Computed tomography compared with standard clinical measurements to assess body composition, facilitating the identification of sarcopenia and cachexia in colorectal malignancy

DOI:
10.1002/jcsm.12087

Journal of Cachexia, Sarcopenia and Muscle 2015; **6**: 398–509
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12087

Abstracts of the 8th International Conference on Cachexia, Sarcopenia and Muscle Wasting, Paris, France, 4-6 December 2015

1-01

NMR imaging characterization of age-related changes in the human quadriceps

Pierre G. Carlier[1], Jean-Yves Hogrel[2], Noura Azzabou[1]
[1]NMR Laboratory, Institute of Myology, CHU Pitie-Salpetriere, Paris, France, [2]Functional evaluation, Institute of Myology, CHU Pitie-Salpetriere, Paris, France

Background: Age-related sarcopenia is a major health issue. To improve elderly person quality of life. It is important to characterize age-associated structural changes within the skeletal muscle. NMR imaging offers quantitative tools to monitor these changes.
Methods: We scanned 93 subjects. 33 young adults aged between 19 and 27 years old and 60 older adults between 69 and 80 years old. Their physical activity was assessed using a tri-axial accelerometer and they were classified either as active or sedentary. A standard multi-slice multi-echo (MSME) sequence was run and water T2 maps were extracted using a tri-exponential fit. Fat fraction was quantified using three-point Dixon technique. Each quadriceps muscle was characterized by: water T2 mean value. Water T2 heterogeneity and the mean fat fraction.
Results: Statistical analysis (ANOVA) showed that water T2 mean values and its heterogeneity indices as well as fat fraction were significantly higher in the elderly group ($p<0.05$). Only fat fraction was significantly lower in the active group compared to the sedentary one ($p<0.05$). Linear regression confirmed the significant impact of age on these NMR parameter whereas physical activity impact was not systematic.
Conclusion:NMR imaging provided a comprehensive assessment of the aging process impact on skeletal muscle composition. Water T2 increase might be related to changes in fiber typology while increased T2 heterogeneities might correlate with some degree of tissue disorganization, like the development of interstitial fibrosis. Fat fraction and water T2 heterogeneity increase was partly slowed down by physical activity. These changes were not gender dependent.

1-02

Prognostic role of skeletal muscle mass and fat distribution on clinical outcomes in post-menopausal women with operable stage breast cancer

Shalini Dalal[1], David Hui[1], Rony Dev[1], Sai-Ching Yeung[2], Nikhil Sobti[1], Maxine De La Cruz[1], Marieberta Vidal[1], Eduardo Bruera[1], Jennifer Litton[3]
[1]Palliative Care Dept, UT MD Anderson Cancer Center, Houston, TX USA, [2]Emergency Medicine Dept, UT MD Anderson Cancer Center, Houston, TX USA, [3]Medical Oncology Dept, UT MD Anderson Cancer Center, Houston, TX USA

Background: High BMI, visceral adiposity and low skeletal muscle (SM) are adverse prognostic factors in several cancers. This study examined associations between BMI, visceral fat (VF), SM and outcomes (pathologic complete-response [pCR], relapse-free [RFS], disease-specific [DSS] and overall survival [OS]) in women with operable (stages I-III) postmenopausal breast cancer (PBC) who received neoadjuvant chemotherapy (NC)
Methods: Records of 1227 women were reviewed. CT images quantified SM and VF, which were normalized for height (reported as indices [I; cm^2/m^2]). Patients were grouped in BMI categories and tertiles for SMI/VFI. Multivariable models adjusted for known prognostic variables.
Results: pCR was achieved in 249 patients and 187 had relapsed disease. Of 187 deaths, 75% were attributed to PBC. In multivariate analyses (Table 1) higher SMI tertiles were independent predictors for pCR achievement, while higher VFI tertiles, and normal-BMI versus obese category were associated with lower pCR rates. Lower VFI (T2 versus T3) was an independent predictor of higher RFS (hazard ratio 0.63, 95% CI 0.43-0.93). Lower VFI tertiles also predicted for higher DSS and OS, but did not remain statistically significant with inclusion of pCR in model.
Conclusion: Low skeletal muscle mass and visceral obesity are independent risk factors for predicting response to NC, while visceral obesity may be a factor for survival. More research into maintaining or increasing muscle mass and lowering visceral fat to improve prognosis in PBC is warranted.

1-03

The potential of bioelectrical impedance vector analysis for the assessment of muscle wasting

Nicole Ebner[1], Lorena Lerner[2], Jeno Gyuris[2], Amir Emami[1], Anja Sandek[1], Jochen Springer[1], Stefan D Anker[1], Wolfram Doehner[3], Stephan von Haehling[1]
[1]University Medical Center Göttingen, Department of Cardiology and Pneumology, Innovative Clinical Trials, Göttingen, Germany, [2]AVEO Pharmaceuticals, Inc., Cambridge, Massachusetts [3]Centre for Stroke Research Berlin, Charité - University Medical School, Berlin, Germany

Purpose: The aim of this study is to investigate whether bioelectrical impedance vector analysis (BIVA) can be a suitable technique for the

Table 1 Multivariate logistic regression analysis for pCR achievement

Variables	OR	95% CI	*P*
BMI Category			
Normal vs. Obese	0.449	0.262-0.768	0.003
Overweight vs. Obese	0.681	0.451-1.028	0.068
VFI Tertiles			
T2 vs T1	0.432	0.281-0.663	0.000
T3 vs. T1	0.281	0.166-0.476	0.000
SMI Tertiles			
T2 vs. T1	1.910	1.269-2.874	0.002
T3 vs. T1	1.749	1.121-2.727	0.014

Included age, race, Stage, nuclear-grade, lymphovascular-invasion, hormone receptor status and type of NC

assessment of muscle wasting. We also analyzed different potential biomarkers and exercise capacity.

Subjects and methods: We included in our study 88 patients with stable chronic heart failure (HF) and 45 healthy elderly individuals of both sexes, with a mean age of 63 years. Dual energy X-ray absorptiometry (DEXA) was used as the reference method for identifying sarcopenic or muscle wasting individuals. The BIVA procedures, which respectively correct bioelectrical values for body height and body geometry, were used. Additionally we analyzed growth differentiating factor 15 [GDF-15], Activin A, and Interleukin-1. Exercise capacity was measured with spiroergometry [peak VO_2] and six minute walk test [6MWT]. The quality of life was analyzed by using the Kansas City Cardiomyopathy Questionnaire [KCCQ]. Muscle wasting was defined as the appendicular muscle mass 2 standard deviation below the mean of a healthy reference group of adults aged 18–40 years, as suggested for the diagnosis of muscle wasting in healthy ageing.

Results: Patients with HF showed significantly higher GDF-15 (mean patients 1.78 ± 1.4 vs. mean controls: 0.89 ± 0.85 p = 0.0002) and lower Activin A levels (mean patients: 0.34 ± 0.19 vs. mean controls: 0.42 ± 0.18 p = 0.014). Surprisingly patients with HF showed lower Interleukin 1- alpha [IL-1α] levels compare controls (mean IL1-α patients:10.34 ± 6.00 vs mean IL-1α controls:14.11 ± 10.24, p = 0.02) and lower Interleukin 1-beta [IL-1β] levels than controls (mean IL-1β patients:640.61 ± 447.99 vs mean IL-1β controls:859.89 ± 619.40, p=0.04). Exercise capacity was significantly reduced in patients (mean peak VO_2:18.31 ± 4.04 kg/mL*min; mean 6MWT:431.88 ± 122.11) compare to controls (mean peak VO_2:29.01 ± 7.96; 6MWT:599.57 ± 109.89, both p<0.0001). Patients with HF showed reduced quality of life (KCCQ symptom score: 54.2 ± 27.1, KCCQ symptom stability: 54.2 ± 27.0, KCCQ quality of life score: 61.6 ± 26.2, KCCQ overall summary score: 54.4 ± 12.6). Quality of life scores are correlated with reduced exercise capacity. A total of 13 patients with HF were defined as with muscle wasting and 4 controls as with muscle wasting in healthy aging. Patients with muscle wasting showed significantly higher values of resistance/height (R/H; p < 0.01) and reactance/height (X/H; p < 0.01), and a lower phase angle (p < 0.01). Moreover we show a significant correlation between appendicular mass and resistance/height (r = +0.151; p<0.0001) and reactance/height (r = + 0.047; p = 0.04). GDF-15, Activin A and IL-1 were not correlated with muscle wasting.

Conclusion: BIVA detected muscle-mass variations in patients with muscle wasting. These procedures are promising tools for screening for muscle wasting in routine practice. Patients with HF showed reduced exercise capacity and reduced quality of life and both are correlated with each other. Moreover we have shown that patients with HF showed higher GDF-15 and lower Activin A and Interleukin-1 levels.

1-04

Exercise to improve function of the rheumatoid hand: The SARAH randomised controlled trial

Sarah E. Lamb[1], Esther M. Williamson[1], Peter J. Heine[2], Jo Adams[3], Sukhdeep Dosanjh[2], Melina Dritsaki[2], Matthew J. Glover[4], Joanne Lord[4], Christopher McConkey[2], Christopher Byrne[1], Vivien Nichols[2], Anisur Rahman[5], Martin Underwood[2], Mark A. Williams[1], on behalf of the Strengthening and Stretching for Rheumatoid Arthritis of the Hand Trial (SARAH) Trial Team

[1]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK, [2]Warwick Clinical Trials Unit, University of Warwick, Coventry, UK, [3]Faculty of Health Sciences, University of Southampton, Southampton, UK, [4]Health Economics Research Group, Brunel University, Uxbridge, UK, [5]University College London, London, UK

Background and aims: In rheumatoid arthritis of the hand (RAH) evidence is lacking whether tailored hand exercise provides additional improvements to drug regimens. We estimated the effectiveness and cost-effectiveness of tailored hand exercise in addition to usual care during 12 months.

Methods: In this pragmatic, multicentre, parallel-group trial, at 17 National Health Service sites across the UK we randomly assigned 490 adults with RAH on a stable drug regimen for at least 3 months, and with pain and dysfunction of the hands, to either usual care or usual care plus a tailored strengthening and stretching hand exercise programme. Participants were randomly assigned with stratification by centre. Participants and therapists delivering treatment were un-blinded after randomisation, whereas all outcome assessors and investigators were blinded to allocation. The primary outcome was the Michigan Hand Outcomes Questionnaire overall hand function score at 12 months. We calculated cost per quality-adjusted life-year.

Results: Between Oct 5, 2009, and May 10, 2011, we screened 1606 people, of whom 490 were randomly assigned to usual care (n = 244) or tailored exercises (n = 246). At 12 month follow-up, 438 of 490 participants (89%) provided data. Overall hand function improved 3°6 points (95% CI 1°5–5°7) in the usual care group and 7°9 points (6°0–9°9) in the exercise group (mean difference between groups 4·3, 95% CI 1·5–7·1; p=0·0028). Pain, drug regimens, and healthcare resource use were stable for 12 months, with no difference between groups. No serious adverse events associated with treatment were recorded. The cost of tailored hand exercise was £156 per person with cost per quality-adjusted life-year being £9549.

Conclusions: Tailored hand exercise is an effective, low-cost intervention as an adjunct to various drug regimens. Additionally, grip strength appeared a key mediator underlying the importance, and potential reversibility of cachexia, in rheumatoid arthritis of the hand.

1-05

Functionality and functional capacity in a community-dwelling older adults in Portugal

Maria Teresa Tomás[1], Beatriz Fernandes[1], Diogo Quirino[2]
[1]Lisbon Higher School of Health Technology, Portugal, [2]Santa Maria House, AAPHSM, Loures, Portugal

Background and aims: Portuguese population has a higher risk of functional decline and frailty. This trend, along with a growing aging index, poses a major economic and social challenge to health in ageing people. The purpose of our study was to characterize functional physical fitness in community-dwelling older adults in order to prevent functional decline and an increase in health care costs.
Methods: Our sample consisted of 128 older adults (95 women, 33 men), aged 65-97 years, independent and living in Loures municipality, Portugal. Functional physical fitness was assessed with *Senior Fitness Test Battery. P*redicted distance was calculated with Troosters et al (1999) equation. Grip strength was assessed with hydraulic dynamometer Jamar® and functional capacity with the Composite Physical Function (CPF) Scale. A basic descriptive analysis was conducted (statistical package SPSS IBM for Windows, v22) and the sample was stratified by age.
Results: Senior Fitness Test Battery and grip strength scores suggested low levels of strength, flexibility, endurance and balance, compared with other similar populations, suggesting a higher risk for sarcopenia. Distance walked by our sample remained at 73% of the estimated distance. When stratified by age, percentage of estimated distance shows a greater decrease. On CPF, 80% of our sample presented moderate or low levels of functional capacity.
Conclusions: Functional fitness of this population appears to have lower values than expected. Distance walked shows a decrement higher than expected with a probable faster ageing than the expected. Our study provides a first assessment of grip strength in an elder Portuguese population showing also lower values for this component of functionality. Compared to other populations, functional capacity (CPF) is at moderate or low level. These results are important to justify an urgent intervention in order to increase functional capacity or at least contribute to a slower decrease.

1-06

Comparison of body composition between nursing home residents and community-dwelling older adults

Tung W. Auyeung[1], Jenny S. W. Lee[2], Jean Woo[2]
[1]Department of Medicine and Geriatrics, Pok Oi Hospital, Yuen Long, Hong Kong, China, [2] The Chinese University of Hong Kong, China

Background: Being underweight is a common observation in nursing home residents. It is uncertain which component of body composition is being affected most in nursing home resident. Muscle mass has been studied extensively while body fat and body water, has been less examined.
Objectives: To study the difference in body composition between nursing home residents and community-dwelling older adults
Participants and Settings: One hundred and eighty three participants were recruited from a Geriatric Day Rehabilitation Centre, among them, 55 were nursing home residents and 128 were community-dwelling. Ninety were men and 93 were women. The mean age of the participants were 80.7 years. Ninety were men and 93 were women.
Methods: Each participant was subjected to body composition analysis by segmental bio-impedance assay method. Their cognitive function was measured by mini-mental status examination and their activities of daily living by modified Barthel Index. We also measured their hand grip strength and gait speed.
Results: The nursing home group and the community-dwelling group differed in water, fat and muscle content. However, after age adjustment, we could still observe a difference in the body water and muscle compartment in men only. In nursing home residents of both genders, fat mass was maintained comparing to the community-dwelling counter-part. Men living in nursing home were demonstrated to have higher ECW despite having less TBW, ICW and ECW prior to muscle mass adjustment. We further examined the independent effect of nursing home on muscle mass by adjustment for Barthel Index. We observed that nursing home by itself was an independent risk factor of lower muscle mass in men only.
Conclusion: Older men living in nursing home were more susceptible to muscle loss despite having a relatively stable fat mass. In women living in nursing home, their body composition was similar to the community-dwelling older women.

1-07

Body composition, nutrient profile and response to pulmonary rehabilitation in patients with advanced COPD

Nanca Cebron Lipovec[1, 2], Annemie Schols[1], Daniel Omersa[3], Ardy van Helvoort[1,4], Mitja Lainscak[5,6]
[1]NUTRIM School of Nutrition and Translational Research in Metabolism, Department of Respiratory Medicine, Maastricht University Medical Centre+, Maastricht, The Netherlands, [2]University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia, [3]National Institute of Public Health, Ljubljana, Slovenia, [4]Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, The Netherlands, [5]Department of Cardiology, General Hospital Celje, Celje, Slovenia, [6]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Background: Body composition abnormalities are frequent in advanced chronic obstructive pulmonary disease (COPD) and may need to be considered when tailoring pulmonary rehabilitation. We therefore investigated baseline exercise capacity, nutrient profile and the response to pulmonary rehabilitation in relation to sarcopenia and (abdominal) obesity in a cohort of advanced COPD.
Methods: Patients were included in a 4-week high intensity supervised in-patient pulmonary rehabilitation program. Sarcopenia was defined by appendicular lean mass index using DEXA. Amino acids profile and vitamin D levels were assessed at baseline. Exercise

performance (6-minute walk test-6MWT, incremental shuttle test-ISWT, incremental cycle ergometry - CPET) and quality of life (QoL) were evaluated at baseline and after rehabilitation.
Results: We included 104 stable COPD patients (66 ± 8 years, 85% GOLD III/IV, 65% men). Sarcopenia, sarcopenic obesity and obesity were present in 38%, 15% and 23% of patients, respectively. Patients with sarcopenia had significantly lower exercise capacity (6MWT 310m, ISWT 227m, max CPET 52 Ws) compared to obese (6MWT 325m, ISWT 247m, max CPET 67 Ws) and normal body composition patients (6MWT 388m, ISWT 319m, max CPET 66 Ws; $p<.0.05$ for all). They also showed the lowest program response based on the proportion of patients reaching minimal clinical important difference of exercise tests (40% to 78%, $p<0.05$) and lowest completion rate (89%). Obese patients all completed the program and improved the most in exercise capacity, especially in CPET ($p<0.05$). The majority of patients were vitamin D deficient (<25nmol/l: 68%) or insufficient (25-50 nmol/l: 23%), irrespective of body composition profile. Furthermore, the sarcopenic patients had significantly lower levels of branched chain amino acids and more frequent exacerbations.
Conclusion: Sarcopenia and nutritional abnormalities are frequent in advanced COPD. Sarcopenia impairs the response to exercise training, which may be modulated by nutritional intervention.

1-08

Spatio-temporal gait characteristics select clinically stable older persons living at home

Anne-Marie De Cock, Maurits Vandewoude
Department of Geriatrics, University of Antwerp, Antwerp, Belgium

Background and aims: Screening for functional decline in geriatric patients can help in medical decision-making. Analysis of gait characteristics can evaluate changes in performance and strength, suggesting a frail or pre-frail state. This study aims to describe the spatio-temporal gait characteristics (STG) of clinically stable older persons living at home The value of a specific cut-off of a gait norm is tested in the identification of unstable people.
Methods: Patients consulting the geriatric day-clinic are asked to volunteer together with their relatives, age 70 to 89 years. A Gaitrite electronic walkway analysis is performed at usual pace. Speed is normalized according leg length (meter per second, m/s). Step length is converted in steps-per-meter (step/m) dividing cadence by speed. The participants are categorized according norms, defined by a published reference group from a longitudinal follow-up with unchanged function and clinical status over one year time matched for age and gender, as clinically stable (CS) or unstable (CU). Demographic parameters, ADL and IADL score, body composition by Bio Impedance Analysis and cognitive status is measured to describe the clinical details in both groups.
Results: 171 participants are included. Sixty-four persons, 22 males (M) and 42 females (F), are selected as CS. The two groups differ in skeletal muscle mass (M p=0.002, F p=<0.001), ADL (M p=0.002, F p=<0.001), IADL (M en F p= < 0.001) and cognition (M p=0.028, F p=0.01). STG's (cadence, base of support, cycle-time-variability, swing-time-variability, steps-per-meter) characterise CS and CU participants. Also at steps-per-meter at normalized speed and normalized speed distinction maintains (p= between <0.001 and 0.06). Cut-off values of 1 step/m and 1 m/s are highly sensitive (both 97.7%) and highly specific (M= 67% and 91.9%, F = 80.8% and 84.1%).
Conclusion: Spatio-temporal gait characteristics differentiate best CS and CU older people with a cut-off value of 1 step/m and 1 m/s.

