of these clinical conditions has resulted in malnutrition-sarcopenia syndrome (MSS) whose identification is relevant due to increased risk of adverse clinical outcomes. The objective of this study is to identify the prevalence of malnutrition, sarcopenia, and MSS in a group of elderly living in nursing homes.

Method: A cross-sectional study was performed in old people over 65 years living in public nursing homes in Mexico City. The diagnosis of sarcopenia was obtained using the EWGSOP criteria (2010), gait speed (< 0.8 mts/sec), hand grip strength (< 30 kg for men and < 20 kg for women), and muscle mass (calf circumference < 31 cm). Malnutrition was assessed using the Mini Nutritional Assessment (< 17 points). The protocol was registered by the Council of the Division of Biological Sciences and Health of Metropolitan Autonomous University Xochimilco campus and accepted by the Ethic Committee in Mexico City. The objectives and procedures of this study were explained to the nursing home residents, and all participants signed a written consent form.

Results: A total of 212 institutionalized elders were evaluated. 70.3% were women with an average age of 83.4 ± 80 years old. The average age of men was 79.9 ± 8.8 years old. The prevalence of sarcopenia was of 61.7% in women and 39.7% in men. The prevalence of malnutrition was of 32.2% in females and of 17.5% in males. Nevertheless, the prevalence of MSS was of 14.3% in old men and 29.5% in old women.

Conclusions: This study demonstrated a high prevalence of MSS among elderly patients living in nursing homes. There is a need to establish intervention programs with nutritional support to prevent and improve nutritional status as well as muscle mass, strength, and function of the skeletal muscle.

7-12

Investigating the relationship between markers of nutritional status, sarcopenia, and frailty and clinical outcomes in older hospital patients

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Background: Malnutrition, sarcopenia, and frailty are likely to interact with each other and may affect clinical outcomes such as length of hospital stay (LOS) and risk of mortality in older hospitalized patients. These conditions should be identified early to inform medical care provision, especially nutritional care. The Nutritional Screening Tool (NST) and Geriatric Nutritional Risk Index (GNRI) are simple malnutrition screening tools, SARC-F, for sarcopenia, and the Clinical Frailty Scale (CFS) is a recognized for frailty screening. Certain routine blood markers, namely albumin and C-reactive protein (CRP), and the CRP/albumin ratio may assist in predicting an adverse clinical outcome. This study aimed to investigate the prevalence of malnutrition, sarcopenia, and frailty in acutely hospitalized older patients and relationships between clinical outcomes (LOS and in-hospital mortality).

Methods: A retrospective clinical audit of 139 hospital medical records of older patients aged over 80 years. Data regarding NST, CFS, SARC-F screening, routine blood markers (urea, albumin, CRP, CRP/Alb ratio), LOS in hospital, and in-hospital mortality were recoded into an excel database.

Results: Over 30% patients were malnourished; 60–65% patients were sarcopenic or frail. NST, SARC-F, CFS, CRP, and CRP/Alb levels were significantly different between alive and deceased groups ($P < 0.05$). The CFS and CRP were the strongest predictors of death (CFS = CRP > SARC-F > NST > GNRI). Only GNRI ($r = 0.45$) and NST ($r = 0.38$) demonstrated a fair negative correlation with LOS, while other markers had relatively poor relationships ($r = 0.2$). There was a significant overlap between patients with sarcopenia, frailty, and malnutrition irrespective of whether the NST or GNRI was used for malnutrition screening.

Conclusions: The results support the hypothesis that sarcopenia and frailty coexist with malnutrition, though the exact relationship has not been demonstrated. CFS, CRP, and CRP/Albumin ratio are useful indicators of clinical outcomes in older patients.

7-13

Obesity as risk factor for frailty in older Chileans

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Background: Although obesity has been shown as a protective factor for survival in older Chileans, this does not necessarily mean that obese people are ageing healthy. The objective of this study is to determine the risk of frailty associated with obesity in older Chileans.

Methods: Follow-up of ALEXANDROS cohorts designed to study disability associated with obesity in community-dwelling people 60 years and older living in Santiago/Chile. From 1416 participants (67.7% women, mean age 72 years \pm 6.7) with baseline anthropometric measurements and those measures needed for the diagnosis of frailty using the Fried's phenotype criteria (unintentional weight loss of ≥ 5 kg in the previous 6 months, fatigue/exhaustion, walking speed < 0.8 m/sec, difficulty walking, weak handgrip strength women ≤ 15 kg; men ≤ 27 kg), 711 subjects were free of frailty at baseline. From them, we were able to follow 463 (median follow-up 5.3 years). At baseline, the subjects were classified as obese or nonobese using WHO standards of BMI. χ^2 test and logistic models were used for the analysis.

Results: The prevalence of obesity at baseline (BMI ≥ 30) was 31.7%. After 3103 person years of follow-up, 125 new cases of frailty were identified. The incidence of frailty in the total sample was 4.0/100 person years (obese 4.3/100 person years; nonobese 3.75/100 person years). After age, sex, and lean mass adjusted regression analysis, the RR of frailty in obese people was RR = 3.97 (95% CI 1.20–9.51).

Conclusions: Incidence of frailty is almost fourfold in obese subjects when compared with nonobese, putting them at high risk of adverse effects on health as functional limitations and disability.

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7-15

Malnutrition is still a big problem in oncology clinics: results form 405 patients

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Background: Weight loss/nutritional deterioration are common features in cancer patients under active treatments. To understand whether or not their incidence is changing during treatments is of major importance, given the theoretical increased awareness in nutrition in clinical practice. Thus, this

study aimed to analyse the impact of cancer treatments on body mass index (BMI) and weight changes throughout the treatments.

Methods: Epidemiological, observational, retrospective study that included 405 patients with various types of solid tumours, submitted to chemotherapy as outpatients in Vila Franca de Xira Hospital between 2014 and 2017. Age, gender, diagnosis (location and stage), height (m), and weight (kg) at the beginning and end of the treatments was obtained from records, and BMI was calculated. Differences in weight and BMI at the beginning and end of the treatments were evaluated, as well as differences between the qualitative and quantitative variables considering cancer location and stage.

Results: A weight loss of 1.1% was observed in all patients ($P < 0.001$), with 39% losing more than 2.4%, as well as a reduction of 0.3 kg/m² in BMI ($P < 0.001$). These results were more relevant for upper gastrointestinal cancer that showed a weight loss of 4.1% ($P < 0.001$) and BMI reduction of 0.9 kg/m² ($P < 0.001$) and also for stage IV disease that lost 1.9% of weight ($P < 0.01$) and had a BMI reduction of 0.5 kg/m² ($P < 0.01$).

Conclusions: Despite clear advances in cancer treatment and nutritional therapy in the last decade, the prevalence of nonintentional weight loss associated with cancer and/or treatments remains alarmingly high. Patients submitted to chemotherapy, especially those with cancer of the upper GI tract and/or advanced disease stage have significant weight loss and deterioration of BMI throughout treatments, indicating a clear need for urgent and consistent nutritional intervention. The present results from a 3 year period might translate a still ineffective nutritional intervention in cancer care.

7-16

The prevalence of sarcopenia and malnutrition in a group of oncologic patient

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Background: Evaluation of nutritional status is a central point of oncologic patient's approach. Therefore, nutritional assessment to identify the risk of malnutrition or malnourishment should be performed in these patients to obtain an early nutritional-metabolic evaluation. This study aims to evaluate nutritional status, body composition, and sarcopenia in a group of oncologic patients candidate to parenteral nutrition (PN).