1-09

Serum neopterin production and tryptophan breakdown rates correlate with decline of grip strength and physical activity in the elderly

Dietmar Fuchs[1], Johanna M Gostner[1], Maria Sánchez-Flores[2], José Carlos Millán-Calenti[3], Diego Marcos-Pérez[2], Ana Maseda[3], Eduardo Pásaro[2], Barbara Strasser[1], Laura Lorenzo-López[3], Blanca Laffon[2], Vanessa Valdiglesias[2]
[1]Biocenter, Medical University Innsbruck, [2]DICOMOSA Group, Department of Psychology, Area of Psychobiology, Universidade da Coruña, Spain, and [3]Gerontology Research Group, Department of Medicine, Universidade da Coruña, Spain

Background and aims: Changes in muscle metabolism play a major role leading to progressive loss of muscle function and frailty especially in older aged persons. Additional ailments like depression and cognitive impairment, and/or unintentional weight loss parallel sarcopenia development. Some of these symptoms could relate to specific inflammation cascades which are detectable by increased neopterin production and tryptophan breakdown rates.
Methods: In 239 individuals (35 non-frail, 118 pre-frail and 86 frail) aged >63 (mean±SD: 79.4±8.86) years, grip strength (the mean of 3 grip strengths on the dominant hand was measured with a Jamar®hydraulic dynamometer, in Kg adjusted for gender and body mass index (BMI, Kg/m^2), and physical activity (registered based on the short version of the Minnesota Leisure Time Activity questionnaire) were monitored. Results were compared to measurements of serum neopterin concentrations by ELISA (BRAHMS, Germany) and of tryptophan metabolism by HPLC. The kynurenine to tryptophan (ratio) Kyn/Trp was calculated and applied as an index of tryptophan breakdown.
Results: Older age and frailty status were associated with higher neopterin concentrations and higher tryptophan breakdown rates (lower tryptophan and higher Kyn/Trp levels). The correlations remained significant after age-adjustment and there was no influence of gender (all p <0.001). Moreover, higher neopterin and Kyn/Trp as well as lower tryptophan levels correlated significantly with lower grip strength and lower physical activity scores (both p <0.001).
Conclusions: Low grip strength and low physical activity scores are related to disturbed metabolism of tryptophan and neopterin. Both these metabolic abnormalities are associated with immune system activation. The diminished tryptophan availability could relate to disturbed muscle metabolism, and the altered metabolism of essential amino acid tryptophan could be particularly important for the development of specific symptoms like depression and cognitive deficits in the elderly. Such individuals could probably benefit from supplementations with 5-hydroxytryptophan.

1-10

Association between grip strength and risk of falling in older adults: Results from the KORA-age study

Barbara Strasser[1], Marjan Arvandi[2], Raffaella Matteucci Gothe[2], Uwe Siebert[2], Konstantinos Volaklis[3], Karl-Heinz Ladwig[4], Eva Grill[5], Alexander Horsch[6], Michael Laxy[7], Annette Peters[4], Barbara Thorand[4*], Christa Meisinger[4*]

[*]contributed equally

[1]Division of Medical Biochemistry, Biocenter, Medical University Innsbruck, Austria, [2]Department of Public Health and Health Technology Assessment, UMIT, Hall in Tirol, Austria, [3]Department of Prevention and Sports Medicine, TUM, Munich, Germany, [4]Institute of Epidemiology II, German Research Center for Environmental Health, Neuherberg, Germany, [5]Institute for Medical Information Processing, Biometrics and Epidemiology (IBE), and German Center for Vertigo and Balance Disorders, Ludwig-Maximilians-University Munich, Munich, Germany, [6]Institute of Medical Statistics and Epidemiology, TUM, Munich, Germany, [7]Institute of Health Economics and Health Care Management, German Research Center for Environmental Health, Neuherberg, Germany

Background: Impaired muscular strength is strongly related to activity limitations and physical disability in middle-aged and aged individuals. However, studies evaluating the relation between muscular strength and risk of falling in old adults are scarce. Thus, the objective of this study was to examine this association in a population-based study.
Methods: Data originate from the KORA (Cooperative Health Research in the Region of Augsburg)-Age study. A total of 1079 persons were enrolled in the baseline examination in 2009. After exclusion of participants with missing information 1043 individuals (524 men / 519 women) aged 76 (mean) ± 11 (standard deviation) years were included in the present analysis. Handgrip strength was measured (in kilogram) using the JAMAR Dynamometer and the best result of three trials was chosen for analyses. Logistic regression analysis was used to determine adjusted odds ratios with 95% confidence intervals (95%CI) for the risk of falls within the last 12 months as the outcome and handgrip strength as the main exposure. Plausible confounders and mediators were pre-selected based on literature and expert opinion. Further variable selection was based on statistical significance and change-in-estimate criteria.
Results: The risk of falling within the last 12 months reduced by 4% (OR, CI: 0.96, 0.94-0.98) per one kilogram increase in maximum grip strength in the unadjusted model and by 3% (OR, CI: 0.97, 0.95-0.99) after adjusting for significant confounders (age, gender, nutritional status, physical activity and number of prescribed drugs).
Conclusion: Muscular strength is inversely and independently associated with falling in old age. Thus, in older adults muscle-strengthening exercises may decrease the risk of falling.

1-11

Factors affecting physical performance in maintenance hemodialysis patients

Jun Chul Kim[1], Sukyung Lee[2], Kisoo Park[3], So-Young Lee[4], Dong Ho Yang[4]

[1]Department of Internal Medicine, CHA Gumi Medical Center, CHA University, Gumi-si, South Korea, [2]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea, [3]Department of Preventive Medicine, School of Medicine Gyeongsang National University, South Korea, [4] Department of Internal Medicine, Bundang CHA Medical Center, CHA University, Seongnam, South Korea

Background: Poorer physical performance (PP) is observed even in relatively healthy maintenance hemodialysis (MHD) patients compared to general population, which is associated with lower quality of life, higher rate of hospitalization and mortality. We therefore assessed PP in MHD patients and age- and gender-matched normal controls and evaluate factors affecting PP in MHD population.
Methods: PP was evaluated in 81 MHD patients and 34 controls using measures such as 6-minute walk test (6MWT, m), sit-to-stand (STS, cycles/30sec) and timed up and go (TUG, sec) test. Body composition was measured with dual energy X-ray absorptiometry (DEXA) and computed tomography (CT). Muscle strength was assessed with hand grip dynamometer. Demographic and blood chemistry data were also obtained.
Results: Patients were 56.1 ± 11.9(SD) years (y), 46.9% female, 54.3% diabetes; dialysis vintage was 4.7 ± 5.2y. Normals were 54.5 ± 13.7 y and 50% female. All PP were greatly reduced in MHD vs. controls (all $p<0.001$): 6MWT (458.9 ± 112.7 vs. 570.4 ± 75.0), STS (17.9 ± 5.6 vs. 24.3 ± 7.2) and TUG (7.3 ± 2.0 vs. 5.7 ± 1.1). In univariate analysis, PP (in order as follows: 6MWT, STS and TUG) correlated with age ($r=-0.477$, $p<0.001$; $r=-0.358$, $p=0.001$; $r=0.468$, $p<0.001$), weight adjusted appendicular skeletal muscle mass (ASM/wt, %) measured by DEXA ($r=0.347$, $p=0.002$; $r=0.148$, $p=0.189$; $r=-0.231$, $p=0.038$), weight adjusted thigh muscle area (TMA/Wt, cm^2/kg) measured by CT ($r=0.527$, $p<0.001$; $r=0.490$, $p=0.004$; $r=-0.466$, $p<0.001$). These PP are also significantly associated with grip strength (kg, $r=0.472$, $p<0.001$; $r=-0.235$, $p=0.035$; $r=-0.474$, $p<0.001$). Even after adjustment for age, gender, hemoglobin and ASM/wt, TMA/Wt shows significant correlation with 6MWT ($r=0.31$, $p<0.001$) and STS ($r=0.51$, $p<0.001$) and grip strength is also related to STS ($r=0.25$, $p=0.017$) and TUG ($r=-0.27$, $p=0.004$).
Conclusions: MHD patients show decreased PP compared to normals, which are significantly related to loss of muscle mass and strength (i.e. sarcopenia). Intervention to overcome sarcopenia must be important to improve PP in this population.

1-12

Pulmonary function in healthy elderly: The contribution of body composition, muscle strength, physical activity and performance

Lisa Schweitzer[1], Corinna Geisler[1], Maike Johannsen[1], Claus-Christian Glüer[2], Manfred J. Müller[1]

[1]Institute of Human Nutrition and Food Science, Christian-Albrechts-University, Kiel, Germany, [2]Clinic for Diagnostic Radiology, Section Biomedical Imaging, Molecular Imaging North Competence Center CC, University Medical Center Schleswig-Holstein, Kiel, Germany

Background and aims: Several studies showed positive associations of pulmonary function with fat free mass and muscle strength. A negative

association was found with waist circumference as an indirect measure of visceral adipose tissue (VAT).

To evaluate the associations between pulmonary function and detailed whole-body as well as regional skeletal muscle (SM) and adipose tissue (AT), muscle strength, physical activity and performance.

Methods: Cross-sectional data were assessed among 40 healthy, free-living elderly (20 M) aged 65.1 to 81.2y (mean ± SD age:72.2 ± 4.3y;BMI:25.6 ± 3.7kg/m^2). Forced vital capacity (FVC) and forced expiratory volume in 1s (FEV_1) were assessed by spirometry to estimate pulmonary function. Total and regional SM and AT were assessed using whole-body magnetic resonance imaging, muscle strength was assessed by handgrip dynamometry. Physical activity (PA) was estimated by the physical activity scale for the elderly (PASE) and physical performance by the 5m-walk as well as sit-to-stand test.

Results: Positive associations of FVC and FEV_1 with SM and handgrip strength (HSG) were found ($r = 0.557–0.689$;$p<0.05$). Percentage of AT correlated negatively with FVC and FEV_1. Subcutaneous AT (SAT) and VAT correlated with FVC ($r = -0.337$ and $r = 0.368$; $p < 0.05$), whereas gait speed and PA showed associations with FEV_1 ($r=-0.314$ and $r = 0.400$; $p < 0.05$). After adjustment for age, height and weight HGS and PA still correlated positively with FEV_1 ($r = 0.451$; $r = 0.324$; $p < 0.05$), whereas no other correlations were observed. Stepwise multiple regression using FVC and FEV_1 as dependent variables and age, height, weight, whole-body SM and regional SM, SAT, VAT, %AT, HGS, PA and physical performance as independent variables showed that (i) only height entered the regression for predicting FVC ($r^2 = 0.597$; SEE = 0.53L) and (ii) HGS, PA and height entered the regression predicting FEV_1 with an explained variance of 59.7% (SEE = 0.49L).

Conclusions: In healthy elderly FVC and FEV_1 are positively associated with skeletal muscle, muscle strength and physical activity; whereas an inverse association was found with %AT.

1-13

Fat and bone loss in advanced heart failure patients

Masaaki Konishi,[1] Eiichi Akiyama[1], Noriaki Iwahashi[1], Nobuhiko Maejima[1], Kengo Tsukahara[1], Kiyoshi Hibi[1], Masami Kosuge[1], Toshiaki Ebina[1], Satoshi Umemura[2], Kazuo Kimura[1]

[1]Division of Cardiology, Yokohama City University Medical Center, Yokohama, JAPAN, [2]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, JAPAN

Background: Heart failure (HF) is considered to provoke fat and bone loss in the association with adverse metabolic influences, and is one of the major underlying diseases in cachexia. Pericardial fat is an ectopic fat depot that can potentially affect the myocardium, but the role of pericardial fat in HF is unclear. We sought to characterize pericardial fat and trabecular bone in HF, particularly in the association with the extent of severity in cardiac function.

Methods: In 61 consecutive hospitalized HF patients with left ventricular ejection fraction (LVEF) ≤50%, pericardial fat volume (PFV) and trabecular bone computed tomography (CT) density in the thoracic vertebrae were assessed simultaneously using electrocardiogram-gated non-contrast-enhanced CT.

Results: The mean PFV was 93.5 ± 50.6 cm^3, which was associated with the total body fat (Pearson's $r = 0.48$, $p = 0.01$) but not total lean mass ($r = 0.17$, $p = 0.42$) measured with dual energy X-ray absorptiometry. Patients with LVEF <30% had significantly lower PFV index, defined as the PFV/body surface area, than those with LVEF ≥30% (45.7 ± 26.3 vs 63.6 ± 29.2, p=0.01), which may suggest pericardial fat loss in advanced HF. In addition, PFV was inversely correlated with LVEF ($r = -0.32$, $p = 0.01$) and positively correlated with BNP level ($r = 0.26$, $p = 0.04$). The body mass index tended to correlate with LVEF ($r = 0.24$, p=0.06). The trabecular bone CT density had no significant association with LVEF ($r = -0.06$, $p = 0.65$) or BNP level($r = -0.18$, p=0.16).

Conclusions: We simultaneously assessed the pericardial fat and bone tissue of HF patients with CT and successfully characterized pericardial fat loss, rather than weight loss or bone loss, in advanced HF. Further studies would be warranted to investigate the prognostic/therapeutic significance of PFV and bone CT density in HF patients.

1-14

A low skeletal muscle mass is independently associated with elevated baseline troponin levels in patients at risk for coronary artery disease undergoing major abdominal cancer surgery

Jeroen L.A. van Vugt[1,2], Djamila Boerma[2], Ineke M. Dijkstra[3], Thomas L. Bollen[4], Jan N.M. IJzermans[1], Peter G. Noordzij[5]

Departments of [1]Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Surgery, [3]Clinical Chemistry, [4]Radiology and [5]Anesthesiology, Intensive Care and Pain Medicine, St Antonius Hospital, Nieuwegein, The Netherlands

Background: Up to 80% of patients with advanced cancer is affected by cachexia. Animal studies suggest that cancer cachexia leads to heart failure, as not only skeletal muscle wasting (sarcopenia) but also cardiac muscle wasting may occur. The aim of this study was to assess the association between skeletal muscle mass and preoperative high-sensitive cardiac troponin T (hs-cTnT) release.

Methods: This study is a post hoc analysis of a subgroup of 130 abdominal cancer patients of the MICOLON study. Preoperative hs-cTnT was measured. Troponin levels ≥0.014 μg/L were considered as elevated. Cross-sectional skeletal muscle area was assessed on preoperative abdominal computed tomography scans and corrected for height (L3 muscle index [cm^2/m^2]). Patients were classified as sarcopenic or non-sarcopenic according to previously defined cut-off values.

Results: In total, 45 (35.7%) patients had elevated preoperative hs-cTnT levels and 82 (65.1%) were sarcopenic. Preoperative cTnT and L3 muscle index showed a significant negative correlation (R^2=0.038; p=0.029) (fig. 1). Patients with elevated hs-cTnT levels had a significantly lower L3 muscle index (44.2 versus 48.5 cm^2/m^2; p=0.001) and higher rate of sarcopenia (91.1 versus 8.9%; p<0.001)

compared with patients with normal preoperative hs-cTnT levels. Moreover, the incidence of hs-cTnT ≥0.020 μg/L was significantly higher in sarcopenic patients compared with non-sarcopenic patients (23.2 vs. 4.5%; p=0.007). Besides higher age, a history of congestive heart failure and low eGFR, sarcopenia was independently associated with elevated preoperative troponin levels (OR 11.8 [95% CI 2.6-53.1]; p=0.001) in multivariable analysis (table 1).

Conclusion: In this cohort of patients at risk for coronary artery disease, low skeletal muscle mass is independently associated with elevated preoperative troponin levels. These findings support the hypothesis of a bilateral effect of cancer cachexia and heart failure in humans.

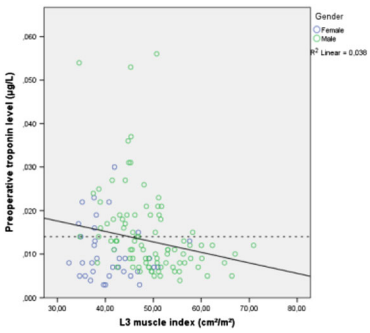


Figure 1 Preoperative hs-cTnT level and L3 muscle index showed a significant negative correlation (p=0.029). Dotted line: hs-cTnT level of 0.014 μg/L.

Table 1 Multivariable logistic regression analysis using a stepwise method (Forward: Conditional) for risk factors for elevated preoperative hs-cTnT levels (≥0.014 μg/L)

	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Sarcopenia (yes)	10.00 (3.28-30.50)	**<0.001**	11.75 (2.60-53.05)	**0.001**
Age (years)	1.23 (1.14-1.32)	**<0.001**	1.22 (1.12-1.34)	**<0.001**
Gender (male)	1.89 (0.80-4.50)	0.150		
Body mass index (kg²/m²)	0.88 (0.8-0.97)	**0.011**		
Medical history of congestive heart failure	7.28 (1.44-36.71)	**0.016**	22.53 (2.03-250.15)	**0.011**
Medical history of atrial fibrillation	4.30 (1.57-11.77)	**0.005**		
Preoperative eGFR (ml/min/1.73 m²)	0.97 (0.96-0.99)	**0.001**	0.96 (0.94-0.99)	**0.002**
ASA classification	3.04 (1.40-6.59)	**0.005**		
POSSUM†	1.07 (1.02-1.11)	**0.004**		

1-15

Muscle quality evaluated by ultrasound and changes related to age and body mass index

Clarissa B. Uezima[1], Andrea Z. Pereira[2], Maria Teresa Zanella[1], Maria Cristina Gonzalez[3], Jolene Zheng[4], Steven B Heymsfield[4]
[1]Endocrinology Division, UNIFESP, S.Paulo, Brazil, [2]Oncology Department, Hospital Israelita Albert Einstein, and Endocrinology Division, UNIFESP, S.Paulo, Brazil, [3]Post-graduation Program in Health and Behaviour, Catholic University of Pelotas, Brazil, [4]Pennington Biomedical Research Center2, Louisiana State University System, Baton Rouge, LA

Introduction: Structural changes occur in skeletal muscles with some disease states and during the aging process when muscle fibers are lost and replaced by fat and fibrous tissue infiltration. This replacement of skeletal muscle fibers decreases muscle quality and the tissue begins to appear whiter on ultrasound images. Skeletal muscle can be evaluated using ultrasound, a non-invasive, portable, easy to use imaging method. Increased muscle whiteness or "echogenicity" represents changes caused by fat and fibrous infiltration and recently developed software can be used for analysis of pixel grayscale. The objective of the present study was to investigate the skeletal muscle quality through echogenicity estimates according to subject body mass index (BMI) and age.

Methods: Cross-sectional study performed at the Pennington Biomedical Research Center, Baton Rouge, EUA with 119 participants (59 men and 60 women), mean age of 38.9 ± 17.0 (19 - 79 years) and average BMI of 28.6 ± 6.2 (19 - 55 kg/m ^{2}). All participants were examined by ultrasound (GE LOGIC®), using 5.0 MHz linear transducer. Each subject had muscle thickness measured by ultrasound in 4 anatomical locations (biceps and triceps brachial, femoral quadriceps and calf triceps). Echogenicity was analyzed with specific software (Pixel Health®) that evaluated image gray scale.

Results: 34% participants were normal weight, 42% were overweight, and 41% were obese. A positive correlation was present between age and thigh muscle echogenicity ($r_p = 0.534/p < 0.0001$) and a negative correlation was present between thigh muscle echogenicity and thickness ($r_p = -0.395/p < 0.0001$). In addition, there was a significant high muscle echogenicity in obese and overweight patients age >=50 years (p<0,05).

Conclusion: Greater age and BMI were associated with a stronger echogenicity signal and smaller muscle thickness. Therefore, overweight and obese subjects and\or patients >50 years of age had reduced muscle quality and more fat and fibrous infiltration with smaller muscle thickness.

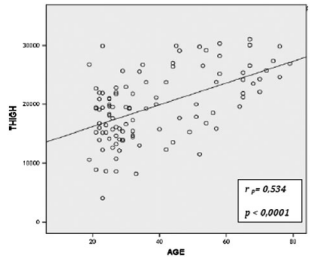


Figure 1 Correlation between thigh muscle echogenicity (pixels) and age (years).

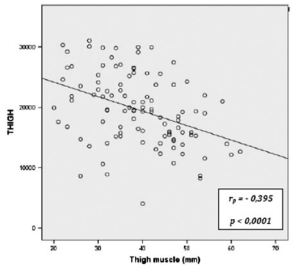


Figure 2 Correlation between thigh muscle echogenicity (pixels) and thickness (mm).

1-16

The value of CT-based body composition analyses in patients with necrotizing pancreatitis

Jeroen L.A. van Vugt*[1,2], Janneke van Grinsven*[2,3], Arvind Gharbaharan[1], Thomas L. Bollen[4], Marc G. Besselink[3], Hjalmar C. van Santvoort[2], Casper H.J. van Eijck[1], Djamila Boerma[2] for the Dutch Pancreatitis Study Group

[1]Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands, [3]Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [4]Department of Radiology, St. Antonius Hospital, Nieuwegein, The Netherlands

*These authors contributed equally to this study

Background and aims: Necrotizing pancreatitis is associated with high mortality and morbidity rates. Early identification of patients at risk for a complicated course could improve outcomes. Low muscle mass and density, muscle wasting, and visceral obesity have been identified as predictive factors for impaired outcome in various diseases, but not in necrotizing pancreatitis. Our aim was to investigate their predictive value in patients with necrotizing pancreatitis.

Methods: A post-hoc analysis was performed in a prospective cohort including 639 patients with necrotizing pancreatitis. Cross-sectional muscle area (CSA) corrected for patients' height (L3- index), skeletal muscle density (SMD), and visceral fat (VF) were measured on CT-scans at the third lumbar vertebra level. Sex-specific tertiles were created. Multivariable analyses were performed to identify independent predictors for mortality and severe complications.

Results: Baseline CT-scans were available in 575 patients (62.4% males, median age 58), follow-up CT-scans at one and three months in 251 and 112 patients, respectively. Median time between admission and admission CT-scan was two days (IQR 0-6). Although L3-index, SMD, and VF were not independent predictors for mortality, low SMD was independently associated with complications requiring ICU admission or intervention (OR 2.37 [95%-CI 1.53-3.69], $p<0.001$). The CSA and L3-index significantly decreased between baseline and one, and three months ($p<0.001$). Deceased patients (14.3%) experienced significantly more muscle wasting during the first month after admission compared with non-deceased patients (CSA -14.1% versus -8.5%, p=0.034), particularly in male (-18.5% versus -10.7%, p=0.002) and younger patients (i.e. <65 years) (-20.6% versus -10.6%, p=0.002), whereas this was not significant after three months (-24.0% versus -15.0%, p = 0.118).

Conclusions: Low skeletal muscle density is independently associated with impaired outcome in patients with necrotizing pancreatitis. Extensive muscle wasting was prevalent, particularly in the first month in those who died.

1-17

Multi-parametric mapping of NMR based biomarkers for tissue characterization of aging skeletal muscle

Benjamin Marty[1], Pierre-Yves Baudin[1], Harmen Reyngoudt[1], Noura Azzabou[1], Ericky C.A. Araujo[1], P.L. De Sousa[2], Pierre G.Carlier[1]

[1]Institute of Myology, NMR Laboratory, G.H. Pitié-Salpêtrière, Paris, France, [2]University of Strasbourg, CNRS, ICUBE, FMTS, Strasbourg, France

Quantitative nuclear magnetic resonance imaging is increasingly used for studying neuromuscular disorders. This approach has recently been applied to monitor muscle structural changes associated to sarcopenia. Skeletal muscle inflammation, necrosis, hydrostatic edema and fatty infiltration are strong indicators of disease activity and progression. Muscle transverse relaxometry and water/fat separation techniques have proven to be efficient non-invasive methods for assessing and monitoring these phenomena. While reflecting inflammatory infiltration, myocyte swelling, sarcoplasmic leakiness, cell necrosis, or simply hydrostatic edema, and therefore being nonspecific, muscle water transverse relaxation time ($T2H_2O$) changes provide relevant information about disease activity, and about muscle physiological status. Fatty infiltration and replacement in muscles, however, reveal the extent and severity of muscle destruction and loss in chronic conditions.

$T2H_20$ and FF are usually measured separately, using dedicated NMR sequences. The muscle $T2H_2O$ estimation is most often derived from standard Multi-Slice Multi-Echo (MSME) acquisitions and exponential fitting of the temporal signal decay, while methods exploiting the chemical shift between water and fat protons (e.g. Dixon) are the most popular approaches for FF estimation. In practice, instrumental imperfections such as non-ideal slice pulse profiles and magnetic field inhomogeneities contaminate the MSME sequence and render $T2H_2O$ determination highly unreliable using exponential models.

Here, we propose to apply a bi-component extended phase graph model that take into account all the instrumental imperfections to simultaneously and accurately quantify the muscle $T2H_20$ and FF from a unique MSME acquisition. The interest of this methodology over standard approaches was demonstrated in term of accuracy and precision on parameters estimation. This simultaneous evaluation of $T2H_2O$ and FF also represent a real advantage for whole-body investigations as it allows a decrease in acquisition time. This novel approach will greatly facilitate the quantitation and the monitoring of the fatty degenerative changes and the shift in typology, revealed by the water T2 changes, which are important processes in sarcopenia.

1-18

Fast and user-friendly interactive segmentation of skeletal muscles in nuclear magnetic resonance images will facilitate quantitation of sarcopenia

Pierre-Yves Baudin[1], Noura Azzabou[2,3], Pierre G Carlier[2,3]

[1]Consultants for Research in Imaging and Spectroscopy, Tournai, Belgium, [2]NMR Laboratory, Institute of Myology, AIM, Paris, France, [3]CEA, I[2]BM, MIRCen, NMR Laboratory, F-75651 Paris, France

Nuclear magnetic resonance imaging (MRI) has proven to be a powerful investigative tool for diagnostic workups and non-invasive quantitative outcome measurements in clinical studies on musculoskeletal pathologies. Due to the often highly heterogeneous involvement of the muscles, it is useful to assess properties such as the muscle's volume, cross-sectional area and trophicity, fatty replacement or edema within the tissue, at the individual muscle's scale. While the aforementioned biomarkers can be entirely extracted from MR images, the necessary delineation of the regions of interest, also called segmentation, is an extremely time consuming task and thus often abandoned for lack of time or workforce. The availability of automatized segmentation techniques would allow for a much wider use in clinical imaging protocols, in particular for longitudinal studies of skeletal muscle wasting and its prevention in elderly populations.
We propose a novel automatized segmentation software to help researchers and clinicians to simply and quickly segmenting large MRI volumes of muscles, with outputs of an as good quality as fully manual segmentations. Our software integrates the efficient interactive Random Walker segmentation algorithm into a convenient graphical user interface, such that the operator quickly builds a segmentation step-by-step, muscle-by-muscle.
The validation of our tool was carried out on images of 18 subjects' quadriceps, which were segmented three times: an expert produced the first one fully manually, while two other experts created new segmentations under a fixed time limit (10 min) using our tool. Comparisons of the resulting segmentations were made using similarity measures (relative volume differences and Dice coefficients) and Bland-Altman plots, and showed an excellent agreement between all segmentations.
While fully manual segmentation of the quadriceps volumes required more than 5 hours, the same volumes were equivalently segmented in less than 10 min with the presented tool, demonstrating its efficiency. This novel approach will facilitate the use of NMR imaging as a powerful tool to monitor progression and possible response to intervention of sarcopenia in elderly subjects.

1-19

Aging alters skeletal muscle associated microRNA expression in circulation at rest and post resistance exercise

Lee M. Margolis, Donato A. Rivas, Yassine Ezzyat, Roger A. Fielding
Nutrition, Exercise, Physiology, and Sarcopenia Laboratory U.S. Department of Agriculture Jean Mayer Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts, USA

Background and aims: Aging results in altered expression of microRNAs (miR; small non-coding RNAs that regulate gene expression) in skeletal muscle. Recently, miR have also been shown to be present in the circulation (c-miR), with physiological states impacting skeletal muscle (e.g., disease and exercise) altering c-miR expression. Whether c-miR expression differs between young and old individuals remains unknown. The objective of this investigation was to determine the influence of aging on c-miR at rest and following resistance exercise (RE).
Methods: Eighteen male volunteers (Younger (YNG) $n = 9$, age 22 ± 1 yrs; Older (OLD) $n = 9$, age 74 ± 2 yrs) performed 3 sets of bilateral knee extension and leg press exercise (10 repetitions at 80% 1 repetition maximum) with blood samples collected at baseline, immediately following RE, and 6 hrs following RE. c-miR were extracted from serum, and expression of 84 miR were assessed on 384 miScript miRNA PCR Array.
Results: At baseline 30 c-miR had a fold difference of ≥ 1.5 in OLD compared to YNG, with 20 c-miR achieving statistical significance ($P < 0.05$), including skeletal muscle associated miR-133a-3p (YNG 1.00 ± 0.26; OLD 2.10 ± 0.37), miR-206 (YNG 1.00 ± 0.19; OLD 3.46 ± 0.86), and miR-486 (YNG 1.00 ± 0.17; OLD 2.85 ± 0.62). Following RE 26 c-miR were significantly different from baseline ($P < 0.05$), with a main effect of age observed in skeletal muscle associated miR-1-3p (YNG 2.46 ± 0.63; OLD 1.54 ± 0.66) and miR-206 (YNG 3.76 ± 0.73; OLD 1.33 ± 0.69) expression 6 hrs following RE.
Conclusion: These findings indicate that similar to disease states which negatively impact skeletal muscle, aging results in elevation of specific c-miR. Furthermore, the differing response of YNG and OLD following RE warrants further investigation to assess its impact on skeletal muscle function.

1-20

Perioperative immunonutrition counteracts rapid skeletal muscle wasting and restrains the expansion of myeloid derived suppressor cells in patients undergoing radical cystectomy

Jill M. Hamilton-Reeves[1,4*], Misty D. Bechtel[1], Thomas M. Yankee[2], Prabhakar Chalise[3], Eugene K. Lee[4], Jeffrey M. Holzbeierlein[4]
[1]Department of Dietetics & Nutrition, University of Kansas Medical Center, Kansas City, Kansas, USA, [2]Department of Microbiology, Molecular Genetics, & Immunology, University of Kansas Medical Center, Kansas City, Kansas, USA, [3]Department of Biostatistics, University of Kansas Medical Center, Kansas City, Kansas, USA, [4]Department of Urology, University of Kansas Medical Center, Kansas City, Kansas, USA

Background and aims: Rapid skeletal muscle wasting is a serious and common complication following the radical cystectomy (RC) surgery to treat advanced bladder cancer. RC induces the expansion of myeloid-derived suppressor cells (MDSC). Emerging data suggest skeletal muscle wasting is partly driven by the expansion of MDSCs. Specialized immunonutrition (SIM) intake before and after RC surgery may help counteract muscle wasting after RC surgery by restraining MDSCs.
Methods: Men with bladder cancer scheduled for surgery were randomly assigned to oral SIM providing supplemental L-arginine, fish oil, vitamin A, and nucleotides (n = 14) or a calorie- and nitrogen-matched oral nutrition supplement [ONS (n = 15)] for 5 days before and 5 days after RC. MDSC counts (Lin- CD11b+ CD33+) were measured and standardized by absolute lymphocyte counts at baseline, surgery, 2, 14, and 30 days after surgery. Dual Energy X-Ray

Absorptiometry scans were obtained at baseline, 14 days, and 30 days after surgery to calculate relative skeletal muscle index (RSMI). Differences in MDSC counts and RSMI between the groups were assessed longitudinally using the generalized linear mixed model.
Results: MDSC count was significantly different between the SIM and ONS groups over time ($P = 0.005$) and was significantly lower in the SIM group two days after RC ($P < 0.0001$). Relative Skeletal Muscle Index (RSMI) was better preserved in the SIM group at 14 days (7% vs. 17% in the ONS group). The expansion in MDSC count from surgery to 2 days after surgery was correlated with the decrease in RSMI at 14 days after surgery ($\rho = -0.065$).
Conclusions: As shown by the presence of a trend, the increase in MDSC is associated with a rapid decrease in RSMI. Improving immune function through specialized immunonutrition could be a low risk, high-impact means of counteracting muscle wasting after RC surgery.

1-21

Skeletal muscle depletion and metabolic markers for cancer cachexia as strong prognostic factors in epithelial ovarian cancer

Stefanie Aust[1], Thomas Knogler[2], Dietmar Pils[1], Anna Bachmayr-Heda[1], Alexander Reinthaller[1], Ilja Radlgruber[2], Marius Erik Mayerhoefer[2], Samuel Matthias Meier[3], Christopher Gerner[3], Stephan Polterauer[1]
[1]Department of Gynaecology and Gynaecological Oncology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [2]Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria, Austria, [3]Department of Analytical Chemistry, Faculty of Chemistry, University of Vienna, Vienna, Austria

Background: Unfortunately, an optimal marker of cancer cachexia and an inclusion in clinical routine is still missing, although various studies highlight the importance to consider cachexia associated changes in cancer patients. In epithelial ovarian cancer (EOC) the provoked metabolic and inflammatory disturbances might be reflected in body composition measurements (BCMs) ascertained by pre-operative computed tomography (CT). The present study aimed to investigate the prognostic value of BCMs assessed by pre-operative CT in EOC patients, in conjunction with a precise analysis of associated metabolic and inflammatory changes.
Methods: We evaluated BCMs and well established markers of nutritional and inflammatory status, as well as clinical-pathological parameters in 140 consecutive EOC patients. Furthermore, a multiplexed inflammatory marker panel of 25 cytokines was used to determine the relationship of BCMs with inflammatory markers and patient's outcome. Metabolome profiling was performed using orbitrap mass spectrometry and the AbsoluteIDQ p180 research assay, combining 188 endogenous metabolites. All relevant parameters were evaluated in uni- and multivariate survival analysis.
Results: Muscle attenuation (MA) - a well-established BCM parameter - is an independent prognostic factor for survival in multivariate analysis (HR 2.25; p=0.028). Low MA, reflecting a state of cachexia, is associated with residual tumor after cytoreductive surgery (p=0.046) and with an unfavorable performance status (p=0.015). Moreover, MA is associated with Eotaxin and IL-10 out of the 25 cytokine multiplex marker panel in multivariate linear regression analysis (p=0.021 and p=0.047, respectively) and metabolomics analysis revealed 8 acyl carnitines, 3 sphingolipids and one amino acid as significantly negatively correlated to MA.
Conclusion: MA – ascertained by routine pre-operative CT – is an independent prognostic parameter in EOC patients. Low MA is associated with the inflammatory, as well as the nutritional component of cachexia. Therefore, the clinical value of pre-operative CT could be enhanced by the assessment of MA.

1-22

NO66 suppress muscle growth via repressive-complex with RBBP4 and HDAC2

Liping Zhang, Jiangling Dong, Zihong Chen, Yanlan Dong, William E. Mitch
Nephrology Division, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

Background and aims: Skeletal muscle mass loss occurs in patients with different catabolic disorders. In a model of chronic kidney disease, we showed that the loss of muscle mass is related to activation of proteases plus a dysfunctional regulation of satellite cell activity. Reportedly, satellite cell activation is regulated by an epigenetic mechanism but details that control muscle growth is largely undefined. We found a chromatin modifying nucleolar protein, NO66, regulates proliferation, and differentiation of muscle cells, via activation of myogenic regulatory factors. The aim of this study is to understand how epigenetic alterations can regulate myogenesis and muscle growth.
Methods: We have created transgenic mice overexpressing NO66 in mesenchymal cells. Mice with whole body deletion of NO66 were created by crossing transgenic, Sox2-cre mice with mice bearing floxed NO66 alleles. Muscle injury was induced by injection of cardiotoxin. Satellite cells (integrin-$\alpha7^+$/$CD31^-$/$CD45^-$/$Scal^-$) were isolated from muscles of mice by FACS Cell Sorting. CHIP assays were performed using a Millipore kit. MyoD and myogenin promoter activity was analyzed by Pierce Gaussia Luciferase Assay Kit. Mass Spectrometry (MS) was performed by "Pathway Discovery Proteomics Core" of Baylor College of Medicine.
Results: In mice, genetic deletion of NO66 causes a 20-30% increase in muscle mass and muscle growth is suppressed with NO66 overexpression in mesenchymal cells. NO66 forms a repressive complex with histone modification proteins, RBBP4 and HDAC2 which physically interact with MyoD to induce its deacetylation while inhibiting its transcription. NO66 repressive complex also suppresses myogenin transcription by inhibiting MyoD binding to the myogenin E-box resulting in demethylation of H3K4me3 in the myogenin gene leading to impaired muscle cell proliferation and myotube formation.
Conclusion: These results provide a new mechanism regulating satellite cell function and muscle growth. Interference with NO66 could lead to strategies that reduce muscle mass losses in catabolic disease.

1-23

Skeletal muscle quality and function in rats fed a low-carbohydrate diet or a Western diet

Andreas N. Kavazis[1], Michael D. Roberts[1], Jacob M. Wilson[2], Ryan P. Lowery[2], A. Maleah Holland[1], Wesley C. Kephart[1], Petey W. Mumford[1], C. Brooks Mobley[1], Hayden W. Hyatt[1]

[1]School of Kinesiology, Auburn University, Auburn, AL, USA, [2]Department of Health Sciences and Human Performance, The University of Tampa, Tampa, FL, USA

Background and aims: Data suggest that a low-carbohydrate diet (LCD) compared to a Western diet (WD) can reduce the incidence of cancer and/or slow down the proliferation of existing cancer cells. This effect is driven by LCD-mediated low insulin levels and the fact that several tumor cells have a reduced capacity to metabolize fatty acids and/or ketones due to mitochondrial dysfunction. However, LCD can reduce skeletal muscle mass that would have a negative effect on the cancer patient. Thus, we tested the hypothesis whether or not skeletal muscle quality and function is hampered with a LCD versus a WD.
Methods: Male Sprague-Dawley rats (~300g) were provided with either a LCD (17 g/day, 5.2 kcal/g, 10.3% carbohydrate, 69.5% fat, 20.2% protein) or a WD (20 g/day, 4.5 kcal/g, 42.7% CHO, 42.0% fat, 15.2% protein) for 6 weeks. All rats were voluntarily exercised using resistance-loaded running wheels. The gastrocnemius muscles were removed and used for analyses.
Results: Animals fed the LCD diet had a lower body mass compared to WD ($p<0.01$). The ratio of gastrocnemius:body mass was higher in LCD ($p<0.01$). Importantly, the LCD gastrocnemius had a higher concentration of myofibrillar protein compared to WD ($p=0.04$). Additionally, following mitochondrial isolation and in the presence of complex I substrates, the respiratory control ratio (RCR) was not different ($p=0.30$) between the two groups. However, in the presence of a complex II substrate, the RCR was significantly ($p<0.01$) increased in animals fed the LCD compared to WD.
Conclusions: Our data show that a LCD can improve skeletal muscle quality and function which would be beneficial to the cancer patient. Furthermore, these findings warrant further investigation since recent data has shown that ketones may have an anti-cancer effect.