Methods: This cross-sectional study included 54 patients: 33 females (57.6 ± 8.5 years; 55.9 ± 16.7 kg; 22.2 ± 6.4 kg/m²) and 21 male (66.4 ± 11.7 years; 68.9 ± 19.2 kg;

23.8 ± 4.7 kg/m²) with a primary or secondary neoplasia admitted to Medicine and Surgery wards of the Federico II University Hospital. All patients were evaluated for risk of malnutrition using BMI < 18.5 kg/m², the new ESPEN criteria (FFM corrected for height: FFMI, fat-free mass index), and the presence of sarcopenia with SM (derived from Janssen's equation) corrected for height (SMI).

Results: Body composition was estimated by bioimpedance (Females: FFM 41.3 ± 8.7 kg; FAT 14.7 ± 11.3 kg; FAT 24.0 ± 12.7%; Males: FFM 55.3 ± 11.7 kg; FAT 13.6 ± 15.1 kg; FAT 17.2 ± 17.4%). The prevalence of malnutrition was

- 1 with BMI < 18.5 kg/m² was 33.3% in female and 4.8% in male,
- 2 with low FFMI, was 27.7%; also, if we consider the combined finding of unintentional weight loss could be >10% of habitual weight combined with a low fat-free mass index FFMI, the prevalence was 6.1%.
- 3 Eleven women (33.3%) and four male (19%) showed severe sarcopenia with a low SMI.

Conclusions: Using ESPEN definition, malnutrition was found more frequently in women with both options. The skeletal muscle mass' loss was significant, and it is reported with a high risk of postsurgical complications, chemotherapy toxicity, and mortality. For these reasons, the evaluation of nutritional status is very important for the prevention of malnutrition, because if not treated, survival of oncologic patients could be worsened.

7-17

The relationship between selenium deficiency and cardiovascular diseases in haemodialysis patients

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Background: Cardiovascular disease is prevalent and main cause of death in haemodialysis (HD) patients. Selenium is an essential trace element, and it has been known to prevent cardiovascular disease by protecting the of oxidative stress using selenium-dependent glutathione peroxidases. HD patients are more likely to have selenium deficiency due to dietary restriction, malabsorption, altered metabolism, haemodialysis, itself etc. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in HD patients.

Methods: A total of 80 HD patients was enrolled in this cross-sectional study. The patients were divided into two groups based on the level of serum selenium: 61 patients were

normal level, and 19 patients were selenium deficient. The cardiovascular diseases were evaluated using echocardiography, coronary computed tomography, or coronary angiography.

Results: There were no significant differences in baseline characteristics, including age, sex, duration of HD, and Kt/V between the two groups. Although there was no significant difference, the prevalence of ischaemic heart disease showed higher tendency in selenium deficient group than that in nonselenium deficient group (52% vs. 32% $P = 0.06$), and it showed similar results in heart failure (HF) and cardiomyopathy between the two groups (HF: 32% vs. 24%, cardiomyopathy: 16% vs 12%).

Conclusions: This study showed the higher tendency of heart disease in HD patients with selenium deficiency. The large sample sized studies are needed.

7-20

Calf circumference and risk of coronary heart disease

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Background: Emerging evidence showed the calf circumference (CC) was an important index for sarcopenia in the aged population. Because little literature focused on the CC on the cardiometabolic risks, our objective of the study was examining the association between the CC and risk of coronary heart disease.

Methods: The data were collected from geriatric physical screenings at the health promotion center in Tri-Service General Hospital (TSGH) in Taiwan in 2017. This study enrolled the community-dwelling elderly who aged greater or equal to 65 years old. The trained staff placed the measuring tape around the participant's right calf to acquire the maximal circumference to the nearest 1.0 millimeter in a sitting position. Framingham risk score of coronary heart disease (FRS-CHD) was calculated.

Results: We examined the CC in 1223 participants (540 in men and 683 in women) with quartiles to identify the demographic characteristics. A significantly negative correlation was noted between the FRS-CHD and the CC in both genders in all models (all $P < 0.05$) (Table 1). Table 2 listed the baseline characteristics of female participants classified by CC quartiles. Relatively younger age, higher BMI, higher uric acid, lower HDL-C, and higher prevalence of hypertension treated with antihypertensive agents were found with statistical significance in the higher CC quartiles compared with the

lowest quartile ($P < 0.05$). The characteristics of male participants divided by CC quartiles with the mean age of 75.60 ± 8.44 years were presented in Table 3. Table 4 exhibited a significantly negative correlation in higher quartiles of CC with FRS-CHD in both genders compared with the lowest quartile ($P < 0.001$). Additionally, both men and women, the individuals in the higher quartiles of CC seemed to have a lower FRS-CHD with the significant association (P for trend < 0.001).

Conclusions: Our findings highlighted that there is a negative association between CC and FRS-CHD in the elderly population. These findings might underscore the importance of recognizing significant CC atrophy or wasting for future cardiovascular event in the clinical practice.

7-21

Evaluation of useful and convenient screening methods for cardiac cachexia in outpatients with heart failure

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Background: Cardiac cachexia is a poor prognosis, and diagnosis is important. However, diagnosis of cardiac cachexia for outpatients is not sufficiently performed because it may be time-consuming. We investigated screening methods useful for the diagnosis of cardiac cachexia in the clinical setting.

Methods: Totally 128 outpatients with CHF aged over 65 years old were enrolled. The criteria for evaluating cachexia by Evans were used. Nutritional status was assessed by the Mini Nutritional Assessment Short Form (MNA^oR-SF) and Geriatric Nutritional Risk Index (GNRI). Frailty was assessed by the "Kihon checklist". We compared and evaluated these assessments and the diagnosis of cachexia.

Results: The mean age was 76.0 ± 7.4 years old, and left ventricular ejection fraction was $43.6 \pm 17.2\%$. Of the study patients, 54.7% patients were male, 20.7% patients had ischaemic heart failure, 45.9% patients had MNA^oR-SF score ≥ 11 , and 14.4% patients had cardiac cachexia. The 1 year event-free survival rates were cardiac cachexia group 64.7% and noncardiac cachexia group 88.5% (log-rank, $P < 0.01$). The multivariate logistic regression analysis suggested that MNA-SF score {odds ratio (OR), 0.51; 95% confidence interval (CI), 0.36–0.66; $P < 0.01$ }, GNRI (OR, 0.86; 95% CI, 0.79–0.92; $P < 0.01$) and Kihon checklist score (OR, 1.35; 95% CI, 1.19–1.59; $P < 0.01$) might be independent predictors for cardiac cachexia in heart failure patients.

Conclusions: Evaluation by MNA^oR-SF, GNRI, and Kihon checklist score was simply performed by blood test or questions, which were useful for diagnosing cachexia.

7-22

Nutritional interventions to improve body composition in persons living with HIV: a systematic review of clinical studies

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Persons living with HIV (PLWH), struggle with side effects of the antiretroviral therapy, which includes body composition changes [fat redistribution and fat-free mass (FFM) reduction], signifying increased risk of developing sarcopenia. Nutrition interventions can be considered important strategies to attenuate this risk. We developed a systematic review identifying nutrition interventions studies aiming to improve body composition in PLWH. We consulted, following Cochrane recommendations, the databases PubMed, Science Direct, Web of Science, Lilacs, Nature, and Google Scholar and hand-searched grey literature. The search resulted in 853 publications; after exclusion criteria (non-human studies and reviews), 31 articles remained, 27 of them investigating FFM [15 open-label or non-randomized (OL/NR), and 12 double-blind randomized clinical trials (RCT)]. We found different interventions and different methods of body composition investigation. From OL/NR, only eight studies showed increase in FFM [supplementation or adequacy of protein intake ($n = 7$); low glycemic index diet ($n = 1$)]. The remained seven studies did not show difference in FFM [supplementations with n-3 fatty acid ($n = 1$), MCT ($n = 1$), protein ($n = 1$), and micronutrient ($n = 1$); nutritional counselling ($n = 2$); dietary modification ($n = 1$)]. From RCT, only three showed significant increase in FFM [supplementations of arginine, glutamine, and HMB ($n = 1$) and protein ($n = 2$)]. The remaining nine studies did not increase in FFM [supplementation with protein ($n = 3$); arginine and n-3 fatty acid ($n = 1$); arginine, glutamine, and HMB ($n = 1$); L-ornithine - alpha-ketoglutarate ($n = 1$); chromium ($n = 1$); vitamin D ($n = 1$); and chocolate intake ($n = 1$)]. The heterogeneity of the studies turned impossible to run any meta-analyses. Concluding, more controlled and randomized studies are necessary to find the best nutrition strategies to deal with the risk of sarcopenia in PLWH.