1-24

Improvement of skeletal muscle performance in aging by the metabolic modulator Trimetazidine

Elisabetta Ferraro[1*], Fabrizio Pin[2,3], Stefania Gorini[1], Laura Pontecorvo[1], Alberto Ferri[4], Vincenzo Mollace[5], Paola Costelli[2,3], Giuseppe Rosano[1,6]

[1] Laboratory of Pathophysiology of Cachexia and Metabolism of Skeletal Muscle, IRCCS San Raffaele Pisana, Rome, Italy, [2]Department of Experimental Medicine and Oncology, University of Torino, Italy, [3]Istituto Interuniversitario di Miologia-IIM, [4]Institute of Cell Biology and Neurobiology, CNR, Rome, Italy, [5]Department of Pharmacobiological Sciences, University Magna Graecia, Catanzaro, Italy, [6]Cardiovascular and Cell Sciences Institute, St George's University of London, Cranmer Terrace, London, UK

Background: The loss of muscle mass (sarcopenia) and the associated reduced muscle strength are key limiting factors for elderly people's quality of life. Improving muscle performance does not necessarily correlate with increasing muscle mass. In fact, particularly in the elderly, the main explanation for muscle weakness is a reduction of muscle quality rather than a loss of muscle mass, and the main goal to be achieved is to increase muscle strength. The effectiveness of Trimetazidine (TMZ) in preventing muscle functional impairment during aging was assessed in our laboratory.
Methods: Aged mice received TMZ or vehicle for 12 consecutive days. Muscle function was evaluated at the end of the treatment by a grip test as well as by an inverted screen test at 0, 5, 7 and 12 days of TMZ treatment. After sacrifice, muscles were stored for myofiber cross sectional area (CSA) assessment and myosin heavy chain (MyHC) expression evaluation by western blotting.
Results: Chronic TMZ treatment does not affect the mass of both *gastrocnemius* (GSN) and *tibialis anterior* (TA) muscles, while it significantly increases muscle strength. Indeed, both latency to fall and grip force are markedly enhanced in TMZ-treated *vs* untreated mice. In addition, TMZ administration results in higher expression of slow MyHC isoform and increased number of small-sized myofibers.
Conclusions: We report here some data showing that the modulation of skeletal muscle metabolism by TMZ increases muscle strength in aged mice. Reprogramming metabolism might therefore be a strategy worth to be further investigated in view of improving muscle performance in the elderly.

1-25

Integrated expression analysis identifies a novel E3 ubiquitin ligase in regulation of muscle hypertrophy and sarcopenia

Jonathan R. Davey[1], Kevin I. Watt[1], Benjamin Parker[2], Rima Chaudhuri[2], James G. Ryall[4,5], Marco Sandri, Vittorio Sartorelli[4], Jeffrey Chamberlain[6], David E. James[2], Paul Gregorevic[1,6]

[1]Baker IDI Heart & Diabetes Institute, Melbourne, Australia, [2]Charles Perkins Centre, School of Molecular Bioscience, The University of Sydney, Australia, [3]Venetian Institute of Molecular Medicine, The University of Padova, Italy, [4]National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA, [5]Department of Physiology, The University of Melbourne, Australia, [6]Department of Neurology, The University of Washington, Seattle, USA

Background and aims: The TGF-beta (TGF-β) signaling network is a critical regulator of skeletal muscle mass and function in health and disease. Member ligands of the TGF-β family that regulate skeletal muscle and are associated with muscle wasting in disease include myostatin, activin A and B, and GDF11. Manipulation of these ligands may hold the potential to address muscle wasting associated with a variety of conditions and with advancing age. We sought to evaluate the impact of inhibiting these ligands by follistatin treatment in sarcopenia.

Methods: In young and adult mice, follistatin treatment generates a profound muscle hypertrophy and here we report a severe blunting of this growth in sarcopenic muscle. This disparity highlights the importance of revealing the mechanisms of TGF-β mediated muscle adaptation. We combined quantitative analyses of proteomic and transcriptomic changes associated with growth of muscles exposed to follistatin. We identified a combined expression signature elicited by acute and chronic follistatin treatment.
Results: This data-set provides the first insight into the program of transcription and translation events governing follistatin-induced adaptation of skeletal muscle attributes. Amongst the features in this analysis was repression of a novel E3 ubiquitin ligase. This ligase is acutely down-regulated by follistatin expression. AAV mediated over-expression of the E3 ligase in skeletal muscle potently induced muscle atrophy. Although follistatin treatment represses expression of this protein in healthy adult mice, we found that the response was specifically lost in sarcopenia. Expression of this ligase in combination with follistatin treatment potently diminished muscle hypertrophy in young mice demonstrating that its regulation is critical for normal growth response during TGF-β inhibition.
Conclusion: We propose that specific elements of the genetic response to TGF-β inhibition which account for muscle hypertrophy are no longer preserved in sarcopenia and this dysfunction contributes to amelioration of hypertrophy in sarcopenic muscle

1-26

Role of DOR/Tp53inp2 in the control of muscle cell proteostasis

Paula Martínez Cristóbal[1], David Sala[1], Caroline Mauvezin[2], Fabio Penna[3], Antonio Zorzano[1]
[1]IRB, Barcelona, Spain, [2]University of Minnesote, Minnesote, USA, [3]University of Torino, Torino, Italy

Background and aims: protein homeostasis (proteostasis), resulting from the fine regulation of synthesis and degradation, is a key mechanism by which cells rapidly respond to their environment to maintain optimum biological activity of cellular proteins. Two major pathways degrade most cellular proteins: the ubiquitin-proteasome system (UPS) and autophagy. The nuclear cofactor DOR was identified originally as a protein expressed in PML nuclear bodies.[1] However, in response to cellular stress, DOR exits the nucleus, localizes to early autophagosomes and regulates autophagy.[2] Moreover, recent data from our laboratory demonstrated that DOR promotes muscle wasting by the activation of basal autophagy in skeletal muscle.[3] Aim of this study was to analyze the role of DOR in combining the regulation of autophagy with other muscle homeostatic processes.
Methods: DOR was knocked down in C2C12 muscle cells and several molecular biology techniques were applied in order to characterize their metabolism and biochemical phenotype.
Results: Here we show that DOR enhances the degradation of proteins through autophagy. Under basal conditions and even upon amino acid starvation, DOR deficiency causes a substantial inhibition of protein degradation and a decrease in the number of autophagosomes. Moreover, DOR is a negative regulator of the accumulation of K48 ubiquitinated proteins as assessed by incubation with the proteasome inhibitor MG132. Based on these data, we suggest that DOR regulates protein turnover in muscle cells by modulating degradation processes. Moreover, preliminary data suggest the participation of DOR in the modulation of protein synthesis.
Conclusions: the comprehension of DOR function in regulating proteostasis will potentially identify new targets against muscle atrophy. Indeed, DOR expression is repressed in wasting conditions such as diabetes and cancer cachexia.

References

1. Baumgartner et al., 2007. PloS one 2,e1183
2. Mauvezin et al., 2010. EMBO reports 11, 37-44
3. Sala et al., 2014. JCI, 124(5):1914-27

1-27

A muscle secretive protein Msp marks ageing related muscular dystrophy

Jie Yin, Yan Liu, Wenjun Yang, Ping Hu
Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, Shanghai, China

Ageing related muscular atrophy (sarcopenia) represents a severe public health threat. The ageing related muscle mass reduction and function loss have been attributed to many inducing factors such as loss of satellite cell activities, reduced physical activities and malnutrition, but the molecular mechanism of sarcopenia has not been completely elucidated out. And there is no generally accepted test and molecular marker for sarcopenia diagnosis. We compared the gene expression profile between young and old muscles. Muscle atrophy related E3 ligase atrogin was highly expressed in old muscles. A secreted protein msp produced by muscle was also high upregulated in old muscles, correlating with the upregulation of atrogin. We further examined the links between msp and atrogin. Msp could help recruiting co-transcription factors of FoxO3, which has been shown to be the critical transcription factor activating atrogin expression, to activate atrogin transcription in old muscles. RNAi of msp both in vitro and in vivo could decrease the expression level of atrogin and recue the muscular atrophy phenotype in old mice. These results suggest that msp could be a key molecule to slow down the muscular atrophy in old muscles.

1-28

Does ER stress in skeletal muscle of old mice contribute to sarcopenia?

Sreeda Chalil[1], Richard T. Jaspers[2], Ralph J. Manders[3], Jenneke Klein-Nulend[4], Astrid D. Bakker[4], Louise Deldicque[1]
[1]Exercise Physiology Research Group, Department of Kinesiology, KU Leuven, Tervuursevest 101, Box 1500, 3001 Leuven, Belgium, [2]Laboratory for Myology, Move Research Institute Amsterdam, Faculty of

Human Movement Sciences, VU University Amsterdam, Van der Boechorststraat 9, 1081 Amsterdam, The Netherlands, [3]Department of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Duke of Kent Building, Guildford, GU2 7TE, Surrey, UK, [4]Department of Oral Cell Biology, Academic Centre for Dentistry Amsterdam (ACTA), MOVE Research Institute Amsterdam, University of Amsterdam and VU University Amsterdam, Gustav Mahler Laan 3004, 1081 Amsterdam, The Netherlands

Objective: Ageing is associated with a loss of muscle mass reportedly with the presence of anabolic resistance. The reasons for which remain unanswered. We hypothesize that the presence of endoplasmic reticulum (ER) stress in muscles of old mice may be involved in the reduced response to anabolic stimuli.
Materials and methods: Extensor digitorum longus (EDL) and soleus of male C57BL/6J wild-type mice (adult mice of 8 months and old mice of 26 months) were incubated with 10μg/ml tunicamycin (ER stress inducer) for 5.5h followed by 4mM leucine (anabolic stimulus) for the last 30min. ER stress markers such as IRE1α, phospho-eIF2α and BiP, as well as phospho-S6K1, a marker for protein synthesis, were measured using western blotting.
Results: In soleus of old mice, phospho-eIF2α was about 2 fold higher ($p<0.05$) and BiP tended to be higher ($p = 0.068$) compared with adult mice. In EDL of old mice, phospho-eIF2α (1.8 fold), BiP (1.5 fold) and IRE1α (2.6 fold) expressions were higher compared with adult mice ($p < 0.05$). No difference in basal phospho-S6K1 was measured in EDL and soleus. Upon stimulation with leucine, phospho-S6K1 increased by 4.1 fold in soleus ($p < 0.01$) and 2.6 fold in EDL ($p < 0.001$) of adult mice compared with 1.8 in soleus (p = NS) and 2.3 fold in EDL ($p < 0.05$) of old mice. These results show that the anabolic response to leucine was impaired in soleus of old mice compared with young mice ($p < 0.05$) but not in EDL. Surprisingly, pre-incubating the muscles with tunicamycin before leucine stimulation further increased phospho-S6K1 in EDL of adult and old mice ($p < 0.001$).
Conclusion/discussion: ER stress markers were higher in both soleus and EDL although anabolic resistance was specifically present in soleus and not in EDL. These results suggest that ER stress contributes to anabolic resistance but that other factors are also involved, such as possibly contractile activity.

1-29

Prevalence of sarcopenia among patients with undernutrition and anorexia nervosa

Igor Khoroshilov, Sergey V. Ivanov, Evgeniy I. Tkachenko
North-Western state medical university named after I.I. Mechnikov, St. Petersburg, Russian Federation

Aim: The aim of our study was the assessment of prevalence of sarcopenia (muscle wasting) among patients with undernutrition and anorexia nervosa.
Materials and methods: 40 patients with undernutrition (20 men, 20 women) and 12 young women with anorexia nervosa were examined. Diagnostics of sarcopenia and its degree of severity was made on the basis of midarm circumference decrease: on 10% below norm — mild, on 20% — moderate and on 30% and lower — severe. The diagnosis has been verified by bioelectrical impedance analysis (BIA) or DXA. Confidence interval analysis was performed by Wilson method.
Results: The decrease of midarm circumference on 10% below norm was estimated in 100% of men (95% CI 84–100%) and 94% of women (95% CI 80-98%). So in these patients sarcopenia has been diagnosed. Among men 30% (95% CI 15–52%) had mild degree of sarcopenia, 60% (95% CI 39–78%) had moderate sarcopenia and 10% (95% CI 3–30%) had severe sarcopenia. 28% (95% CI 16–45%) women had mild rate of sarcopenia, 50% (95% CI 34–66%) had moderate sarcopenia and 22% (95% CI 11–39%) had severe sarcopenia. Sarcopenia also has been diagnosed in 100% (95% CI 76–100%) young women with anorexia nervosa: 8% (95% CI 1–35%) had moderate sarcopenia, and 92% (95% CI 64–99%) had severe sarcopenia.
Conclusions: sarcopenia (muscle wasting) is a typical clinical feature among patients with undernutrition and anorexia nervosa.

1-30

Development and validation of a self-administrated quality of life questionnaire specific to sarcopenia: the SarQoL

Charlotte Beaudart[1], Emmanuel Biver[2], Jean-Yves Reginster[3], René Rizzoli[2], Yves Rolland[4], Ivan Bautmans[5], Jean Petermans[6], Sophie Gillain[6], Fanny Buckinx[1], Olivier Bruyère[1]
[1]Department of Public Health, Epidemiology and Health Economics, University of Liège, Belgium, [2]Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, [3]Bone, Cartilage and Muscle Metabolism Unit, CHU Liège, Belgium, [4]Clinical Gerontology, CHU Toulouse, France, [5]Ageing research department, Vrije Universiteit Brussel, Belgium, [6]Geriatric Department, CHU Liège, Belgium

Background and aims: The impact of sarcopenia on quality of life is currently assessed by generic tools. However, these tools may not detect subtle effects of this specific condition on quality of life. The aim of this study was to develop and validate a sarcopenia-specific quality of life questionnaire (SarQoL, Sarcopenia & Quality of Life questionnaire).
Methods: The development part of the questionnaire was articulated in four stages: 1. Item generation; 2. Item reduction; 3. Questionnaire generation; 4. Pre-test of the questionnaire. To validate the SarQoL, we assessed its discriminative power (logistic regression), internal consistency (Cronbach's alpha), construct validity (Spearman Correlation), test-retest reliability (ICC) and floor and ceiling effects.
Results: The final version of the questionnaire consists of 55 items divided into 7 domains, translated into 22 questions to be rated on a 4-point Likert scale. The pre-test indicates that the SarQoL is easy to complete independently, in approximately 10 minutes. The SarQoL significantly discriminated sarcopenic subjects from non-sarcopenic ones ($p < 0.001$). Internal consistency was good with a Cronbach's alpha = 0.87. The SarQoL had a good convergent validity with, for example, the domain of functional score ($r = 0.52$, $p < 0.001$) and vitality ($r = 0.72$, $p < 0.001$) of the SF-36 questionnaire. Divergent validity has been found with, for example, the EQ-5D pain ($r = -0.12$). Test-retest reliability was good with an ICC of 0.91 (0.82—0.95). Neither floor nor ceiling effects has been found.

Conclusions: The first version of the SarQoL, a quality of life questionnaire specific for sarcopenic subjects, has been developed and has been shown to be understandable by the target population. This French version of the SarQoL is valid, consistent and reliable and can therefore be recommended for clinical and research purposes, and for translation in various languages.

1-31

Skeletal muscle density is independently prognostic of outcomes in newly diagnosed mantle cell lymphoma (MCL) patients: post hoc analysis of LYM 3002

Michael P. Chu[1], Andrew R. Belch[1], Lixia Pei[2], Loya Yang[2], Tadeusz Robak[3], Brendan Rooney[4], Andrew Cakana[4], Helgi van de Velde[5], Michael B. Sawyer[1]

[1]Department of Oncology, Cross Cancer institute, Edmonton, Alberta, Canada, [2]Research and Development, Janssen Pharmaceuticals, Raritan, New Jersey, USA, [3]Department of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland, [4]Research and Development, Janssen Pharmaceuticals, High Wycombe, United Kingdom, [5]Clinical Oncology, Takeda Oncology, Antwerp, Belgium

Background: Before cachexia, cancer patients may develop muscle changes seen as reduced radiation attenuation on computed tomography (CT) imaging. Low skeletal muscle radiographic density (SMD) is prognostic in retrospective studies. This post hoc analysis of LYM 3002, a phase III randomized trial, sought to investigate SMD's impact in MCL.

Methods: 487 newly diagnosed MCL patients were randomized 1:1 between R-CHOP or VR-CAP (vincristine or bortezomib at 1.3 mg/m2 d1, 4, 8, 11 q3wk) for 6-8 cycles in LYM 3002. Pre-treatment, 12-weeks, and 26-weeks post treatment CT images were reviewed to measure L3 vertebral body level SMD. Progression free (PFS) and overall survival (OS) were compared between normal vs. low SMD patients. Cox proportional hazards multivariate analysis weighed SMD's significance against other prognostic factors: gender, MIPIb score, and treatment received.

Results: Of 487 patients, 478 had CT images available for review and were split equally between treatment arms. 42.5% (n = 203) were found to have low SMD at baseline. Patients with low vs. normal baseline SMD had poorer median PFS (16.3 vs. 23.7 months, hazard ratio [HR] 1.52, $p < 0.001$) and OS (HR 1.85, $p < 0.001$). 3-year OS rate was 61.6 vs. 76.8%, respectively. In multivariate analysis, low SMD retained its impact on OS (HR 1.86, p=0.005) and trended to significance on PFS (HR 1.27, p = 0.12). Median PFS based on change in SMD over time showed a stepwise trend from those who remained low, those who became low, those who became normal, and those who stayed normal throughout (23.7 vs. 25.4 vs. 29.4 vs. 37.5 months, respectively).

Conclusions: This study validates SMD's MCL prognostic ability in MCL. SMD can change due to treatment, which may predict for better outcomes. SMD assessment can be a strong and simple prognostication complement. Low SMD is hypothesized to represent an inflammatory cytokine milieu similarly seen in cachexia.

1-32

Non-invasive monitoring of emphysema and muscle wasting in an experimental model of COPD exacerbation

Judith JM Ceelen[1], Annemie MWJ Schols[1], Stefan J van Hoof[2], Chiel C de Theije[1], Frank Verhaegen[2], Ramon CJ Langen[1]

Maastricht University Medical Center, Maastricht, The Netherlands: [1]Department of Respiratory Medicine, [2]Department of Radiation Oncology (MaastRO)

Background: Exacerbations in chronic obstructive pulmonary disease (COPD) are often accompanied by pulmonary and systemic inflammation, and are associated with an increased susceptibility to and prevalence of weight loss and muscle wasting. We hypothesize that the cumulative effects of active loss of muscle mass during disease exacerbations and impaired muscle regrowth during stable disease underlies COPD-associated muscle atrophy. Therefore the aims of this study were to develop a model of COPD disease exacerbation and evaluate whether skeletal muscle mass changes can be monitored non-invasively.

Methods: Emphysema was induced by 3 weekly intra-tracheal (IT) elastase instillations followed by the induction of acute pulmonary inflammation (single bolus of IT-LPS, mimicking exacerbation). Using micro cone-beam CT-scans, emphysema development and changes in skeletal muscle mass were monitored non-invasively, and linked to muscle mass and cell and molecular analyses in skeletal muscle tissue.

Results: CT image analysis to assess lung emphysema after exposure to IT-elastase revealed a substantial decrease in lung voxel density, reflected by a marked increase in low-attenuation area (LAA%) (30.3% ± 2.2%) compared to PBS-treated mice (5.6% ± 1.3%). This LAA% correlated highly ($R^2 = 0.947$, $p > 0.001$) with the mean linear intercept, which is considered the golden standard to evaluate emphysema. 48h following administration of IT-LPS, a significant decrease in body weight (12.9% ± 1.4%) as well as skeletal muscle weight (11.5% ± 1.3%) and volume (13.7% ± 1.1%) was observed irrespective of the presence of emphysema. Muscle wet weights and CT-determined muscle volume correlated highly ($R^2 = 0.859$, $p > 0.001$). mRNA expression and protein levels of genes involved in the ubiquitin-proteasome pathway (UPS) and the autophagy-lysosomal pathway (ALP) were significantly upregulated 24 hours after IT-LPS.

Conclusion: These results demonstrate that IT-LPS administration in the elastase model evokes acute loss of muscle mass. Changes in lung tissue density and muscle volume can be monitored non-invasively to evaluate emphysema and muscle atrophy longitudinally.

This study was supported by a grant from the Lung Foundation Netherlands (3.2.11.036).

1-33

Mechanisms of impaired myogenesis in cancer-induced skeletal muscle atrophy

Domiziana Costamagna[1], Fabio Penna[2], Paola Costelli[2], Maurilio Sampaolesi[1,3]

[1]Translational Cardiomyology, Stem Cell Biology and Embryology, Department of Development and Regeneration, University Hospital

Gasthuisberg, Leuven, Belgium, [2]Department of Clinical and Biological Sciences, University of Turin, Italy, [3]Division of Human Anatomy, Dept. of Public Health, Experimental and Forensic Medicine, University of Pavia, Italy

Background and aims: Cancer cachexia is a syndrome frequently occurring in terminal cancer patients, causing fat and skeletal muscle weight loss and interfering with antineoplastic therapies. Lately, an impaired myogenesis has been pointed out as contributing to cancer-induced muscle depletion, increasing the number of activated myogenic precursors, likely unable to complete the regeneration in vivo (Penna et al., 2010). In addition to Satellite Cells (SCs), other cell populations are endowed with myogenic potential, such as mesoangioblasts (MABs), vessel-associated muscle progenitors (Sampaolesi et al., 2003). Recently, we demonstrated that BMP-SMAD-signaling blockade improves MAB myogenic differentiation. Interestingly, MABs isolated from the muscles of Smad8-LacZ mouse, a transgenic model where Smad8 expression is disrupted by LacZ gene insertion (Arnold et al., 2006), are more prone to differentiate in vitro into myotubes (Costamagna et al., 2015). Moreover, these mice exhibit a regenerative potential higher than wild-type animals, as shown by the increased myofiber cross sectional area, following cardiotoxin-induced muscle damage.
Methods: Different cell types isolated from the skeletal muscle of control (C) and adenocarcinoma C26-tumor bearing mice were induced to myogenic differentiation in vitro. The same cells were then injected into αSarcoglycan-null mice (αSG-null), to monitor by immunofluorescence and western blot their contribution in vivo to skeletal muscle regeneration.
Results: SCs isolated from C26 mice fully differentiate into myotubes in vitro, such as C, excluding a cell autonomous defect. Analogously, the myogenic potential of C26-MABs is comparable to C-MABs in vitro. Finally, C26-MABs, as C-MABs, implanted into the muscle of αSG-null mice, fuse and give rise to αSG+ myofibers.
Conclusions: The results demonstrate that C26-mouse myogenic compartment maintains the differentiation potential in vitro and in vivo. Further analysis will be needed to understand which of the skeletal muscle precursors is also involved in muscle regeneration and how they can interact during cancer-induced muscle wasting.

1-34

Sarcopenia evaluated by computerized tomography is common after chemotherapy in elderly lymphoma patients, and is related to inferior survival

Andrea Z. Pereira[1], Guilherme F. Perini[1], Sergio Simon[1], Auro Del Giglio[1], Juliana Todaro[1], Ronaldo Hueb Baroni[3], Fernanda M. Abatepaulo[3], Jairo Sobrinho[1]; Silvia M.F. Piovacari[2], Andreza A.F. Ribeiro[1], Nelson Hamerschlak[1]
[1]Oncology Department, Hospital Israelita Albert Einstein, S. Paulo, SP, Brazil, [2]Nutrition Department, Hospital Israelita Albert Einstein, S. Paulo, SP, Brazil, [3]Radiology Department, Hospital Israelita Albert Einstein, S. Paulo, SP, Brazil

Abstract: Introduction: Computerized tomography (CT) is considered the gold standard method for evaluating fat-free and fat mass and have emerged as an important predictor of outcome in cancer patients. Acquired images can define precisely components of body composition and weight changes, as well as help in the identification of patients at risk of developing cachexia. Elderly patients are at more risk of developing sarcopenia, related to decreased quality of life, treatment outcomes and increased chemotherapy complications.
Objectives: To evaluate fat free mass and visceral fat by CT in elderly lymphoma patients before chemotherapy and after at least 3 chemotherapy cycles, as well as its relation with survival. Material and Methods: We retrospectively studied 25 lymphoma patients, >65 years (mean: 77 ± 7years). CT Images were analyzed from Third Lumbar Vertebra before chemo and at least after 3 chemo cycles. A radiology technician blinded for outcome identified and quantified fat free mass and visceral fat.
Results: We found a significant reduction of fat free mass and an increase of visceral fat between baseline and after at least 3 chemo cycles ($p < 0{,}005$). Moreover, a positive relation between FFM and survival (in years) was observed ($p < 0{,}005$).
Conclusion: Body composition evaluation is very important in oncology patients, mainly in elderly ones. In our cohort, elderly patients developing sarcopenia had inferior survival outcomes. A better understanding of chemotherapy related body composition changes is important, as well as its impact on outcome. The impact of nutritional interventions in these patients should also be studied.

1-35

Prevalence and determinant factors of muscle wasting in hospitalized elderly Chinese

Xu Ling Jie[1], Xiao Qian[1], Cheng Wen[1], Luo Hui Qiong[1], Zhang Dong Ling[1], Miao Jing[2], Zhao Ke Xiang[1], Huang Yi Huan[1], Wang Xue Qin[1], Zhou Ling Shan[1]
[1]Department of Geriatrics, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Public Health School, Chongqing Medical University, Chongqing, China

Background and aims: The age-related skeletal muscle loss was associated with various adverse outcomes, and was strongly related to mortality and physical disability of older people, which denoted the concept of sarcopenia. The main purpose of this study was to research the prevalence of muscle wasting in hospitalized elderly people in China. Furthermore, we evaluated the relationship of skeletal muscle loss with its relevant factors.
Methods: Our research included 694 subjects (324 men and 370 women) who were examined using dual-energy X-ray absorptiometry. The prevalence of muscle wasting was defined separately using the cut-off values of the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia. We also evaluated the relationship of skeletal muscle loss with relevant factors.
Results: The prevalence of muscle wasting was 45.9% in men and 36.7% in women using the AWGS's definition, and it was 56.6% in men and 28.6% in women using the EWGSOP's definition. The difference in prevalence was significant in men but not in women using the two working groups' cut-off values. Multiple regression analysis showed that appendicular skeletal muscle mass/height^2

was associated with total skeletal muscle mass/height^2(TSM/height^2), BMI, android/gynoid fat ratio, thyroid-stimulating hormone, HDL-C, estimated visceral adipose tissue mass, body fat percentage, HbA1c and high-sensitivity C-reactive protein in men and with TSM/height^2, BMI, number of lymphocytes, prealbumin, HDL-C, body fat percentage and fasting blood glucose in women. **Conclusions:** The AWGS's cut-off values seemed to be more suitable for defining muscle wasting in China than the EWGSOP's. Relatively high weight and low levels of metabolism were protective factors against muscle wasting. Obesity, high blood glucose or diabetes, a poor nutritional state and a high inflammatory response level were risk factors for muscle wasting.

1-36

Improvement of muscle strength in frail elderly people by combination of electrical muscle stimulation and dietary supplementation with whey protein isolate, omega 3 fatty acids and polyphenols

Claire Boutry[1], Gerard Vinyes-Pares[2], Fabrizio Arigoni[3], Denis Breuillé[1], Toshio Moritani[4]
[1]Nestle Research Center, Nutrition and Health, Vers Chez les Blanc, Lausanne, Switzerland, [2]Nestle Research Center, Beijing, China, [3]Nestle Research Tokyo, Japan, [4]Laboratory of Applied Physiology, Graduate School of Human and Environmental Studies, Kyoto University, Japan

Age-related sarcopenia is defined by a decrease in muscle mass and function, resulting in a decrease of muscle strength, functional capacity and quality of life of elderly. The causes are multifactorial and one of them is the blunted response of muscle protein synthesis after meal ingestion also called "anabolic resistance". This metabolic disturbance could be related to insulin resistance, inflammation and oxidative stress. We tested a specific nutritional intervention aiming at restoring the anabolic effect of protein ingestion combined with electrical muscle stimulation (EMS).

Forty one frail elderly subjects (65 to 90 yo) were submitted to EMS twice a week and asked to daily ingest an isocaloric beverage (95 kcal) and capsules three times per day for 12 weeks. Subjects have been assigned to one of three groups: 1) 20 g of carbohydrate + placebo capsules (CHO, n = 13), 2) 20g of whey protein isolate + placebo capsules (WPI, n = 15) and 3) 20g of whey protein isolate + capsules containing rutin (500 mg.d^{-1}), omega 3 fatty acids (1.5 g.d^{-1}) and curcumin (500 mg.d^{-1}) (WPI+BIO, n = 13).

Left knee extension strength was 19% significantly improved in the WPI+BIO group compared to the CHO and WPI groups after 12 weeks of nutritional supplementation and EMS. The WPI+BIO group demonstrated the largest improvement in gait speed (10%) but this one was not significantly higher than in other groups. This benefit on muscle strength was not related to an increase in muscle size. There was no effect on body composition among the groups.

Thus, the combination of EMS and specific nutritional intervention with whey protein isolate, omega 3 fatty acids, rutin and curcumin improved muscle strength in frail elderly and tends to improve mobility (gait speed) and functionality that are important for maintenance of the quality of life of elderly people.

1-37

Skeleton Muscle Index in patients with chronic heart failure

Shuhei Tsuji, Yukihito Sato
Department of Cardiology, Hyogo Prefectual Amagasaki Medical Center, Amagasaki city, Hyogo, Japan

Background: Sarcopenia is a common complication in severe chronic heart failure (CHF). Patients with HF complicated with sarcopenia showed increased mortality, but its pathophysiology is not fully understood. Hence, this study aimed at identifying relationship between body composition such as skeleton muscle index (SMI), and blood samples such as brain natriuretic peptide (BNP) and amino acid concentration in HF patients.
Methods: We enrolled 31 patients (65% men, mean∓SD, age 72.5 ∓ 9.6 years, left ventricular ejection fraction 47 ∓ 16%, median BNP 126.8pg/ml) with stable CHF at Hyogo Prefectural Amagasaki Hospital. We collected blood samples from them and measured their body composition using InBody720, Bioelectrical Impedance Analysis (BIA). Patients with signs of acute heart failure, acute inflammatory processes, or undergoing artificial dialysis or coronary intervention within 6 months were excluded.
Results: Average SMI was 8.8 ∓ 1.4kg/m2. Patients with higher SMI was younger ($P < 0.001$), and had lower high-density lipoprotein (HDL) cholesterol ($P < 0.001$), and BNP ($P < 0.001$), and higher hemoglobin ($P < 0.001$), triglyceride ($P = 0.002$), estimate Glomerular Filtration Rate (eGFR) ($P = 0.009$), and Fischer ratio ($P < 0.001$). In the multivariable analysis, SMI was positively correlated with Fischer ratio (correlation coefficient (CC): 0.53, 95% confidence interval (CI): 0.05 ~ 1.01, $P = 0.003$) and negatively correlated with BNP (CC: −1.1, 95% CI: −1.7 ~ −0.6, $P < 0.001$) and HDL cholesterol (CC: −0.04, 95% CI: −0.06 ~ −0.02, $P < 0.001$).
Conclusions: In the patients with HF, SMI was paralleled with poor control of HF represented as a high BNP concentration. Thus, HF patients may have poor nutritional status and waste skeleton muscle.

1-38

Effects of low-loads medium intensity exercise on the proteome differential expression of the aged rat's skeletal muscle

Fang H. Li
School of Physical Education and Health, Zhao Qing University, Zhaoqing, China

Background and aims: The differential proteome expression map of rats'skeletal muscle between aging and exercise group was established to screen significant target protein response to low-loads

medium intensity exercise by means of proteomics, and filtrating out the objective proteins which exercise postpone sarcopenia.
Methods: Dividing 20 male Aged(18 month old) SD rats into exercise and parallel control groups at random(n = 10),the exercise group had a 8 weeks treadmill training with medium intensity (60% VO2max~75%VO2max), low-loads (15 min/days, 5 days/week), together with the control group, preparing for whole proteins samples of gastrocnemius, and separating the protein samples by utilizing two dimensional gel electrophoresis(2-DG), and analyzing image and collecting data by using PD Quest. The alternatively objective protein spots whose differential expression volume >2 folds were selected for elenzymologic extraction and MS/MS identification.
Result: There were 19 points expressed >1 fold. Taking out 6 whose differential expression volume >2 folds were selected for elenzymologic extraction and MS/MS identification, they were heat shock cognate 70kDa protein(HSC70), 26S protease regulatory subunit 6B(S6B), actin binding protein(Cofilin), aldehyde dehydrogenase 2 (ALDH2), α-ketoglutarate dehydrogenase complex(α-KGDH), membrane repair relative protein tripartite motif-containing protein 72(TRIM72).
Conclusion: 1) Using the methods of proteoimcs, the change of gastrocnemius protein in exercise rat s were identified. 2) We succeeded in filtrating 6 objective proteins which their expression volume had an adaptive changes, it indicated that low-loads medium intensity exercise may protect sarcopenia by regulation three pathways: (1) it could bring a series of well changes such as improving the aging skeletal muscle mitochondrial metabolizing enzymes, Cofilin, HSC70 which inhibit myocyte apoptosis; (2) it could downregulate S6B expression to inhibit protein degradation, which antagonizes the aged rat's skeletal muscle protein loss; (3) it could upregulate TRIM72 expression to improving the sarcopenia myocyte plasma membrane repair dysfunction.

1-39

Quantitative assessment of muscle in dogs using ultrasound

Lisa M. Freeman, James Sutherland-Smith, Lori R. Prantil, Amy F. Sato, John E. Rush
Tufts Cummings School of Veterinary Medicine

Background and aims: Cardiac cachexia occurs in >50% of pet dogs with naturally-occurring congestive heart failure (CHF), but muscle loss is difficult to quantify because most technologies (eg, CT, DEXA) require general anesthesia. Therefore, clinically relevant methods for quantifying muscle loss are needed. We previously validated an ultrasound method of quantifying muscle size in dogs of a single breed using CT as the gold standard. To further develop this ultrasound method, the goal of this study was to assess its feasibility and validity in other dog breeds, especially those predisposed to cardiac disease (eg, the Cavalier King Charles Spaniel, in which 80-90% of dogs develop mitral valve prolapse).
Methods: Pet dogs of 5 different breeds of varying sizes and body conformation were studied (n=10/breed). All were healthy and between 1-5 years old. Static ultrasound images were obtained and maximal transverse right epaxial muscle height and area at the level of the 13th thoracic vertebrae were obtained (mean of 3 measurements).
Length of the 4th thoracic vertebrae (T4) was measured from thoracic radiography. Ratios of the muscle height and area to vertebral length (height/T4 and area/T4, respectively) were calculated to account for differences in body size among breeds. Reproducibility testing was performed on 20% (n=10) of the dogs to determine inter-investigator, within-probe placement, and inter-probe placement variability.
Methods: Mean height/T4 = 1.00 ± 0.22 and mean area/T4 = 2.94 ± 1.47. There was no significant difference for height/T4 (P=0.42) among breeds, but breeds were significantly different in area/T4 ($P<0.001$). Reproducibility was significantly higher for height/T4 than for area/T4.
Conclusions: The ratio of epaxial muscle height to vertebral length (height/T4) was valid and reproducible for healthy dogs of different sizes and body conformation. Studies assessing this method in dogs with CHF and other diseases associated with muscle loss are warranted.

1-40

Prevalence and associated factors of frailty among adults and elderly in Brazil: Findings from the EPES study

Lidiane Isabel Filippin[1,2], Nathalia Cardoso de Oliveira[2], Magali Pilz Monteiro da Silva[2], Fernanda Miraglia[1], Vivian Nunes de Oliveira Teixeira[3], Ricardo Machado Xaiver[3]
[1]Mestrado em Saúde e Desenvolvimento Humano, Centro Universitário La Salle, Canoas, Brazil, [2]Faculdade de Fisioterapia, Centro Universitário La Salle, Canoas, Brazil, [3]Faculdade de Medicina, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil

Introduction: Frailty is considered to be highly prevalent with increasing age and to enhance risk for adverse health outcomes, including mortality, institutionalization, falls, and hospitalization. A number of definitions of frailty have been reported, in which three different domains have been used to construct frailty models: functional, deficit accumulation (burden) and biological/physiological.
Aim: Identification of the prevalence and indicators of frailty syndrome in residents of a municipality Vale do Rio dos Sinos, Brazil.
Methods: This is a cross-section study of the population of residents from the urban city of Nova Santa Rita. Individuals included had 40-80 years, of both gender (n=550), and signed a consent form. Data collection was conducted in an individual's home and followed a sample of 40% of each district elected randomly. The following variables were assessed: sociodemographic status, functional status (functional performance, cognitive status, physical activity level). The prevalence of frailty was estimated and logistic regression analysis was used to detect factors associated with fragility, presented as odds ratio and 95% confidence interval (CI95%).
Results: The prevalence of frailty in the study population was 32% (n=171), 34% female and 58% above 65 years. The factors associated to fragility in the model of logistic regression were: 1.91(1.02-3.58) for females, 1.72(1.00-2.97) for individuals above 65 years, 5.25 (2.15-12.83) for low income (<US$777.63). Low functional performance, evaluated by timed-up-and-go test, is responsible by 5.53 (3.09-9.89) and insufficient physical activity for 1.16(0.49-2.74). The history of falls and hospitalizations in the last 12 months answered by 2.31(1.29-4.14) and 3.89(1.54-9.84), respectively.

Conclusion: Our data showed high prevalence of frailty, whereupon risk factors are: female sex, above 65 years, low income and physical activity, history of falls and hospitalizations. Early detection of frailty is important to slow down the functional decline in these individuals with the perspective of prevention and promotion of active aging.

1-41

Sarcopenia, inflammation and malnutrition in cancer patients

Sílvia F. Mauricio, Maria Isabel T.D.Correia, Helem S. Ribeiro, Tínzia M. A. Carvalho
Universidade Federal de Minas Gerais, Hospital das Clínicas, Belo Horizonte, Minas Gerais, Brazil

Background: Researches suggest that sarcopenia is an inflammatory state driven by cytokines and oxidative stress which coexist with malnutrition in cancer patients. These impact muscle strength, functionality and physical performance as well as quality of life.
Objective: to assess the relationship of sarcopenia with inflammation and malnutrition in cancer patients.
Methods: This is an observational study of 229 cancer patients assessed before chemotherapy. Low muscle mass (sarcopenia) was defined as fat-free mass index (fat-free mass divided by the square of height). The cutoffs used were 17.5 (men) and 15.1 (women). Inflammation was determined when the level of C-reactive protein (CRP) was above 10 mg/L. Patients were classified according to the SGA as nourished (SGA A), suspected malnutrition or moderately malnourished (SGA B), or severely malnourished (SGA C) and, the latter two were assessed together for the purpose of comparisons. $P < 0.05$ was considered statistically significant.
Results: Most patients were women (70.4%) and had a mean age of 57.9 ± 13.1 years. Fifty five per cent of the patients presented with disease stage 3 or 4. Most patients were moderately malnourished or severely malnourished (59.6%) according to SGA. Thirty seven per cent of the patients were classified as sarcopenic. There was a statistically significant association between SGA categories and sarcopenia classification (chi-square = 36.6, $P < 0.05$). There was also a statistically significant association between inflammation and sarcopenia (chi-square = 6.6, $P < 0.05$).
Conclusion: Sarcopenia was associated with malnutrition and inflammation in cancer patients.