7-23

Malnutrition, treatment interruptions, and adverse events in head and neck cancer undergoing radiotherapy: still a reality?

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Background: Nutrition has been recognized for over three decades as a fundamental long-term prognostic factor in head and neck cancer patients. Yet still profound impairments are seen in the nutritional status of these patients. To understand how patients are embarking on cancer treatments and whether or not the incidence of weight loss throughout cancer therapy is improving is of major importance. This study aimed to analyse the impact of cancer and cancer treatments on body weight and the relation between weight loss and treatment interruptions, unplanned admissions, and adverse events occurrence.

Methods: Age, gender, tumour location and stage, height, and weight at the beginning and end of the treatments were obtained from the records of 139 patients with head and neck cancer submitted to radiotherapy at the Portuguese Oncology Institute of Coimbra between 1 January 2017 and 4 October 2017. Weight loss at the beginning and end of radiotherapy was evaluated, as well as differences between groups considering cancer location, stage, and treatment modality. Treatment interruptions, unplanned admissions, and adverse events were analysed considering the occurrence of critical weight loss.

Results: At baseline, critical weight loss was seen in 60% of the patients with a mean weight loss of 7%. During radiotherapy, 31% of the patients had lost >5% of weight; mean weight loss of 3%. Those undergoing intensive chemoradiation group had a mean weight loss of 7% before and 5% during chemoradiation. No statistically significant differences regarding treatment interruptions, hospital admissions, and adverse events between the two groups of weight loss (critical versus not critical) were found.

Conclusions: Despite clear advances in cancer treatment and nutritional therapy, the prevalence of nonintentional weight loss associated with cancer remains high. Patients submitted to chemoradiotherapy have significant weight loss before the diagnosis and throughout treatments, indicating a clear need for an early nutritional intervention.

7-24

Effects of sarcopenia and malnutrition on morbidity and mortality in gynecologic cancer surgery: Results of a prospective cohort study in 237 patients

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Background: Decreased nutritional parameters and muscle attenuation have been associated with poor postoperative outcomes in gynecologic cancer patients. The aim of this study is to evaluate the effect of malnutrition and sarcopenia on postoperative complications.

Methods: This is a prospective cohort study of 237 patients undergoing gynecologic cancer surgery at a gynecological cancer center from October 2015 through January 2017. Preoperatively we assessed nutritional parameters including albumin, BMI, the Nutritional Risk Score 2002 and weight loss $\geq 10\%$. Bio Impedance Analysis (BIA) parameters, such as phase angle alpha, ECM/BCM index, fat mass (FM) and fat free mass (FFM) were evaluated. To assess if patients suffer from sarcopenia we calculated a skeletal muscle index, performed hand grip strength and run the timed up and go test (TUG). More than 400 variables were collected including performance status (ECOG), geriatric assessments and quality of life parameters. Surgical complications were graded using validated Clavien-Dindo criteria. Using ROC analysis and logistic regression, we identified predictive clinical characters for postoperative complications.

Results: Out of the 226 enrolled patients 40 (17.3%) experienced a grade $\geq 3b$ complication. Within 30 days of surgery, mortality rate was 3.8%. In the regression analysis ECOG > 1 ($p = 0.003$, OR 6.78, 95% CI: 1.88-24.48) as well as obesity ($p = 0.008$, OR 6.63, 95% CI: 1.63-27) emerged as significant predictors of postoperative complications. Moreover complications were predicted by low albumin $< 3,6$ g/dl ($p = 0.032$, OR 3.93, 95% CI: 1.13-13.69), ECM/BCM ratio (BIA) $> 1,35$ ($p = 0.021$, OR 4.21, 95% CI: 1.24-14.30) and FM > 27.5 kg ($p = 0.038$, OR 3.06, 95% CI: 1.06-8.82) to be independent predictors of increased postoperative complications.

Conclusion: In patients undergoing gynecological cancer surgery preoperative evaluation of functional and nutritional health status might help to identify high risk patients to reduce the surgery induced morbidity and mortality in gynecological patients.

8-11

Myosin activity triggers muscle growth through a novel mechanotransduction signalling pathway involving Forcin

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Background: Physical inactivity leads to skeletal muscle atrophy and weakness in the elderly, hospitalized, and diseased patients and contributes to the obesity epidemic.

Methods: To investigate how high-force exercise promotes muscle growth, we developed a rapid *in vivo* muscle growth assay in the zebrafish larva which was used to test the effect of electrical and optogenetic stimulation and drug treatments on muscle growth. Molecular genetic and biochemical studies analysed signal transduction pathways.

Results: Reduced growth of inactive muscle was restored by a brief burst of electrically or optogenetically imposed activity. Activity-dependent growth involved both increase in muscle fibre size and muscle fibre number, indicating an effect on muscle precursor cells. Growth only occurs if myosin hydrolyses ATP and generates force; imposition of electrical activity in the presence of myosin inhibitors that block contraction without affecting muscle calcium transients fails to elicit growth. Mechanistically, activity promotes TORC1 activity, as assayed by S6 phosphorylation, but myosin blockade does not inhibit TORC1, suggesting that force induces muscle growth through a previously unknown pathway. RNAseq revealed that inactivity reduces and transient imposed activity rescues, in a myosin-dependent manner, expression of Forcin, an enzyme expressed in striated muscle. Addition of a drug that mimics Forcin activity can substitute for activity and promote growth of inactive muscle. Genome editing was used to ablate Forcin function, and results will be presented.

Conclusions: Muscle tissue thus senses activity through several signalling pathways, and a novel mechanosensitive pathway dependent on myosin function is required to trigger growth.

8-12

Muscular strength, physical function, and quality of life in community-dwelling old adults

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Background: Quality of life (QoL) has been regarded as a critical predictor of successful ageing in gerontological research. The aim of this study was to examine the associations

between physical activity, muscle strength, body composition, physical/cognitive function, and disease with quality of life community-dwelling older adults.

Methods: Participants ($N = 225$, 73.7 ± 5.7 years, 58.2% female) from the Reykjavik capital area in Iceland took part in this cross-sectional study. Socio-economics, QoL, body composition, muscular strength, timed up and go test (TUG), 6 min walk for distance (6MWD), and disease-related information were measured. Fasting blood samples were analysed for routine clinical measures.

Results: In our subjects, only 19.1% had QoL below the age and gender corrected norm score of 50. A simple comparison between subjects with QoL below 50 vs subjects with a score above 50 indicated that participants with higher QoL had higher physical and cognitive function, higher muscular strength, lower blood glucose, exercised more, and used a lower number of medicines. Differences in education, smoking, alcohol consumption, dietary intake, and gender distribution were not significant. According to age and gender corrected linear models, TUG ($B = -0.54$, $P = 0.022$), number of drugs ($B = -0.67$, $P = 0.018$), and fasting glucose ($B = -0.96$, $P = 0.025$) were the strongest independent correlates of QoL. In the models, insulin/glucose and TUG/6MWD were interchangeable.