1-42

Systematic review and meta-analysis of the impact of computed tomography assessed skeletal muscle mass in patients awaiting or undergoing liver transplantation

Jeroen L.A. van Vugt[1*], Stef Levolger[1*], Ron W.F. de Bruin[1], Herold J. Metselaar[2], Jan N.M. IJzermans[1]
[1]Department of Surgery, division of HPB and transplant surgery, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Department of Gastroenterology, division of hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands
*Contributed equally to this study

Background and aims: Although liver transplant outcome has improved significantly, the shortage of human organs remains prevalent. Therefore, strict patient selection remains of paramount importance. Recently, low CT-assessed skeletal muscle mass was identified as a novel prognostic parameter to predict outcome in liver transplant candidates. Our aim was to perform a systematic review and meta-analysis on the association between CT-assessed muscle mass and outcome in liver transplant candidates.
Methods: A systematic search was performed according to the PRISMA-guidelines. Eligibility and quality assessment, and data-extraction were performed in duplicate. Meta-analyses were performed using fixed effects models. Overall effects were assessed using the Z-test and heterogeneity using the χ^2-test and I^2-statistics.
Results: Nineteen studies, including 3803 patients (65% male, mean age 52–62), fulfilled the inclusion criteria. Main indications for transplantation were viral infections, followed by alcoholic liver cirrhosis. Median MELD-score ranged from 9–21, albumin level 2.8-3.4 g/dl, and BMI 24.0-29.4 kg/m^2. Sarcopenia prevalence ranged from 30-70%. Nine studies reported the cross-sectional muscle area (CSA) with corresponding skeletal muscle index (SMI), whereas the psoas area (PA) and dorsal muscle group area were reported in nine and one study, respectively. The mean SMI ranged from 43.0-54.3 cm^2/m^2. Eleven of sixteen studies reporting long-term outcomes described an independent association between low muscle mass and survival. The pooled hazard ratio of sarcopenia for decreased overall survival was 2.10 (95%-CI 1.68-2.61, Z=6.61, $p<0.001$), particularly in patients with low MELD-scores. Less heterogeneity was observed for pooled data of studies using CSA rather than PA (I^2 26% versus 48%). No meta-analysis was performed for studies using continuous measures for muscle mass due to great heterogeneity. Less consistent evidence suggested a higher complication rate, particularly infections, in sarcopenic patients.
Conclusions: Sarcopenia impairs outcome in patients awaiting or undergoing liver transplantation. Skeletal muscle mass assessment may contribute to pre-transplant risk assessment.

1-43

Sarcopenia risk and affecting factors in 65-79 years-old living in city of Izmir District of Balcova

Erdem Erkoyun, Reyhan Ucku
Dokuz Eylul University Faculty of Medicine Department of Public Health, Izmir, Turkey

Introduction: This study aimed to determine the prevalence of sarcopenia risk and associated factors of this risk in community-dwelling 65-79 years-old individuals in Balcova district, Izmir.
Methods: In this cross-sectional study, a list of people living in Balcova was obtained from municipality to select483 individuals from target population.Two hundred fifty four people (52.6%) agreed to participate. Gait speed was measured on 4 m. Usual gait

speed lower than 0.8 m/s was accepted as low gait speed. A hydraulic hand-held dynamometer was used to measure grip strength. Having grip strength lower than 30 kg for men and 20 kg for women was accepted as low grip strength. The assessment was made at the individuals home or if desired work-place. Four conditions were identified as sarcopenia risk: Having low gait speed, having low grip strength, having both or being under sarcopenia risk according to European Working Group on Sarcopenia for Older People (EWGSOP) algorithm. A logistic regression model was used to predict sarcopenia risk.

Results: Forty five per cent of the participants had low gait speed49.8%had low grip strength, 30.1% had both low gait speed and low grip strength, 64.4% had sarcopenia risk according to EWGSOP algorithm. Main predictors of these risks were increasing age and being sedentary or under-active relative to being under-active regular or active.

Conclusion: This study suggests that sarcopenia risk is common among elderly in Balcova. As this risk predicts adverse health outcomes, primary and secondary preventive interventions and the effectivity of these interventions should be conducted. Increasing physical exercise levels of elderly in Balcova may be the first target for intervention.

1-44

Can sarcopenia predict post-operative outcomes in patients undergoing elective abdominal aortic aneurysm surgery?

Nikhil Shah[1], Priti Dutta[2], Toby Richards[3], Nick Schofield[4]
[1]University College London, London, UK, [2]Department of Radiology, Royal Free Hospital, London, UK, [3]Department of Surgery, University College London and Royal Free Hospital, London, UK, [4]Department of Anaesthesia, Royal Free Hospital, London, UK

Patients undergoing Abdominal Aortic Aneurysm (AAA) surgery are at significant risk of post-operative complications. Sarcopenia is the degenerative loss of core skeletal muscle mass and is a component of the frailty syndrome.

This study aimed to assess the impact of sarcopenia on post-operative outcomes after elective AAA surgery. To assess sarcopenia, cross sectional images from pre-operative CT scans were analysed by a single radiologist in a semi-automated fashion using PACS image software to determine total psoas muscle area (TPA)(mm2) at the L4 vertebral level. TPA was normalised for patient height (TPA/height squared (m2)), defining the L4 psoas muscle index (L4-PMI) (mm2/m2). Patients in the lowest L4-PMI quartile (n=35) were considered sarcopenic, and those in the upper three L4-PMI quartiles (n=103) non-sarcopenic. 138 patients undergoing elective endovascular (n=132,95.7%) or open repair (n=6,4.3%) of an AAA were analysed. Age and height did not differ significantly. Median hospital length of stay (LOS,days) was 7(IQR 5-13.5) and 5(IQR 3-8)(p=0.004), and median Intensive Care LOS was 2.5(IQR 1-4.25) and 2(IQR 1-2.25) (p=0.038) in sarcopenic and non-sarcopenic patients respectively. 7 patients (20.0%) in the sarcopenic group required secondary operations compared to 8 patients (7.8%) in the non-sarcopenic group (p=0.045). In both the sarcopenic and non-sarcopenic groups 6 patients required further care, representing 17.1% and 5.8% of their respective patient populations (p=0.04). Similar rates of post-operative complications were found between both groups, with 13 sarcopenic patients (37.1%) suffering complications compared to 35 non-sarcopenic patients (34.0%)(p=0.734). Two sarcopenic patients (5.7%) died within a year post-operatively, compared with 3 non-sarcopenic patients (2.9%)(p=0.444).

Our study shows that sarcopenic patients undergoing elective AAA repair have worse outcomes than non-sarcopenic patients, with significantly longer length of stay, higher rates of secondary operations and further care required. Measuring psoas muscle area is a simple way of objectively identifying frailty as a predictor of poorer outcomes in aortic patients.

1-45

Indexes of voice quality as new tools for the diagnosis of sarcopenia and muscle weakness

Tiziana Montalcini, Yvelise Ferro, Rosa Terracciano, Francesco Provenzano, Giovanna Piazzetta, Rocco Savino, Nicola Lombardo, Arturo Pujia
Pole of Innovation, health technology - Biotecnomed, University Magna Grecia, Catanzaro, Italy

Background: Reduced muscular strength is a feature of sarcopenia. Several investigation suggested a relationship between sarcopenia and voice disorders but sarcopenia is often an undiagnosed condition. Furthermore a relationship between muscular strength and parameters of voice quality has not been yet investigated. The aim of this study was to investigate the relation between Handgrip strength and indexes of vocal function.

Methods: We performed a cross-sectional study using a convenience sampling method. One hundred and twenty nine university students volunteers, 37 community-dwelling individuals and 32 institutionalized individuals aged 65 years and older participate in the study. Handgrip strength, maximal phonation time, noise- to-harmonic ratio and other voice quality parameters were measured.

Results: In males, the univariate and multivariate linear regression analysis showed that noise -to-harmonic ratio was negatively (model I) and maximal phonation time was positively (model II) associated to Grip Strength (p=0.015 and B=-148; p=0.001 and B=0.45 respectively). Maximal phonation time was significant different between all categories in both gender. In males the area under the ROC curve for maximal phonation time to predict the presence of a high Handgrip strength was 0,86 (SE= 0,04; p= 0,001) and in females was 0,92 (SE= 0,02; p= 0,001). In males a maximal phonation time equal to 17 sec achieved satisfactory sensitivity (71%) and high specificity (94%) while in females of 11 sec achieved adequate sensitivity (74%) and excellent specificity (100%) to predict a high HGS.

Conclusion: We find, for the first time, an association between a parameter for the diagnosis of sarcopenia and voice quality indexes. In particular, maximal phonation time predicts a reduced muscular strength in both gender. Thus, maximal phonation time may

represent a useful and universally tool for the early identification of muscle weakness and sarcopenia probably also for the self-test.

1-46

Prevalence of sarcopenia in patients with acute ischemic stroke and during early post-stroke rehabilitation

Nadja Scherbakov[1,2], Michael Knops[1], Anja Sandek[3], Nicole Ebner[3], Miroslava Valentova[3,4], Stephan von Haehling[3], Stefan D. Anker[3], Karl Georg Haeusler[1,5], Michael Joebges[6], Wolfram Doehner[1,7]
[1]Center for Stroke Research CSB, Charité - Universitätsmedizin Berlin, Germany, [2]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Germany, [3]Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Göttingen, Germany, [4]1st Department of Internal Medicine, Comenius University, Bratislava, Slovak Republic, [5]Department of Neurology, Charité - Universitätsmedizin Berlin, Germany, [6]Department of Neurology, Brandenburgklinik Bernau, Germany, [7]Department of Cardiology, Charité - Universitätsmedizin Berlin, Germany

Introduction: The prevalence of age-related sarcopenia between 3 and 52% has been reported. The prevalence of sarcopenia is investigated in chronic heart failure, chronic obstructive pulmonary disease, and chronic kidney disease. The aim of the present study was to determinate the prevalence and trends of sarcopenia in patients with cerebral stroke.
Methods: 120 patients with acute ischemic stroke (AIS) (mean ± SD: age 67 ± 13y, BMI 27.3 ± 5.6kg/m^2, 4 ± 2 days post-stroke, d.p.s.) and 120 patients with ischemic or hemorrhagic stroke at admission (70 ± 10y, 26.8 ± 4.9kg/m^2, 21 ± 14d.p.s.) and at discharge (48 ± 17d.p.s.) from post-stroke rehabilitation were studied. 25 healthy subjects of similar age and BMI were included as controls. Skeletal muscle mass (SMM) and fat mass were assessed by bioelectrical impedance assessments (BIA). Muscle strength was assessed by handgrip strength test. Sarcopenia was defined according to the European consensus definition: low SMM (skeletal mass index < 37.0% in males, <27.6% in females) and low muscle strength (<30 kg in males, <20 kg in females). Obesity was considered as fat mass >27% in males and >38% in females.
Results: The prevalence of sarcopenia was 14% in the patients with AIS and 22.5% at admission to post-stroke rehabilitation. At discharge the prevalence decreased to 16%. All of sarcopenic patients with AIS and at discharge as well as 18% of the patients at admission were obese. Reduced handgrip strength was observed in 24% of the patients with AIS vs. 36% of the patients at admission ($p<0.05$), compared to 27.5% of patients at discharge (n.s.). At discharge 32.5% of patients were presented with low SMM compared to 53% of patients at admission and to 55% of patients with AIS ($p<0.001$).
Conclusion: The prevalence of sarcopenia increased in subacute stroke. Loss of muscle strength played a crucial role in the development of sarcopenia. Sarcopenic stroke patients were presented mainly with sarcopenic obesity.

1-47

Sarcopenia in adult polycystic kidney disease (APCKD) organomegaly: A CT scan body composition analysis

Oroog Ali[1], Zergham Zia[2], Aurangzaib Khawaja[1], Robert Jones[2], Nicholas Inston[1]
[1]Department of Renal Surgery, The Queen Elizabeth Hospital Birmingham, Birmingham, UK, [2]Department of Radiology, The Queen Elizabeth Hospital Birmingham, Birmingham, UK

Background and aim: Patients with APCKD commonly develop marked abdominal distension secondary to massively enlarged kidneys. The organomegaly may give a deceptive physical appearance masking a state of nutritional compromise. Markers of nutritional status including body weight and body mass index (BMI) are unreliable due to raised organ mass. Skeletal muscle mass as a marker of nutritional status has been used in patients being assessed for surgery and may be calculated from pre-operative CT scans. The aim of this study is to assess the body composition of APCKD patients with organomegaly using CT body morphometry.
Methods: Using standard techniques for CT body composition assesment, a retrospective review was carried out on patients referred for consideration of polycystic nephrectomy. Pre-operative CT imaging were quantified and lumbar skeletal muscle index (L3 SMI) calculated. This was compared to standard cut offs where sarcopenia is defined as an L3 SMI <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women. Measures of BMI and body weight were also determined.
Results: CT scans which were identified in 17 patients with APCKD with organomegaly were analyzed (m=6:f=11). The mean weight and BMI for males was 82.7 kg +/−13.5 and 26.0kg/m^2 +/− 3.4 respectively. For the female group, 69.0kg +/−12.9 and 27.1 kg/m^2 +/−5.9. Using WHO criteria this would be classified as overweight. The mean L3 SMI for male was 45.5 cm^2/m^2 +/−10.99 and females 41.5 cm^2/m^2 +/−8.97 with sarcopenia identified in 5 males (83.3%) and 5 females (45.5%).
Conclusions: Sarcopenia is prevalent in APCKD patients despite being classed as overweight on BMI. The mechanisms of sarcopenia may be due to early satiety from a mass effect or due to chronic inflammatory mechanism, recurrent infections and renal failure. Identifying sarcopenia in APCKD patients may allow dietary intervention particularly prior to nephrectomy.

1-48

Prevalence of sarcopenia and classification agreement according to different operational definitions

Andrea Trombetti, Mélany Hars, Emmanuel Biver, Thierry Chevalley, Serge Ferrari, René Rizzoli
Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Background and aims: Sarcopenia is a devastating feature of aging associated with extensive burden. However, consensus on an

operational definition has not been reached yet. In a homogenous cohort of 68-year old community-dwellers, we applied different criteria and cutpoints to evaluate disease prevalence and classification agreement according to various operational diagnostic criteria, as proposed by the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWG), and the Foundation for the National Institutes of Health Sarcopenia Project (FNIH).

Methods: Seven hundred sixty-seven subjects (608 women; age 67.9 ± 1.5 years), enrolled in the Geneva Retirees Cohort (GERICO), were studied. Appendicular lean mass (ALM), ALM/height^2 and ALM/BMI ratios were determined by DXA. Gait speed was measured over 4 meters and grip strength using a handheld dynamometer. Sarcopenia prevalence was estimated using EWGSOP, IWG and FNIH proposed criteria, and degree of agreement assessed using kappa statistics.

Results: Low lean mass prevalence ranged from 3.8% (FNIH) to 16.0% (EWGSOP). Weakness prevalence ranged from 0.7% (FNIH) to 3.9% (EWGSOP). Prevalence of low lean mass combined with either weakness or slowness fulfilling various proposed sarcopenia definitions was the lowest for FNIH (0.3%) compared with IWG (1.2%) and EWGSOP (1.6%) criteria, with higher prevalence in women across all definitions. There was poor agreement between the groups identified according to the different definitions (kappa values below 0.3).

Conclusions: Our results obtained in a large cohort of 68-year old subjects indicate that the prevalence of sarcopenia is low at that age independently of the definition. They also suggest that muscle weakness, slowness and low lean mass prevalence widely vary depending on the criteria and cutpoints applied. Similarly, sarcopenia prevalence considerably varies according to the definitions, with poor agreement between classifications. Further studies should compare the predictive ability of candidate sarcopenia criteria for hard outcomes.

1-49

Financial impact of sarcopenia on hospitalization costs

Ana S. Sousa[1], Rita S.Guerra[2,3], Isabel Fonseca[4], Fernando Pichel[4], Susana Ferreira[5], Teresa F. Amaral[1,3]

[1]Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto, Porto, Portugal, [2]Departamento de Bioquímica da Faculdade de Medicina, Universidade do Porto, Porto, Portugal, [3]UISPA-INEGI, Faculdade de Engenharia, Universidade do Porto, Porto, Portugal, [4]Serviço de Nutrição e Alimentação, Centro Hospitalar do Porto, Porto, Portugal; [5]Centro Hospitalar do Porto, Porto, Portugal

Background and aims: Data on the association of sarcopenia with costs among hospitalized patients are limited to surgical patients. This study aims to increase knowledge regarding the association of sarcopenia with these costs among a wide-ranging sample of surgical and non-surgical patients.

Methods: A prospective study was conducted among hospitalized adult patients. Sarcopenia was identified according to the European Working Group on Sarcopenia in Older People, as low muscle mass, assessed by bioelectrical impedance analysis and low muscle function evaluated by handgrip strength. Hospitalization cost was calculated for each patient based on discharge diagnosis related group codes. Costs were defined as the percentage of deviation from the cost of a patient with a relative weight equal to one. Multivariable linear regression models were performed to identify if sarcopenia and if sarcopenic overweight were independently associated with hospitalization costs.

Results: Study sample is composed of 656 hospitalized patients aged ≥18 years, 24.2% were sarcopenic. Sarcopenia increased hospitalization costs by €1240 (95% CI: €596-1887) for patients aged <65 years and by €721 (95% CI: €13-1429) for those aged ≥65 years. Sarcopenic overweight was related to an increase in hospitalization costs of €884 (95% CI: €295-1476).

Conclusions: Sarcopenia independently increases hospitalization costs by 58.5% for patients aged <65 years and 34% for patients aged ≥65 years. The present results show the financial burden of this condition in adult and older adult hospitalized patients.

1-50

Sarcopenia predicts fracture risk in 65-year old healthy community-dwellers

Andrea Trombetti, Mélany Hars, Emmanuel Biver, Thierry Chevalley, Serge Ferrari, René Rizzoli

Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Background and aims: Sarcopenia is associated with an increased risk of adverse outcomes. However, the contribution of low skeletal muscle mass to fracture risk remains unknown. In this study, we investigated the prevalence of low lean mass and its association with 3-year fracture incidence in a homogeneous cohort of healthy 65-year old community-dwellers.

Methods: Nine hundred thirteen subjects (729 women; 65.0 ± 1.4 years), enrolled in the GERICO study, were prospectively followed-up. Total (TLM) and appendicular (ALM) lean masses were assessed using DXA. The thresholds proposed by Baumgartner, the European Working Group on Sarcopenia in Older People (EWGSOP 1 and 2), the International Working Group on Sarcopenia (IWG), and the Foundation for the National Institutes of Health (FNIH) were applied. Low trauma clinical fracture incidence over a 3-year period was recorded. The associations were assessed using univariate and multivariate logistic regression models.

Results: During an average follow-up of 3.4 ± 0.9 years, 40 (4.4%) subjects sustained at least one incident low trauma fracture. Baseline low lean mass prevalence ranged from 3.5% (FNIH) to 17.1% (EWGSOP 2 or IWG). ALM and TLM were lower in subjects with incident fractures compared to those without fractures ($p<0.02$ and $p<0.04$, respectively). After adjusting for sex, age, length of follow-up and FRAX probability with BMD, low lean mass was associated with a 2.3 (CI95%: 1.0-5.1; $p<0.05$) (Baumgartner or EWGSOP 1) and 1.3 (CI95%: 0.6-2.7; ns) (EWGSOP 2 or IWG)-fold increase in

low trauma fracture risk. No patient with FNIH low lean mass criteria experienced any low trauma fracture.
Conclusions: Our results show that low appendicular lean mass, as defined with Baumgartner or EWGSOP 1 threshold, is a predictor of incident fractures in a large cohort of 65-year old community-dwellers, independently of FRAX score. Whether assessing in addition muscle function improves low trauma fracture risk prediction remains to be determined.

1-51

Comparison of the Sarc-F definition and the FNIH sarcopenia defintion. Results from a large cross-sectional population-based EPIDOS study

Charlotte Dupuy[1,2], Gabor Abellan van Kan[1,2], Bruno Vellas[1,2], Yves Rolland[1,2]
[1]Gérontopôle de Toulouse, CHU Toulouse, [2]INSERM 1027, France

Objective: There is still a lack of the universal diagnostic criteria for sarcopenia. Recently, two definitions were proposed: 1-the SarcoFNIH definition: FNIH experts have determined and suggested different clinical criteria as Grip Strength (GS) and Appendicular Skeletal Muscle mass (ASM) adjusted for Body mass Index (BMI) (for women: GS$<$16kg and ASM/BMI$<$0.512);[1] 2- the sarc-F based on composite score varying from 0 to 10 (sarcopenic if the score $\geq$4) included 5 self-reported items (regarding the ability to walking, rising from a chair, climbing stairs, lifting an heavy object, falls with possible answers no, a little, a lot).[2] Our objective was to compare these 2 definitions and to evaluate their association with functional performances tests (knee extension strength, gait speed, repeated chair stand test) at baseline.
Methods: 3025 community-dwelling women (mean age 80.5 ± 3.9 years) at inclusion, from the Toulouse and Lyon EPIDOS study. A multiple linear regression models were built for each functional performance and the predictive capacity of sarcopenia (one model for each definition) was assessed using the adjusted R^2.
Results: In our study, the sarc-F definition affected 16.7 % (n=504) of the elderly women however the sarcoFNIH involved only 1.8% (n=49). All sarcopenic women defined by both definitions had significantly lower functional performance than non sarcopenic women (except for the sarc-F and the repeated chair stand test). Based on our statistical approach, in spite of the significant association and the improvement of model fit, the sarc-F only significantly improved the predictive capacity of the reference model (difference in adjusted R^2 varied between 7.5 and 9.6%).
Conclusions: Compared to the sarcoFNIH definition, the sarc-F increment significantly the predictive value of clinical characteristics to predict knee extension strength, gait speed and repeated chair stand test.

References
1. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, et al., The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-558.
2. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle. 2014 Dec;5(4):253-259.

1-52

Sarcopenia is predictive of major cardiovascular events in older men – prospective STRAMBO study

Pawel Szulc, Roland Chapurlat
INSERM UMR 1033, University of Lyon, Hospices Civils de Lyon, Lyon, France

Background and aims: Sarcopenia is associated with high mortality. Data on the association between sarcopenia and cardiovascular risk in men are scanty. We assessed the association between baseline muscle mass and risk of incident major cardiovascular event in a cohort of 795 home-dwelling men aged 60 and over.
Methods: Body composition was assessed by dual X-ray absorptiometry (Hologic Discovery A). Relative appendicular skeletal muscle mass (RASM) is the sum of lean mass of four limbs divided by (height)^2. Incident major cardiovascular event was defined as acute coronary syndrome (myocardial infarction, coronary insufficiency with or without ST-T elevation confirmed by angiography), stroke or sudden death. During the median follow-up of 7.8 years, 82 men sustained major cardiovascular events. We used Cox model adjusted for age, central fat, physical activity, current smoking, co-morbidities, aortic calcification, blood pressure, treatments, and serum levels of osteoprotegerin, C-reactive protein, FGF23 and 25-hydroxycholecalciferol.
Results: The incidence of major cardiovascular events increased from 6% in the upper RASM quartile ($>$8.8 kg/m^2) to 13% in the lowest quartile ($<$7.6 kg/m^2) (trend p$<$0.05). After adjustment for confounders, the incidence of cardiovascular events increased with decreasing RASM (HR = 1.52 per SD, 95%CI: 1.17–1.96, $p < 0.005$). Their incidence was higher in the second quartile (HR = 2.38, 95%CI: 1.07–5.29, $p < 0.05$) and in the lowest quartile (HR = 4.07, 95%CI: 1.79–9.28, $p < 0.001$) vs. the upper quartile. Grip strength was not associated with cardiovascular risk and adjustment for grip strength did not change the results. Hypertensive men with low RASM (lowest quartile) had higher cardiovascular risk (HR = 13.50, 95%CI: 3.37–54.08, p$<$0.001) vs. normotensive men with high RASM (upper quartile). Diabetic men with low RASM had higher cardiovascular risk (HR = 22.40, 95%CI: 5.47-97.76, p$<$0.001) vs. non-diabetic men with high RASM.
Conclusions: Our data suggest that sarcopenia is an independent indicator of cardiovascular risk in older home-dwelling men.

1-53

Does sarcopenia affect the mass and strength of suprahyoid muscles?

Nami Machida, Haruka Tohara, Shunsuke Minakuchi
Department of Gerontology and Gerodontology, Tokyo Medical and Dental University, Japan

Background: Sarcopenia causes the decrease of the swallowing muscle mass and strength.

There were a few reports about the effect of sarcopenia on tongue pressure, but there were no reports about suprahyoid muscles.
Mylohyoid muscle is one of suprahyoid muscles and is involved in both jaw-opening and elevating hyoid bone during swallowing.
In this study, we conducted how sarcopenia affects the mass and strength of mylohyoid muscle.
Material and Methods: 29 elderly men (80.5 ± 5.5years) were enrolled in this study. Participants who had dementia and neurodegenerative diseases were not included.
According to the Asian Working group for sarcopenia, participants were divided into a sarcopenia group and a non-sarcopenia group. We compared mylohyoid muscle mass and strength between 2groups. The muscle mass was defined by the thickness by using an ultrasound (SONIMAGE P3) and the strength was measured by using a jaw-opening sthnometer. The data was analyzed by using Mann-Whitney Utest.
Results: The average muscle thickness and strength were 5.9 ± 1.1mm and6.5 ± 1.8kg (non-sarcopenia group) and 4.8 ± 0.1mm and 4.7 ± 1.3kg (sarcopenia group).
Both of the mass and strength were significantly lower in sarcopenia group ($p<0.05$).
Discussion: This study shows that sarcopenia can cause the decrease both of the mass and strength of mylohyoid muscle. Ultrasound was an innovative and portable method. It will be a useful method for measuring swallowing muscle mass near future.
This study was preliminary. Future studies are needed whether sarcopenia also decreases the mass and strength of other swallowing muscles, and clarify the association between the mass and strength.

1-54

Computed tomography scans in ICU patients with acute lung injury reveal the sarcopenic skeleton in the ICU closet cloaked in adiposity and undetected by Subjective Global Assessment

Sarah J. Peterson[1], Patricia M. Sheean[2], Urvi Taylor[3], Joy S. Sclamberg[3], Omar B. Lateef[4], Carol A. Braunschweig[5]
[1]Department of Food and Nutrition, Rush University Medical Center, Chicago, IL, USA, [2]Marcella Niehoff School of Nursing, Loyola University, Maywood, IL, USA, [3]Department of Diagnostic Radiology and Nuclear Medicine, Rush University Medical Center, Chicago, IL, USA, [4]Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA; [5]Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL, USA

Background and aims: The objective of the current study is to describe the prevalence of sarcopenia and determine the agreement between subjective global assessment (SGA) in ICU patients with acute lung injury (ALI).
Methods: Patient met inclusion criteria for our prospective randomized feeding trial (INTACT) and had a computed tomography (CT) scan of the third lumbar (L3) region within 7 days of ALI diagnosis. Dosing body weight was recorded. Patients were categorized as normal nourished or moderate/severely malnourished by SGA. Cross-sectional muscle area (cm^2) was computed from L3 CT scans by summing muscle tissue pixels (Hounsfield Units of -29 to +150) and multiplying by pixel surface area. Skeletal muscle index (SMI, cm^2/m^2) was calculated; sarcopenia was defined as SMI$\leq$ 38.5 for women and $\leq$52.4 for men. Estimated whole-body fat free mass (EFFM, kg) was calculated from an equation reported by Mourtzakis, et al; difference in dosing weight and EFFM was calculated.
Results: 95 patients met inclusion criteria; 46/95 were categorized as normal nourished by SGA and 73/95 were classified as sarcopenic by CT scans. 72% of patients classified as normal nourished by SGA were categorized as sarcopenic by CT scans; of these 61% were overweight/obese. Sarcopenic patients had a higher disparity between dosing weight and EFFM compared to non-sarcopenic patients (30.7 ± 9.5 vs. 20.3 ± 7.7 kg, $p < 0.01$).
Conclusion: The inability to detect muscle wasting and the large difference between dosing weight and EFMM in sarcopenic patients has profound clinical implications for excessive prescription of nutrition support and medications that rely on weight-based dosing as an estimate of lean body mass. The current skeleton in the ICU closet appears to be cloaked in plain sight with excess adiposity.

1-55

Sarcopenia, balance and risk of falling in a sample of Portuguese community-dwelling older adults

Beatriz Fernandes[1], Maria Teresa Tomás[1], Diogo Quirino[2]
[1]Lisbon School of Health Technology – IPL, Lisboa, Portugal, [2]Casa de Santa Maria – AAPHSM, Loures, Portugal

Background and aims: Given the growing aging index, Portuguese population is particularly exposed to a higher risk of falls, which is related to decreased levels of lower limbs muscle mass and strength. These factors are consequence of sarcopenia which has been associated with higher risk of falling. Handgrip strength is a clinical marker of risk of disability and cut-off points for defining sarcopenia through handgrip strength have been identified. The purpose of this study was to characterise the risk of falls and related factors in community-dwelling older adults.
Methods: The sample consisted of 128 community-dwelling older adults (95 women, 33 men), aged 65–97 years, apparently healthy. Outcome measures were Berg Balance Scale (BBS) to assess the risk of falling, 30s chair stand test for lower limbs strength, 8-foot up and go test for mobility and handgrip strength with the dynamometer Jamar®.
Results: BBS values were above cutt-off points for risk of falling, meanwhile scores from the other tests showed lower values comparatively to other similar populations. 36% reported at least one fall in the past year. Lower limbs strength was lower for fallers and this was different (p = 0,023) from non-fallers. 21.2% of males and 24.2% of females showed values of handgrip strength lower than cut-off points for risk of sarcopenia.
Conclusions: Although the risk of falling in this sample is not increased, strength, lower limbs strength and mobility are decreased. This study reinforces the evidence that lower limbs muscle strength is lower in fallers than in non-fallers, which is described as a risk factor for falling. Assessment of these factors seems to be recommended in order to design rehabilitation programs as

countermeasures for further muscle and functional deterioration and consequently decrease risk of falling.

1-56

Prevalence and clinical implications of sarcopenic obesity among community-dwelling older adults: Results from Taichung community health study for elders

Yen-Ting Chen[1,2], Chia-ing Li[3], Tsai-Chung Li[4,5,6], Chih-Hsueh Lin[1,7], Chiu-Shong Liu[1,3,7], Cheng-Chieh Lin[1,3,4,7,8]

[1]Department of Family Medicine, China Medical University & Hospital, Taichung, Taiwan, [2]Department of Public Health, College of Public Health, China Medical University & Hospital, Taichung, Taiwan, [3]Medical Research, China Medical University & Hospital, Taichung, Taiwan, [4]Institute of Health Care Administration, College of Public Health, China Medical University & Hospital, Taichung, Taiwan, [5]Biostatistics Center, China Medical University & Hospital, Taichung, Taiwan, [6]Graduate Institute of Biostatistics & Chinese Medicine Science, China Medical University & Hospital, Taichung, Taiwan, [7]Department of Family Medicine, College of Medicine, China Medical University & Hospital, Taichung, Taiwan, [8]Department of Healthcare Administration, College of Health Science, Asia University, Taichung, Taiwan

Background and aims: Recent evidence shows that sarcopenic obesity might related to more physical functional decline, higher risk for metabolic syndrome and higher mortality. However, due to lack of a standard definition of sarcopenic obesity, the prevalence differs substantially among current studies. The aim of the present study was to examine the prevalence of sarcopenic obesity among community-dwelling older adults in Taiwan, by using different indices, and its relationship with obese group.

Methods: This population-based, cross-sectional study recruited 865 participants aged 65 years or older. Participants who meet both criteria for sarcopenia and obesity were classified as having sarcopenic obesity. Sarcopenia was defined according to the Asian Working Group for Sarcopenia consensus criteria, and sarcopenic participants with low height-adjusted or weight-adjusted appendicular skeletal muscle mass (ASM) were classified as having h-sarcopenia or w-sarcopenia, respectively. Lean soft tissue mass and fat mass were determined by dual- energy X-ray absorptiometry. Obesity was defined as body-mass index (BMI) > 25 Kg/m^2.

Results: Of the 865 participants initially identified, the prevalence of nonsarcopenic nonobese, nonsarcopenic obese, sarcopenic nonobese, and sarcopenic obese was 55.8%, 27.4%, 5.8% and 11.0% respectively. All participants with h-sarcopenic obesity (N = 14) also meet criteria of w-sarcopenic obesity. The present study revealed older adults with sarcopenic obesity are more aged, higher BMI, more central obesity, less total body learn muscle mass, and higher risk of metabolic syndrome than normal, sarcopenia-only, or obesity-only population. However, the sarcopenic obesity population has better physical performance and better bone marrow density than sarcopenia-only population.

Conclusions: We suggested using weight-adjusted skeletal muscle index might be more properly than height-adjusted in evaluation of sarcopenic obesity groups among Asian people.

1-57

Relationships between sarcopenia and sarcopenic obesity with disability in community dwelling older men: The Concord health and ageing in men project

Vasant Hirani[1], Vasi Naganathan[1], Fiona Blyth[1], David Le Couteur[2], Robert Cumming[3]

[1]Centre for Education and Research on Ageing, Concord Hospital, University of Sydney, New South Wales, Sydney, Australia, [2]ANZAC Research Institute & Charles Perkins Centre, University of Sydney, New South Wales, Sydney, Australia, [3]School of Public Health, University of Sydney, New South Wales, Sydney, Australia

Background and aims: Sarcopenia and sarcopenic obesity, age-related changes in body composition, are increasingly recognised as a major clinical problem for older people. The aims of this study were to explore the cross-sectional and longitudinal associations between sarcopenia and sarcopenic obesity with activities of daily living (ADL) and instrumental ADL (IADL) disability among community-dwelling older men participating in the Concord Health and Ageing in men project (CHAMP), using recently developed definitions for sarcopenia from the Foundation for the National Institutes of Health (FNIH).

Methods: 1678 men aged 70 years and older had baseline (2005-2007) body composition measures by dual-energy x-ray absorptiometry (DEXA). 1314 men came for the 2-year follow-up and 917 men returned for the five year follow-up. The main outcome measures were ADL and IADL disability. The independent variables were sarcopenic obesity, obesity without sarcopenia and sarcopenia without obesity (with no sarcopenia/obesity as the referent category). Sarcopenia was defined as $<$19.75 kg of appendicular lean mass (ALM), using the FNIH criteria. Obesity was defined as total body fat $>$30.7% (i.e. the upper two quintiles of the study population). Logistic regression models were used to assess baseline associations with ADL and IADL disability. Generalized estimating equations (GEE) were used to examine the longitudinal associations between repeated assessments of sarcopenic obesity, obesity alone and sarcopenia alone and ADL and IADL disability.

Results: At baseline, 9.0% (n = 151) of men had sarcopenic obesity, 15.6% (n = 262) of men had sarcopenia alone, 30.9% (n = 519) of men had obesity alone and 44.5% (n = 746) of men had neither sarcopenia nor obesity. Fully adjusted analyses revealed that obesity alone was not associated with ADL or IADL disability at baseline or longitudinally. In contrast, sarcopenia alone and sarcopenic obesity were associated with a higher prevalence of ADL and IADL disability at baseline. Furthermore, there were significant longitudinal associations between sarcopenia alone and sarcopenic obesity with ADL disability in unadjusted, age adjusted and fully adjusted analysis, but no longitudinal associations between these measures and IADL disability after adjusting for age.

Conclusions: In community-dwelling older men, sarcopenia and sarcopenic obesity are risk factors for the development of ADL disability.

1-58

Prevalence of sarcopenia in adult obese patients

Rosa Sammarco[1], Maurizio Marra[1], Valeria Amato[1], Eliana De Rosa[1], Michele Onufrio[1], Franco Contaldo[1,2], Fabrizio Pasanisi[1,2]
[1]Department of Clinical Medicine and Surgery, Federico II University Hospital, [2]Interuniversity Centre for Obesity and Eating Disorders, (CISRO), Naples, Italy

Backgrounds and aims: Sarcopenic obesity is a condition where fat mass (FM) excess and muscle mass depletion coexist and it's usually described in the elderly. Our study aims to evaluate the prevalence of sarcopenia in adult obese outpatients, using BIA and three indexes of body composition as screening tools.
Methods: We studied 1994 subjects, 758 men (age 33 ± 12 years; weight 133 ± 25.3 kg, BMI 43.7 ± 8.06 kg/m^2, fat free mass (FFM) 75.5 ± 12.0 kg, FAT 57.6 ± 17.7 kg, PFAT 42.5 ± 6.6 %) and 1236 women (age 34 ± 12 years, weight 112 ± 22.2, BMI 43.9 ± 8.02 kg/m^2, FFM 55.8 ± 9.12 kg, FAT 55.9 ± 15.2kg, PFAT 49.5 ± 4.97%) divided in five age groups: 1) ≤ 20 years, 2) > 20–30 years, 3) > 30–40 years, 4) > 40–50 years, 5) > 50 years. Sarcopenic obesity was defined with trhee different criteria: 1) FM > 38.4% in women and > 26.5% in men; 2) FM index > 7 kg/m^2 in men and > 10.6 kg/m^2 in women; 3) lean body mass was < 90% of the subjects ideal fat free mass for both sexes.
Results: Based on FM and FM index, all patients met the definition of sarcopenic obesity. Based on criteria 3(FFM/FFM ideal) 28.9% of men and 43.6 % of women were defined sarcopenic obese. Both in man and women, the relationship between age and prevalence of sarcopenia was not linear: in particular, in men the highest prevalence of sarcopenia was observed in group 1 (52.4%) whereas the lowest prevalence of sarcopenia was observed in group 4 (16.1%); in women the highest prevalence of sarcopenia was in group 1 (52.4%) whereas the lowest prevalece of sarcopenia was reported in group 4 (32.1%).
Conclusion: Sarcopenia rates vary widely, based on different definitions. According to ideal fat free mass, we observed that the prevalence of sarcopenic obesity decreased with the age, both in men and women, from young age to middle age group < 50 years. Anyway the diagnosis of sarcopenia needs to be confirmed with functional data on muscle strenght.