Conclusions: Physical function, number of drugs, and glucose metabolism are independently related to QoL and represent therefore potentially modifiable targets for future interventions in order to improve QoL in community-dwelling old adults.

8-13

Five times sit-to-stand test and wrist fracture risk in community-dwelling obese Icelandic adults

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Background: The associations between obesity, physical function, falls, and fractures are unclear. The aim was to investigate whether obese adults have poorer sensory function, physical function as well as higher fracture risk than normal weight peers; and whether confounders explain potential differences between body mass index (BMI) categories.

Methods: A case-control study was conducted using 98 wrist fracture cases (50–75 years) and 48 matched controls. Measurements included among others: anthropometrics, sensory function (Semmes–Weinstein monofilaments), physical function [five times sit-to-stand test (FTSTS)], questionnaires on previous fractures and fall history, the activities-specific

balance confidence (ABC), and the Dizziness-Handicap-Inventory (DHI) scales.

Results: Obese participants had lower physical function (FTSTS: $+2.8$ s, $P < 0.001$), lower tactile sensitivity (monofilaments: $+3.4$ g, $P = 0.013$), poorer ABC score (14.0, $P < 0.001$), higher DHI score (11.6, $P < 0.001$), and experienced more falls the previous 12 months ($+0.8$, $P = 0.006$) compared to normal weight subjects. According to crude logistic regression analysis, the hazard ratios for wrist fracture in overweight and obese subjects were 2.7 ($P = 0.012$) and 5.6 ($P = 0.002$), respectively. When FTSTS was included in the statistical model (HR: 1.7, $P = 0.004$), it reduced the hazard ratios of overweight and obesity close to 1. Lifetime fractures (HR: 5.5, $P < 0.001$) and fall history (HR: 4.3, $P < 0.001$) were associated with an increased fracture risk independently from the BMI categories.

Conclusions: Obese individuals have poorer physical function, higher risk of falls, and increased wrist fracture risk compared to normal weight peers. Lower physical function is the main driver for the increased risk in obese subjects. Lifetime fractures and fall history are associated with a fracture independently from obesity.

8-14

Muscle mass, physical function, and bone health in Icelandic community-dwelling old adults living alone

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Background: Loneliness and living alone have been significant public health concerns among older adults given their association with a wide range of adverse health outcomes. The aim of this study was to examine whether living alone is associated with physical function and bone health in community-dwelling older adults.

Methods: This was a secondary analysis of existing cross-sectional data of old adults ($N = 182$, 73.7 ± 5.7 years, 58.2% female) from the Reykjavik capital area in Iceland. Information on socio-economics, health, dietary intake, and physical function was collected. 25-hydroxy-vitamin D (25OHD) and bone mineral density (BMD) were measured. Participants were grouped retrospectively into “living alone” and into “in cohabitation”.

Results: Of our subjects, 76.4% were in cohabitation, and 23.6% lived alone. Participants who lived alone were older (74.5 ± 5.6 vs. 72.1 ± 5.0 , $P = 0.008$) and more often female (74.4 vs. 53.2% , $P = 0.014$), but there were no differences in education, smoking, number of medications, physical activity (PA), muscle mass, or body mass index (BMI). According to

age and gender corrected analyses, participants in cohabitation had higher grip strength (6.2 ± 2.4 lb, $P = 0.011$), higher 25OHD (13.1 ± 6.3 nmol/L, $P = 0.037$), and higher BMD (z-score lumbar: 1.195 ± 0.417 , $P = 0.005$; z-score femur: 0.421 ± 0.219 , $P = 0.054$; z-score total: 0.846 ± 0.290 , $P = 0.004$). Statistical correction for PA, BMI, education, and fish oil intake did not change the results.

Conclusions: In comparison to old adults who live in cohabitation, Icelandic old adults who live alone have poorer physical function, lower 25OHD, and lower BMD, which increases their risk for wrist or hip fracture. These differences between groups were not explained by physical, dietary, or social confounding variables.

8-15

Muscle mass, physical function, and quality of life in community-dwelling old adults who adhere to physical activity according to the Nordic Nutrient Recommendations 2012

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Background: Regular physical activity (PA) is associated with better health outcomes in gerontological research. The Nordic Nutrient Recommendations 2012 advise to engage in >30 min of PA/day. The aim of this study was to (i) characterize physically active community-dwelling older adults compared to nonphysically active and (ii) to examine the associations between physical activity and muscle strength, body composition, physical/cognitive function, and disease in this group.

Methods: Participants ($N = 225$, 73.7 ± 5.7 years, 58.2% female) from the Reykjavik, Iceland took part in this cross-sectional study. Physical activity, socio-economics, quality of life (QoL), anthropometrics, strength, timed up and go test (TUG), 6 min walk for distance (6MWD), and disease-related information were measured.

Results: Of our subjects, 57.2% exercised at least 30 min a day (77 ± 47 min/day), 42.8% exercise less than recommended (11 ± 9 min/day, $P < 0.001$). Physically active participants were younger (72.6 ± 5.7 vs. 74.8 ± 5.5 years, $P = 0.003$) and more often female (65.2 vs. 49.5%, $P = 0.016$), but other socio-economic differences or dietary intake were not significant. According to linear models corrected for age and gender, PA as recommended was associated with lower BMI ($B = -1.458$ kg/m², $P = 0.029$), lower fat mass ($B = -3.482$ kg, $P = 0.014$), lower muscle mass ($B = -1.674$, $P = 0.022$), higher quadriceps strength ($B = 36.2$ N, $P = 0.010$), higher 6MWD ($B = 41.2$ m, $P = 0.001$), lower TUG ($B = -0.68$ s, $P = 0.002$), and higher

QoL ($B = 2.2$, $P = 0.022$) but not with any blood chemical variables, cognitive function, or number of drugs.

Conclusions: Physical activity was common in this group of community-dwelling old adults. Female participants were more active, but otherwise, physical activity was independent from socio-economic variables. Not unexpected, physical activity was related to better body composition and physical function but neither to medication use nor to blood chemical variables. It can be speculated that a more structured/intense exercise programme is needed to improve these parameters.

8-16

90 day continuous activity recording to characterize physical frailty trajectories in older adults: a tool for modelling wax-and-waning conditions in real-world context

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Background: We had previously shown (Magistro et al., 2018) how to measure the levels of spontaneous mobility of the elderly subject in a nonintrusive way using a connected accelerometer (ADAMO, worn as an electronic wristwatch). The mobility index (MI) was then defined, a synthetic variable quantifying intensity and temporal distribution of physical activity, on medium-long term. We also estimated and analysed the gait speed, normalized on the first 15 monitored days (Mulasso et al, 2019). After defining an analytic procedure based on both mean speed and activity level distribution, we applied it to a reference data set, namely the European collaborative study "DECI".

Methodology: We selected the observations lasting 90 days or longer. As Adamo device allows to separate information of outdoor/indoor recording, we restricted the analysis on outdoor activity. The "mobility index distribution" was modelled by assigning a weight to each activity level. Then its "variability" was estimated along the observed period, at least 90 days. Next, the "mean speed" and the "activity level variability" trajectories were compared and merged into a third aggregated trajectory, defining a frailty index. The "frailty index trajectory" was estimated for all 90 day or longer observations available in DECI data set.

Results and conclusions: We expected that a mean speed declining trajectory would lead to a worsen frail patient status if the variability trajectory increases. This data behaviour was confirmed within the DECI data set. Then it was possible to define a "frailty index trajectory" as the ratio between the mobility index variability and the mean speed trajectories. The results in the DECI data set are promising. The next step is to apply this approach to a different population, e.g., sarcopenic oncologic patients who underwent

multicomponent regimens with the aim of using the frailty trajectory to model the comprehensive longitudinal effect of treatment, in a real-world context.

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8–17

The relationship between preoperative body composition and aerobic fitness in patients scheduled for colorectal surgery

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Background: The cardiopulmonary exercise test (CPET) is the golden standard to measure aerobic fitness for preoperative risk stratification; however, it is relatively time-consuming and stressful. Body composition variables from preoperative computer tomography (CT scan) may estimate aerobic fitness. This study aimed to determine the relationship between body composition variables and aerobic fitness prior to colorectal surgery.

Methods: This study analysed data from patients who underwent colorectal surgery, who underwent preoperative CPET and an abdominal CT scan. CT scans were analysed using a single-slice CT-image at L3 level to assess skeletal muscle mass, skeletal muscle radiation attenuation (SM-RA), visceral adipose tissue (VAT) mass, and subcutaneous adipose tissue (SAT) mass. Linear regression analyses were performed to investigate the relation between CPET variables [e.g. anaerobic threshold (AT)], CT scan-derived body composition variables, and other preoperative patient-related variables.

Multivariable logistic regression analysis was performed to predict whether a patient had an AT ≤ 11.1 mL/kg/min.

Results: Data of 78 patients (45 males; mean \pm SD age 74.5 ± 6.4 years) were analysed. In the univariable analysis, a Pearson correlation coefficient of 0.55 ($P < 0.001$) was observed between the absolute AT and skeletal muscle mass index. The multivariable regression model demonstrated that the absolute AT (R^2 of 51.1%) was lower in patients with a lower skeletal muscle mass index, together with a higher age, a lower body mass, and a higher ASA score. A higher ASA score (OR 5.64; 95% CI of 1.15;27.69) and a higher VAT mass (OR 1.02; 95% CI of 1.00;1.03) were associated with an increased risk of a relative AT ≤ 11.1 mL/kg/min as a cut-off to classify patients as having an increased risk for postoperative morbidity.

Conclusions: Body composition variables derived from the preoperative CT scan were moderately associated with aerobic fitness as determined from preoperative CPET. A higher ASA score and a higher VAT mass were associated with an increased risk of a relative AT ≤ 11.1 mL/kg/min.

8-18

Effect of physical exercise on lean body mass and functional capacity in patients with myotonic dystrophy type 2

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Background: Myotonic dystrophy type 2 is an autosomal dominant disease resulting from an unstable tetranucleotide CCTG repeat expansion in intron 1 of the nucleic acid-binding protein (CNBP) gene. The disease is multisystemic and is characterized by proximal symmetrical muscle weakness, myotonia, early cataracts, endocrinological, and cardiological manifestations with no known therapy. Physical exercise is an effective method for improving functional capacity in various neuromuscular diseases. However, it remains unknown whether exercise is effective for improving the functional capacity of patients with myotonic dystrophy type 2. The purpose of the study was to investigate the effect of physical exercise on the functional capacity of patients with myotonic dystrophy type 2.

Methods: Seven patients with myotonic dystrophy type 2 participated (63.2 ± 9.2 years, 168.4 ± 7.6 cm, 82.4 ± 11.7 kg). The body composition (dual-energy X-ray absorptiometry), grip strength, timed up and go test (TUG), and 6 min walking (6MW) were evaluated at baseline (T1), after 3 months without any intervention (T2, internal control period), and after another 3 months (T3) when physical exercise

was performed. Between T2 and T3, patients followed aerobic exercise on a stationary bicycle and resistance exercise for all body parts, twice weekly. Statistical analysis included repeated measures ANOVA ($P < 0.05$ significance level).

Results: Body composition and functional capacity were not altered between T1 and T2. Grip strength and time in TUG test increased significantly between T2 and T3 ($P < 0.05$). Distance covered in 6MW was also increased (T2: 377 ± 132 m, T3: 389 ± 122 m, $P < 0.05$). Total lean mass and lean mass of the upper and lower extremities, total and femoral head bone mineral density, increased significantly between T2 and T3. None of the patients expressed any complaint about pain or discomfort during the period of physical exercise.

Conclusions: These results suggest that physical exercise is safe and improves significantly the functional capacity, lean mass, and bone mineral density of patients with type 2 myotonic dystrophy.

8-20

The impact of heart failure, atrial fibrillation, and renal function comorbidity on outcome of rehabilitation after acute phase of stroke

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Background: An early and reliable prognosis of outcome after stroke is important for early stroke management and the optimal planning of post stroke care. The aim of this study was to evaluate the impact of heart failure (HF), atrial fibrillation (AF), and chronic kidney disease (CKD) on outcome of rehabilitation in stroke patients.

Methods: We enrolled 402 patients with ischaemic stroke and 154 patients with haemorrhagic stroke, who are admitted in the rehabilitation center. Clinical characteristics of patients are obtained from medical records. The comorbidity of HF, AF, and CKD were analysed in association with outcome and incidence of medical complications during rehabilitation.

Results: HF (odds ratio, 2.58 [1.47–4.53]), CKD (odds ratio, 1.73 [1.06–2.83]), and their combination (odds ratio, 2.76 [1.28–5.94]) as well as the combination of HF and AF (odds ratio, 2.93 [1.57–5.45]) were associated with increased risk of unfavorable functional long-term outcome of rehabilitation (fatal and nonfatal adverse events), while the length of stay in rehabilitation center did not have any significant difference between these groups. The cumulative survival of stroke patients was adversely affected in patients with HF (hazard ratio 2.26, 95% CI 1.06–4.8, $P = 0.028$).

Conclusions: The comorbid HF, CKD, and the coexistence of HF-CKD and HF-AF are an independent predictor of unfavorable functional long-term outcome in stroke patients. These data suggest that comorbid HF is the only significant determinant of survival following rehabilitation after acute phase of stroke.

8-21

Determinants of quality of life in patients with cancer

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Background: Quality of life is an important factor in the treatment of cancer patients. In order to monitor the patients during cancer therapy, the Karnofsky Performance Status is frequently used to objectively assess the quality of life. We conducted a multicentre study, in which we used cardiovascular functional parameters to assess the patient's physical and psychological status.

Methods: A total of 395 patients [age 61.63 ± 12.64 years, 48.4% female, body mass index (BMI) 25.26 ± 4.81 kg/m², EQ-5D-5L level of self-assessed subjective health 65% (50–80%)], diagnosed with advanced cancer, were enrolled at the University Medical Centre Göttingen as well as at the Charité - University Medicine Berlin, Campus Benjamin Franklin. According to the Karnofsky Index, the patients were divided into two groups with Karnofsky Index value higher or lower than 90%. In order to evaluate the target variables in the context of cardiovascular predictors, following measurements were performed: 6 min walking test [6MWT], 4 m gait speed test [4mGST], hand grip strength [HGS], resting-ECG, EQ-5D-5L, mini nutritional assessment [MNA], medication assessment, standard laboratory, troponin T, NT-proBNP, albumin, LDH, CK-MB, and transferrin saturation.

Results: A total of 66.3% of the patients had a tumour UICC stage IV, and 25.8% are deceased. The percentage of patients with Karnofsky Index under 90%, who died until the study's censor date, was higher in comparison with deceased patients with Karnofsky Index above 90% (34% vs. 18.4%, $P = 0.001$). The patients with lower Karnofsky Index

were also more often diagnosed with tumour UICC stage IV (72.19% vs. 60.98%, $P = 0.024$). In the EQ-5D-5 L questionnaire, the patients assessed their health status with values from 0 to 100%; patients with lower Karnofsky Index assessed themselves significantly lower than patients with higher Karnofsky Index {50% [interquartile range (IQR): 35–60%] vs. 75% [IQR: 60–86.5%], $P < 0.001$ }. In the MNA questionnaire, the patient's risk for malnutrition (malnutrition being a value under 17 points) was examined and patients with lower Karnofsky Index were just above the cut-off for malnutrition (17.44 ± 7.06 , $P < 0.001$). The Karnofsky Index correlated with albumin, CRP, CK-MB, LDH, haemoglobin, 6MWT, 4mGST, HGS, NYHA class (all $P < 0.001$) and with the usage of opioids (25.41% vs. 14.56%, $P = 0.008$).

In a univariate logistic regression model, the variables albumin, log. troponin T, log. NT-proBNP, log. CRP, haemoglobin, EQ-5D-5 L self-assessment, MNA, 6MWT, and mean HGS on the right hand were highly significant (all $P < 0.001$). Further variables were significant independent predictors of a Karnofsky Index under 90% such as age, weight, transferrin saturation, log. LDH, mean heart rate [HR] (all $P < 0.01$), and log. TSH ($P = 0.040$). The univariate cox regression mortality analysis showed that tumour stage UICC IV compared to UICC I-III, Karnofsky Index, ECOG-status, albumin, log. LDH, log. CRP, 6MWT, and smoking status are independent predictors of survival (all $P < 0.001$). Furthermore, weight ($P = 0.004$), delta weight loss in the last 12 months ($P = 0.002$), log. troponin ($P = 0.008$), log. NT-proBNP ($P = 0.001$), haemoglobin ($P = 0.005$), mean HR ($P = 0.001$) are independent predictors of survival. The self-assessment in the EQ-5D-5L questionnaire ($P = 0.110$) and the number of pack years ($P = 0.057$) were not significant.

Conclusions: In our study cohort, a Karnofsky Index lower than 90% and the diagnosis of metastatic tumour (UICC IV) influenced the quality of life and the survival. The self-assessment has an impact on the quality of life; however, it is not a predictor of mortality. Therapeutic intervention on cardiovascular functional parameters may serve as a starting point for improvement of the quality of life and survival.

8-22

Cardiovascular determinants of exercise capacity in patients with cancer

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Background: Patients with advanced cancer often display cardiovascular comorbidities which manifest clinically as fatigue, shortness of breath, and/or reduced exercise capacity. These symptoms even appear independently of ongoing chemotherapy. In this multicenter study, we sought to determine cardiovascular factors in patients with cancer that have an impact on exercise capacity in the 6 min walk test [6MWT].

Methods: We enrolled a total of 255 patients with cancer [age 60 ± 13 years; 57,3% male; body mass index (BMI) 25.4 ± 4.7 kg/m²; cachexia 43.9%; New York Heart Association (NYHA) class \geq II: 39.1%; median Karnofsky Index 90%] at the University of Göttingen Medical Center as well as at the Charité—Universitätsmedizin Berlin, Campus Benjamin Franklin. All participants underwent 6MWT, 12 lead resting electrocardiogram (ECG) and measurements of blood pressure. Quality of life (QoL) was evaluated using the EQ-5D questionnaire. Blood samples were taken to assess not only standard laboratory but also NT-proBNP and troponin T.

Results: Among all patients, median 6MWT was 458 m [interquartile range (IQR) 380–507 m], the mean 441 ± 109 m. The mean heart rate (HR) was at 76.4 ± 11.3 bps. Exercise capacity correlated with age ($r = -0.316$), NYHA class ($r = -0.363$), Karnofsky Index ($r = 0.549$), systolic blood pressure ($r = -0.149$), haemoglobin (Hb) ($r = 0.278$), troponin T ($r = -0.306$), NT-proBNP ($r = -0.346$), and creatine kinase (CK) ($r = 0.150$, all $P < 0.05$). Using multivariable linear regression, we found that the 6MWT distance correlated with age [standardized coefficient (SC) = -0.221 ; $P = 0.001$], BMI (SC = -0.206 ; $P = 0.001$), log troponin T (SC = -0.159 ; $P = 0.022$), log NT-proBNP (SC = -0.194 ; $P = 0.007$), creatinine (SC = 0.129 ; $P = 0.043$), Hb (SC = 0.185 ; $P = 0.005$) but not with heart rate (SC = 0.083 ; $P = 0.181$). In a multivariable logistic regression model, we could show that hypertension [odds ratio (OR) = 3.652 ; $P = 0.001$], Hb (OR = 0.667 ; $P < 0.001$), and creatinine (OR = 0.121 ; $P = 0.008$) are independent predictors of an impaired 6MWT distance below the median. We found a trend for BMI (OR = 1.076 ; $P = 0.062$), log troponin T (OR = 2.998 ; $P = 0.068$), and log NT-proBNP (OR = 2.252 ; $P = 0.076$), whereas age (OR = 1.018 ;

$P = 0.238$), HR (OR = 1.016; $P = 0.310$), and diabetes mellitus (OR = 1.281; $P = 0.667$) did not influence exercise capacity.

Conclusions: Cardiovascular parameters such as troponin T and NT-proBNP are independent predictors of exercise capacity assessed using the 6MWT in patients with advanced cancer. Cardiovascular risk factors such as hypertension have an impact as well. A better understanding of the pathophysiology will help to determine therapy strategies to maintain mobility in patients with cancer.

9-09

Multimodal intervention “PROGEPHY”: implementing a prevention care path into daily life of elderly people with mobility disability risk

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Background: Physical inactivity is highly related to ageing and contributes to muscle wasting. An adverse consequence of a sedentary lifestyle is increasing the risk of mobility disability. Increasing physical activity represents a key therapeutic intervention to prevent the loss of strength and muscle mass for enhancing health related quality of life. Hence, we have set up a primary and secondary prevention program “PROGEPHY” through physical training and nutrition to reduce mobility disability prevalence and incidence. Our primary goal is to integrate a prevention care path into daily life of elders who may present a mobility disability. We aim to improve quality of life and then reduce physical dependence prevalence.

Method: “PROGEPHY” includes 70 years or more elderly people who present a risk of developing a mobility disability. Initially, we identify and screen a risk of mobility disability in wide elders’ communities. We diagnose mobility disability risk factors, sarcopenia, and frailty, in Day Hospital within a triple consultation: dietician, geriatrician, and a physiotherapist. We use The EWGSOP2 algorithm to diagnose sarcopenia. The patient then attends a 3 month training program, including two sessions per week. Sessions combine resistance exercises and balance training during 60 min. After 20 sessions, we analyse the benefits. We support the patient for his own project of long-term maintenance quality of life between physical activity and nutrition.

Results: A total of 304 patients have been included. One hundred forty-seven patients have been seen after 20 sessions. Physical performance was significantly improved after 3 months of intervention (SPPB $P < 0.0001$, gait speed

$P < 0.0001$, and time up and go $P < 0.0001$) likewise grip strength ($P < 0.0002$). The “SarQoL” score was also significantly higher ($P < 0.0001$). Subgroup SPPB ≤ 8 with severe sarcopenia improve significantly more its score ($+1.6 \pm 1.9$ $P < 0.0002$) comparing to the overall population ($+0.6 \pm 1.7$). Moreover, there was a significant difference ($P < 0.0001$) for SPPB at baseline between responders (7.6 ± 2.3) and non-responders (9.8 ± 2.0).

Conclusions: “PROGEPHY” intervention enhances mobility through strength and physical performance benefits. We can make the assumption that adverse events will be occurring less and physical dependence will be appearing later, regarding gait speed improvement. Thus, it seems that patients with low physical performance are responding better than the overall population meaning that our intervention is significantly better for patients with severe sarcopenia. More importantly, our program sustains motivation for physical activity after 3 months. Therefore, “PROGEPHY” triggers changes by promoting health related behaviors through regular physical activity and good diet habits. This type of innovative intervention is at the uppermost for reducing mobility disability prevalence and incidence.

9-10

Safety and efficacy of bimagrumab in community-dwelling older adults with sarcopenia

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Background: Sarcopenia is a major health concern among older adults. We assessed safety and efficacy of bimagrumab on physical function, skeletal muscle mass, and strength in community-dwelling older adults with sarcopenia.

Methods: This was a 28 week, randomized, double-blind, placebo-controlled, parallel-arm, multicentre, Phase 2 study in patients receiving optimized standard-of-care (SOC) with diet (protein, calories, and vitamin D) and exercise. Participants aged ≥ 70 years with short physical performance battery (SPPB) scores ≤ 9.0 , gait speed over 4 m of ≥ 0.3 to < 0.8 m/s, and appendicular skeletal muscle index (ASMI) ≤ 7.26 kg/m² (men) or ≤ 5.5 kg/m² (women) were included. Participants ($N = 180$) received bimagrumab 700 mg or

placebo monthly for 24 weeks. Key end points were change from baseline to Week 25 in SPPB score (primary), gait speed, 6 min walk distance (6MWD), total lean body mass (LBM), and handgrip strength.

Results: A total of 159/180 (88.3%) participants [mean age: 79.1 years, Caucasian [81.7%], women (60.6%)] completed the study. Bimagrumab was safe and well-tolerated. At Week 25, increases in SPPB score were 1.82 (1.29–2.36, mean, 95% CI) with bimagrumab versus 1.46 (0.87–2.04) placebo ($P = 0.102$). Gait speed improved 0.14 m/s (0.09–0.18) versus 0.11 m/s (0.05–0.16) ($P = 0.161$), and 6MWD by 24.60 m (7.65–41.56) versus 14.30 m (–4.64 to 33.23) in placebo ($P = 0.163$). Bimagrumab increased LBM by 6.0% over placebo ($P < 0.001$). Handgrip strength did not change.

Conclusions: Bimagrumab treatment over 24 weeks was safe, well-tolerated, and increased LBM in older adults with sarcopenia. Optimised SOC improved LBM and physical performance; bimagrumab did not significantly add to this. At end of study, the majority of participants in both groups no longer met sarcopenia criteria.

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Author disclosures: Daniel Rooks, Therese Swan, Lee Anne Filosa, Ola Bunte, Nicolas Panchaud, Laura Coleman, Ram Miller, Jens Praestgaard, Didier Laurent, Olivier Petricoul, and Ronenn Roubenoff are employees of Novartis and as such may be eligible for Novartis stock and stock options. Budhaditya Goswami was employed with Novartis at the time of study conduct. His present affiliation is MorphoSys AG, Planegg, Germany. Robert Perry, Chris Recknor, Charles Fogarty, Hidenori Arai, Liang-Kung Chen, and Yoon-Sok Chung report no conflict.

9-11

Effect of leucine supplementation on the reversal of muscle mass loss in cancer patients and the elderly subjects

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Background: The purpose of the study was to verify the effect of leucine (LEU) supplementation, an essential amino acid, in the gain of muscle mass and/or in the reversal of muscle loss in patients with cancer or in elderly subjects.

Methods: Patients with cancer (C) ($n = 15$) and elderly volunteers (nongroup—NC) ($n = 13$) were enrolled in a double-blind, randomized, placebo-controlled study and were divided into two subgroups: LEU or placebo (PLA), 6 g/day for 28 days. The supplementation effects were analysed and compared (intragroup and intergroup). The skeletal muscle mass index (SMI) was evaluated by dual-energy X-ray absorptiometry (DEXA); functional evaluations were performed using gait speed (GS) and handgrip strength (HG). The classification of muscle loss and cut-off points followed the EWGSOP2 protocol. Statistical analysis included a three-way ANOVA with Tukey or Bonferroni correction to compare the groups, the effects of supplementation versus placebo and presupplementation and postsupplementation; two-way ANOVA or Mann–Whitney were used to compare the variations between presupplementation and postsupplementation. The significance level adopted was $P < 0.05$.

Results: The SMI variation between preintervention and postintervention was greater in NC group than C group when supplemented with LEU ($P = 0.046$). Handgrip strength was higher in the C group when compared to NC group, regardless of the supplementation type or preintervention and post-intervention ($P = 0.004$).

Conclusions: The supplementation protocol failed to elicit major differences in the groups studied.

9-13

Prognosis pancreatic cancer patients with cachexia on nutritional protein-rich supplementation

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Background: Pancreatic cancer has the highest mortality rate among all major malignancies. The advent of novel chemotherapeutic agents, combined with radiotherapy and advancing surgical techniques, has improved the prognosis and longevity of pancreatic cancer patients. Prognostic implications of nutritional status and immunity have been elucidated in many diseases in recent years, but evidence is lacking in pancreatic cancer. Additional prognostic variables must be explored to optimize patient outcomes. The objective of this study is to examine the relationship between the prognostic impact of nutritional supplementation with protein-rich and cachexia among pancreatic cancer patients.

Method: A total of 106 pancreatic cancer patients admitted between January 2009 to March 2019 were included. Treatment: 43 surgeries, 48 radiation, 92 chemotherapy, and 8 palliative care. Twenty-nine patients showed cachexia at the time of admission. Patients were categorized according to

their nutritional status using nonprotein calorie/nitrogen (NPC/N) model. Adequate nutrition was defined as NPC/N \leq 150 lasting longer than 71% of admission period. Fifty-six patients met these criteria.

Results: Seventy-seven patients were displayed no cachexia on admission. These patients showed longer survival than those who presented with cachexia. Average survival was 634 days compared with 295 days by log-rank test ($P = 0.002$). Univariate and multivariate COX regression analyses evaluated nine factors associated with performance status by ECOG, L3 skeletal muscle index (SMI), clinical stages, therapies etc. The hazard ratios among patients those who presented with cachexia was Exp(B) 2.15. With nutritional protein-rich supplementation, 50% survival rate among noncachexic patients extended from 328 to 877 days while the rate improved from 233 to 436 days among cachexic patients (Log rank (Mantel-Cox) $\chi^2 = 20.423$, $P < 0.001$). The hazard ratios among patients who received nutritional protein-rich intervention was Exp(B) 0.968. This result indicated that the survival rate was 1.033 times higher for the intervention group.

Conclusions: The presence of cachexia at the time of cancer diagnosis is prognostically more important than the degree of improvement seen in the clinical status after protein-rich nutritional interventions are started. Administering protein-rich nutritional supplementation significantly improves the prognosis among pancreatic cancer patients.

9-14

Oral magnesium supplementation and low-magnitude, high-frequency vibration treatment attenuate age-related muscular changes in sarcopenia

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Background: Sarcopenia is an age-related geriatric syndrome which is associated with subsequent disability and morbidity. Low-magnitude high-frequency vibration (LMHFV) is non-invasive biophysical modality providing mechanical cyclic loading to whole body. Magnesium (Mg) is associated with better indices of skeletal muscle mass, strength, and power in elder adults. The study aims to investigate treatment effects of LMHFV, Mg, and their combination on sarcopenia skeletal muscles and explore related mechanisms *in vivo*.

Methods: Sarcopenia senescence-accelerated mouse P8 (SAMP8) mice at Month 6 were randomized into control (Ctrl), vibration treatment (VT), Mg only, or Mg + VT groups. The mice in the VT group were given LMHFV treatment at 0.3 g, 35 Hz, 20 min/day, and 5 days/week. Mg was

administered to animals through oral gavage of 0.2 mL Mg solution in water at the dosage of 200 mg/kg/day, 5 days/week. Both LMHFV and Mg supplement were given in the Mg + VT group. *Ex vivo* functional assessment, staining of myofibers, and DXA were performed at Months 1, 2, 3, 4 post-treatment for all groups. Data analysis was done with one-way ANOVA, and the significant level was set at $P \leq 0.05$.

Results: At late stage on Month 4 post-treatment, partial lean mass in Mg, VT, and Mg + VT groups were higher than control group. Mg and VT groups showed more type IIa and IIb muscle fibers than the control group at Month 10. The mice in the combination group showed significantly higher muscle strength (twitch force, $P = 0.0436$, specific twitch force, $P = 0.01$). Generally, contractibility was significantly improved by Mg and combination groups (tetanic force, $P = 0.0138$, $P = 0.04$, respectively).

Conclusions: In this study, the results suggest that Mg and LMHFV individually, or in combination could increase muscle strength and function *in vivo*; results also support clinical translation of Mg and LMHFV to suppress skeletal muscle deterioration in sarcopenia.

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9-15

Peripheral endothelial dysfunction in chronic fatigue syndrome (CFS)

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Background: Chronic fatigue syndrome (CFS) is a complex multisystem disease. Evidence for disturbed vascular regulation comes from various studies showing cerebral hypoperfusion and orthostatic intolerance. The peripheral endothelial dysfunction (ED) has not been sufficiently investigated in patients with CFS. The aim of the present study was to examine peripheral endothelial function in patients with CFS.

Methods: Thirty-five patients [median age 40 (range 18–70) years, mean body mass index (BMI) 23.8 ± 4.2 kg/m², 31% male] with CFS were studied for peripheral endothelial function assessed by peripheral arterial tonometry (EndoPAT2000). Clinical diagnosis of CFS was based on Canadian Criteria. Nine of these patients with elevated antibodies against β_2 -adrenergic receptor underwent immunoabsorption and endothelial function was measured at baseline and 3, 6, and 12 months follow-up. ED was

defined by reactive hyperemia index (RHI) ≤ 1.81 . Twenty healthy subjects of similar age, and BMI were used as a control group.

Results: Peripheral ED was found in 18 of 35 patients (51%) with CFS and in four healthy subjects (20%, $P < 0.05$). Patients with ED, in contrast to patients with normal endothelial function, reported more severe disease according to Bell score (31 ± 12 vs. 40 ± 16 , $P = 0.04$), as well as more severe fatigue related symptoms (8.62 ± 0.87 vs. 7.75 ± 1.40 , $P = 0.04$) including a higher demand for breaks [9.0 (IQR 7.0–10.0) vs. 7.5 (IQR 6.0–9.25), $P = 0.04$]. Peripheral ED showed correlations with more severe immune-associated symptoms ($r = -0.41$, $P = 0.026$), such as sore throat ($r = -0.38$, $P = 0.038$) and painful lymph nodes ($r = -0.37$, $P = 0.042$), as well as more severe disease according to Bell score ($r = 0.41$, $P = 0.008$) and Symptom score ($r = -0.59$, $P = 0.005$). There were no differences between the patient group with ED compared to the patient group with normal endothelial function regarding demographic, metabolic, and laboratory parameters. Further, there was no difference in sVCAM and sICAM levels.

At baseline, peripheral ED was observed in six patients who underwent immunoabsorption. After 12 months, endothelial function had improved in five of these six patients (RHI 1.58 ± 0.15 vs. 2.02 ± 0.46 , $P = 0.06$).

Conclusions: Peripheral ED is frequent in patients with CFS and associated with disease severity and severity of immune symptoms. As ED is a risk factor for cardiovascular disease, it is important to elucidate if peripheral ED is associated with increased cardiovascular morbidity and mortality in CFS.

9-16

Iodide reduces cachexia in a BALB/c CT26 mouse tumor model

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Background: Faraday Pharmaceuticals is focused on the research and development of elemental reducing agents (ERAs) and their potential applications for the treatment of critical care diseases with a focus on cardiac and skeletal muscle disease. In this study, we investigated the utility of FDY-5301 (sodium iodide) or Bucindolol (as a positive control) in reducing cachexia in a CT26 mouse tumour model.

Methods: Male Balb/c mice were injected subcutaneously with a CT26 tumor cell line. Once the tumour volume reached $\sim 125 \text{ mm}^3$, the animals were randomized into four treatment groups: vehicle control, 2 mg/kg/day FDY-5301 i.v., 2 mg/kg/day Bucindolol p.o., and 40 $\mu\text{g}/\text{day}$ FDY-5301 delivered continuously by subcutaneous osmotic pump. Clinical signs, body weight, and food consumption were monitored daily, and

tumour volume was monitored every 3 days. A subset of animals was sacrificed on Day 14 for plasma iodide analysis. At the end of the experimental period (Day 20), the remaining animals were sacrificed, and blood was collected for biochemical analysis of glucose, total protein, a lipid panel, and cytokine analysis. Various tissues and organs were weighed including tumour, liver, heart, lung, spleen, kidney, and epididymal fat. The muscles: gastrocnemius, tibialis anterior, and soleus were weighed and then fixed, H&E stained, and analysed morphometrically.

Results: Administration of FDY-5301 and Bucindolol significantly increased overall body weight, liver, heart, and tibialis anterior muscle weight compared to vehicle treatment, and significantly inhibited tumour growth. The group receiving continuous delivery of FDY-5301 showed a significant increase in tibialis anterior muscle fiber area compared to vehicle control. FDY-5301 (i.v.) and Bucindolol helped preserve epididymal fat weight, while FDY-5301 (continuous delivery) and Bucindolol stemmed the rise in triglycerides and VLDL.

Conclusions: Administration of FDY-5301 and Bucindolol helped retain the body weight of animals, prevented organ and skeletal muscle cachexia, and reduced tumour growth.

9-17

BST204 Upregulates myotube regeneration and mitochondrial function in TNF- α -induced atrophic C2C12 myotubes

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Cancer cachexia is a multifactorial syndrome with involuntary chronic muscle atrophy and weight loss, chemotherapy may be its major aetiologic factor. Recent reports showed that almost 20% of cancer patients are suffering from cancer cachexia. The *Panax ginseng* dry purified extract, BST204 reduced the loss in gastrocnemius muscle and tibialis anterior in the cancer cachectic animal models after daily oral administration for 2 weeks. And Phase IIa is in progress for cancer cachexia patient in Europe. In this study, we investigated the myogenic effect and underlying molecular mechanisms of BST204 on TNF- α -induced myotube atrophy. BST204 induces myotube hypertrophy and promotes myotube diameter through activation of Akt/mTOR signalling. BST204 recovers myotube formation and increases myotube diameters in TNF- α -treated myotubes. BST204 suppresses the expression of Atrogin-1 and MuRF1 in TNF- α -treated myotubes. In addition, BST204 in TNF- α -treated myotubes significantly inhibits the mitochondrial ROS production and promotes mitochondrial membrane potential (MMP) and ATP contents.

Furthermore, BST204 upregulates the activities and expression of PGC1- α and the mitochondrial biogenetic transcription factors in TNF- α -induced myotube atrophy. This study provides a mechanistic insight into the effect of BST204 on

mitochondrial biogenesis and myotube atrophy, suggesting that BST204 has a promising potential as a therapeutic medicine for the management of cancer cachexia patient with severe weight loss and muscle atrophy.