1-59

Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis

Gotaro Kojima
Japan Green Medical Centre, London, United Kingdom

Background and aims: Fractures are becoming more prevalent as the population ages worldwide. Osteoporosis predisposes older people to increases fracture risks. Frailty shares various risk factors and pathways with osteoporosis and can be a predictor of fractures. The objectives of this study were to identify prospective studies examining frailty as a risk factor of fractures and to combine the data regarding fracture risks according to frailty among community-dwelling older people.
Methods: A systematic literature search was conducted in August 2015 using five electronic databases: Embase, MEDLINE, CINAHL Plus, PsycINFO, and the Cochrane Library for prospective studies on associations between frailty and fracture risk published in 2000 or later using Medical Subject Heading terms and text words without language restriction. Odds ratios (OR) and hazard ratios (HR) extracted from the studies or calculated from available data were combined to synthesize pooled effect measures using random-effects or fixed-effects models. Heterogeneity, methodological quality, and publication bias were assessed. Meta-regression analyses were performed to explore the cause of high heterogeneity.
Results: Of 1,305 studies identified, six studies involving 96,564 older people in the community were included in this review. Frailty and prefrailty were significantly associated with future fractures among five studies with OR (pooled OR = 1.70, 95% confidence interval (95%CI) = 1.34–2.15, p<0.0001; pooled OR = 1.31, 95%CI = 1.18–1.46, p < 0.0001, respectively) and four studies with HR (pooled HR = 1.57, 95%CI = 1.31–1.89, p < 0.00001; pooled HR = 1.30, 95% CI = 1.12–1.51, p = 0.0006, respectively). High heterogeneity was observed among five studies with OR of frailty (I^2 = 66%). The studies from the United States were found to have higher fracture risks than those from other countries in a meta-regression analysis (regression coefficient = 0.39, p = 0.04). No evidence of publication bias was identified.
Conclusions: This systematic review and meta-analysis showed evidence that frailty and prefrailty are significant predictors of fractures among community-dwelling older people. Treating frailty may potentially lead to lowering fracture risks.

1-60

Frequency of frailty and its association with mental health and survival in Chilean older people

Cecilia Albala, Lydia Lera, Hugo Sánchez, Barbara Angel, Carlos Marquez, Florencia Insunza, Mario Moya, Patricio Fuentes
Institute of Nutrition and Food Technologie, Universidad de Chile

Background: Age–associated brain physiologic decline and reduced mobility are key elements of increased age-associated vulnerability.
Objective: To study the frequency of frailty phenotype and its association with mental health and survival in older Chileans.
Methods: Follow up of ALEXANDROS cohorts designed to study disability associated with obesity in community dwelling people 60y and older living in Santiago/Chile. At baseline 2099 (67% women) from 2372 participating subjects had the necessary measurements for the identification of frailty phenotype: weak hand-grip dynamometry, unintentional weight loss, fatigue/exhaustion, five chair-stands (slow walking speed) and difficulty for walking across a room (low physical activity). After 5-years 1298 people were evaluated and 373 were died. Information about deaths was available for the 2099 subjects.
Results: Prevalence of Frailty at baseline (≥3criteria) was 22,3% higher in women than men (31.5% vs.3.8%) and the Pre-frailty prevalence

(1-2criteria) was 63,7% (59,8% vs 65,7) respectively. Frailty was strongly associated with mild cognitive impairment (Frail 41.6%; pre-frail 21.6%; non frail17.9%, $p<0.001$) and depression (frail 55.1%; pre-frail 27.3%; non-frail 18.8%, $p<0.001$). At 5y there was increasing risk of falls associated with frailty: pre-frail RR = 1.81 (95%CI:1.21-2.80) frail RR = 3.05 (95% CI:1.99–4.82). Age and sex adjusted Hazard ratios for death showed increasing risk with increasing frailty: pre-frail HR = 1.56 (95% CI:1.07-2.29, p = 0.022), frail HR = 1.91 (95%CI:1.15–3.19, p = 0.013); the HR for death associated with frailty was independent of nutritional state but when cognitive impairment is included in the model frailty was no more significant: cognitive impairment HR = 11.72 (95%CI:5.4–39.2, $p < 0.001$); frailty HR 1.08 (95%CI:0.37–3.22).

Conclusion: Frailty is highly prevalent and strongly associated with cognitive impairment and depression in older Chileans. At follow up increasing risk of falls associated with frailty was observed. The risk for death was higher for Frail people but underlying cognitive impairment is probably the key component of lower survival.

Funding: Fondecyt Grant 1130947

1-61

Sarcopenia prevalence around the world: A systematic review

Paulo Nascimento, Stéphane Poitras, Martin Bilodeau
School of Rehabilitation Sciences, University of Ottawa/Bruyere Research Institute, Ottawa, Ontario, Canada

Musculoskeletal disorders are the most common cause of physical disability in different populations,[1,2] and can lead to premature death in older adults.[3,4] Because sarcopenia is a geriatric syndrome affecting the musculoskeletal system, it is important to document its presence in the general population of older adults. The specific aim of the current study is to perform a systematic review of the global prevalence of sarcopenia, and the influence of case definition in estimates of prevalence.

Two independent evaluators conducted an electronic search using the databases Medline, EMBASE, CINAHL, SPORTDISCUSS, LILACS, and SCIELO; looking for articles reporting the prevalence of sarcopenia in community dwelling older adults. The for prevalence validity of eligible studies was assessed using a tool developed specifically for systematic reviews aiming to answer questions about prevalence.[5]

The search strategy retrieved 1852 articles and 56 were considered eligible, with 37 of them having been published after the publication of the "sarcopenia consensus".[6] However, methods utilized to define sarcopenia varied, and only 21 studies used the "sarcopenia consensus" definition. Among the studies that did not use the consensus definition, loss of muscle mass assessed through different methods was the diagnosis criterion for sarcopenia.

Prevalence estimates varied according to different sarcopenia definitions and methods used to assess participant's muscle mass, strength and performance. Studies that used the consensus definition, reported prevalence rates between 1,2-29,2%[7,8] in men younger than 80 years old, and up to 7-59,4%[9,10] in men older than 80 years old. For women, the values varied from 0-26,1%[8,9] to 1,6-44,9%[9,10] in those younger and older than 80 years old, respectively.

Despite the increase in the number of studies reporting the prevalence of sarcopenia, and their general good quality, our review showed a lack of standardization for the diagnosis of the condition, which makes comparisons between studies difficult.

1-62

Evaluation of a novel exercise protocol using MOTOmed® as a quantifiable endpoint to assess functional capacity in stroke patients

Antje Meyer[1], Nadja Scherbakov[1,2], Michael Joebges[3], Wolfram Doehner[1,2,4]
[1]Center of Stroke Research CSB, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]German Center for Cardiovascular Disease (DZHK), partner site Berlin, Germany, [3]Brandenburg Klinik, Bernau, Berlin, Germany, [4]Department of Cardiology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: Assessment of muscle functional capacity in stroke patient requires novel tools. Due to the one-sided paretic impairment in strength and coordination standard tools like gait speed, stair climbing power or treadmill are not applicable in patients with stroke.

Objective: To evaluate a novel tool for quantitative assessment of muscle function particularly in patients with stroke.

Methods: Patients with ischemic or hemorrhagic stroke (n=35, mean age 68.9±8.4 y, 69% men) with an average Barthel index of 57±16 were examined within three weeks after the event. The MOTOmed® is an ergometer-like training device for patients with restricted movement ability applied while sitting on a stable chair during the test.

Cycling exercise with am individually defined resistance (80% of maximum strength) was performed and timed until exhaustion. Repeated tests were performed on two separate days (mean interval 2.7 days). Reproducibility of the MOTOmed® exercise protocol was calculated as the coefficient of variance (CV). Additionally, the MOTOmed® test was performed in a healthy young control group (n=40, mean age 32.4±6.6 y, 20% men) representing a higher level of exercise capacity.

Results: All stroke patients were able to perform this exercise protocol in repeated tests. No ceiling effect and no floor effect were observed. Mean duration until exhaustion at 80% of the maximum resistance in stroke patients was 127±58 s and 132±62 s on the first and second exercise test, respectively (mean difference 5±12 s). The CV of this test protocol was 7.3%. In the younger control group a similar CV value of 7.2% was obtained.

Conclusion: The MOTOmed® exercise protocol as applied in this test may be a reliable method for quantitative assessment of physical capacity in stroke patients with paretic impairment. The test may therefore be suitable as a quantifiable endpoint measurement in clinical trials in those patients. Further testing should be performed in other cohorts with restricted movement ability to confirm the validity of the test.

1-63

Short- and long-term efficacy of specific nutritional supplementation integrated in a pulmonary rehabilitation program in muscle wasted patients with COPD. A randomized, double blind placebo controlled multi-centre trial

Coby van de Bool[1], Erica P.A. Rutten[2], Ardy van Helvoort[1,3] Frits M.E. Franssen[2], Emiel F.M. Wouters[1,2], Annemie M.W.J. Schols[1]

[1]Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, the Netherlands, [2]on behalf of the CIRO network, [3]Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, the Netherlands

Previously the INTERCOM-trial showed in muscle-wasted COPD patients a prolonged positive response to nutritional intervention integrated in a community-based rehabilitation programme. Here a multimodal intervention was compared to usual care and the specific contribution of nutritional intervention could not be disentangled.

In this NUTRAIN-trial, 81 clinically stable, muscle wasted COPD patients, admitted to out-patient pulmonary rehabilitation were randomised to receive 4 months supervised exercise training with oral nutritional supplementation (3 servings of 187kCal, 20EN% protein; 60EN% CHO; 20EN% fat, enriched with leucine, vitamin D and polyunsaturated fatty acids (FA) (*intervention*) or flavoured non-caloric *placebo*. Subsequently, both groups received an 8-month maintenance programme involving feedback on physical activity level monitored by accelerometry. Additionally, *intervention* received nutritional counselling and tailored supplementation.

The study population (51% M) resembled a typical "wasted" emphysematous COPD phenotype (mean± SD) (DLCO: 49.4±14.6%, BMI: 22.7±2.7kg/m^2, FFMI: 15.8±1.6kg/m^2) with moderate airflow obstruction (FEV_1: 55.1±19.5%pred). After 4 months, between-group comparison revealed significant differences in favour of *intervention* for plasma vitamin D and n-3 FA levels and fat mass (FM) by DEXA. Skeletal muscle mass (SM), quadriceps muscle strength (Biodex) and cycle endurance (CWRT) increased in both groups, whereas inspiratory muscle strength only improved in *intervention* (+7.4%, P=0.001). Total daily activity and step count decreased in *placebo* (-13 and -18% respectively, $P<0.05$), but remained stable in *intervention*.

After 1 year, between-group changes in nutritional status were in favour of *intervention* for vitamin D, n-3 FA, leucine levels (all $P<0.05$) and FM and SM significantly declined between 4-12 months only in *placebo*. During this period improved muscle and exercise performance maintained in both groups, but physical activity level increased (+12%, $P<0.05$) compared to 4 months in *intervention* only. Specific nutritional intervention is able to extend short- and long-term benefits of pulmonary rehabilitation in muscle wasted COPD patients.

This study was a public private collaboration between Lung Foundation Netherlands, Centre of expertise for chronic organ failure (CIRO) Horn, Maastricht University/NUTRIM and Nutricia Research (grant number: 3.4.09.003).

1-64

Inheriting a high aerobic fitness predisposes to skeletal muscle and endothelial dysfunction in chronic heart failure

T. Scott Bowen[1], Sophia Eisenkolb[1], Sarah Werner[1], Michael Schwarzer[2], Gerhard Schuler[1], Volker Adams[1]

[1]Department of Internal Medicine and Cardiology, Leipzig University-Heart Center, Leipzig, Germany, [2]Department of Cardiothoracic Surgery, University of Jena, Jena, Germany

Background and aims: Chronic heart failure (CHF) is characterized by a reduced aerobic capacity and thus exercise intolerance, which is underpinned by skeletal muscle and endothelial dysfunction. However, whether an inherited fitness of high rather than low aerobic capacity may prevent skeletal muscle and endothelial dysfunction induced by CHF remains unclear.

Methods: Rats selectively bred for aerobic capacity, termed high (HCR) or low (LCR) capacity runners, underwent sham operation or ligation of the left coronary artery to induce CHF: HCR-sham (n=8) or HCR-CHF (n=10); and LCR-sham (n=8) or LCR-CHF (n=9). *In vitro* skeletal muscle and endothelial function was assessed in the soleus and aorta respectively, and protein expression determined by western blot.

Results: Physical and echocardiographic data confirmed ligated rats developed CHF ($P<0.05$). Compared to shams, HCR with CHF demonstrated skeletal muscle weakness ($P<0.01$) and increased fatigability ($P<0.01$), with impaired endothelial-dependent relaxation in the aorta ($P<0.05$). HCR with CHF also demonstrated significant reductions in protein expression of the key skeletal muscle contractile proteins sarcomeric actin (31%), troponin T (58%) and troponin C (85%), with NADPH oxidase higher (25%) and a trend (P=0.10) towards lower eNOS expression (39%) in the aorta. In contrast, no alterations in the skeletal muscle or aorta were found in LCR with CHF.

Conclusion: This study provides the first evidence that inheriting a high aerobic fitness does not prevent skeletal muscle and endothelial dysfunction induced by CHF. In contrast, our data suggest that a genetically determined high aerobic capacity predisposes to skeletal muscle and endothelial impairments in CHF.

1-65

Gene expression signatures in blood correlate with muscle mass and function in COPD

Merry-Lynn N. McDonald[1], J. Morrow[1], Erica Rutten[2], S. Rennard[3], R. Casaburi[4], Emiel Wouters[2,5], D. Lomas[6], B. Celli[7], E.A. Regan[8], P. Castaldi[1], K. Kechris[8], C.P. Hersh[1,7], G. Washko[7], R. Bowler[9], E.K. Silverman[1,7]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Channing Division of Network Medicine, Boston, MA, USA, [2]Ciro+, Centre of expertise for chronic organ failure, Horn, the Netherlands, [3]Department of Medicine, Nebraska Medical Center, Omaha, Nebraska, USA, [4]Division of Respiratory and Critical

Care Physiology and Medicine at Harbor-UCLA Medical Center, University of California Los Angeles, Torrance, CA, USA, [5]Department of Respiratory Medicine, Maastricht University Medical Center Maastricht, The Netherlands, [6]Wolfson Institute for Biomedical Research, University College London, London, UK, [7]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA, [8]Division of Pulmonary Medicine, Department of Medicine, National Jewish Health, Denver CO, USA, [9]Department of Biostatistics, University of Colorado Denver, Denver, CO, USA

Background and Aims: In chronic obstructive pulmonary disease (COPD) patients, the presence of reduced muscle mass and related functions are correlated with poor prognosis. However, it is remains uncertain if gene expression profiles from blood are correlated with traits related to muscle mass and function. Our group recently has developed techniques to quantify pectoralis muscle area (PMA) from chest computed tomography (CT) images that are correlated with fat-free mass in COPD cases[1].
Methods: We performed a weighted-gene co-expression network analysis (WGCNA)[2,3] assessing the relationships between gene expression data from 136 COPDGene study participants with BMI, PMA and 6-minute walk distance (6MWD).
Results: WGCNA generated 49 modules from 56,675 Affymetrix HGU133plus2 array probes measured in the study population. Three of the 49 modules, termed pink, purple and orange, were significantly correlated both with PMA and 6MWD, suggesting that these modules are relevant to muscle mass and function. The pink and purple modules remained significantly associated with 6MWD ($\log(\text{Fold Change})_{pink}$=-8.1x10^{-5}, P_{adj}=0.035, $\log(FC)_{purple}$=-7.8x10^{-5}, P_{adj}=0.035) and marginally associated with PMA ($\log(FC)_{pink}$=-3.6x10^{-5}, P_{adj}=0.073, $\log(FC)_{purple}$=-3.6x10^{-5}, P_{adj}=0.073) when the analysis was restricted to COPD cases (n=73). No module was significantly correlated with BMI. Gene-set enrichment analysis was used to investigate if the pink and purple module genes were involved in known biological processes/ pathways annotated in the REACTOME database and indicated significant enrichment for metabolism genes (FDR P_{pink}=9.9x10^{-3}, FDR P_{purple}=1.7x10^{-9}).
Conclusions: These results support the concept that gene expression in blood may eventually be used to non-invasively monitor patients at risk of muscle mass compromise and worse disease prognosis. Future research will include testing if these modules are preserved in additional populations and examining the relationship of network hub genes with PMA and 6MWD.
Acknowledgements: NIH 1K99HL121087-01A1, R01HL089856, R01HL089897, P01HL105339, R01HL107246, R01HL122464, American Thoracic Society Foundation, Parker B. Francis Fellowship Program, Butcher Foundation.

References:
1. McDonald ML, Diaz AA, Ross JC, et al. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Annals of the American Thoracic Society.* Mar 2014;11(3):326–334.
2. Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics.* 2008;9:559.
3. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. *Statistical applications in genetics and molecular biology.* 2005;4:Article 17.

1-66

REGN1033, a human monoclonal antibody specific to myostatin, increases lean mass in patients with sarcopenia

Stephen Donahue[1], Shehzad Basaria[2], Shalender Bhasin[2], Thomas Storer[2], Roger Fielding[3], Rinal Patel[1], Xiaobing Qian[1], Shazia Ali[1], Brad Shumel[1], Richard Kao[1]

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Section on Men's Health, Aging & Metabolism, Brigham and Women's Hospital, Boston, MA, [3]Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA

Background: REGN1033 is a fully human monoclonal antibody administered subcutaneously (SC) that specifically blocks myostatin.
Methods: This 12-week, randomized, double-blind, placebo-controlled phase 2 dose-finding study was the first of its kind in older adults with objectively measured sarcopenia: appendicular lean mass/height^2 $\leq$7.23 kg/m^2 for men or $\leq$5.67 kg/m^2 for women together with a 4-meter gait speed $<$1.0 m/s. Patients (n=253) received either placebo SC every 2 weeks (Q2W) or REGN1033 at 100 mg SC Q4W, 300 mg SC Q4W or 300 mg SC Q2W. The primary endpoint was the percent change in total lean body mass (LBM, via DXA) from baseline to week 12.
Results: Mean age was 78 years, mean LBM was 43 kg and 95% of patients completed the study. At each of the three dose regimens tested, REGN1033 treatment significantly increased LBM from baseline to week 12 compared with placebo; mean differences from placebo were 1.7% (p=0.008), 1.8% (p=0.004) and 2.3% (p$<$0.001) for REGN1033 100 mg SC Q4W, 300mg Q4W, and 300mg Q2W respectively, corresponding to lean mass increases of 0.7, 0.8 and 1.0 kg. Appendicular lean mass also significantly increased in patients treated with REGN1033: placebo-adjusted changes ranged from 2.3–2.8%. REGN1033 treatment resulted in directionally greater mean changes from baseline in various measures of strength and function relative to placebo.
REGN1033 was generally safe and well tolerated. The frequency of adverse events was similar across treatment groups. The percentage of patients experiencing at least one SAE was also similar across all treatment groups (7.7% in placebo group vs. 7.4% in REGN1033-treated groups). There was no discernable pattern to the distribution of SAEs. There were no clinically significant trends observed for laboratory tests, vital signs, ECGs and echocardiograms.
Conclusions: REGN1033 treatment significantly increased total lean and appendicular lean mass in patients with sarcopenia and was well tolerated.

1-67

The extracellular to intracellular water ratio in upper legs is negatively associated with skeletal muscle strength and gait speed in the elderly

Yosuke Yamada[1], Tsukasa Yoshida[2,3], Keiichi Yokoyama[4], Yuya Watanabe[5], Motoko Miyake[5], Emi Yamagata[6], Minoru Yamada[7], Misaka Kimura[5], Kyoto-Kameoka Study

[1]Department of Nutritional Science, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8636, Japan, [2]Graduate School of Science and Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan, [3]Senior Citizen's Welfare Section, Kameoka City, Kyoto 621-8501, Japan, [4]Department of Business Administration, Kyoto Gakuen University, 1-1, Nanjo-Otani, Sogabe, Kameoka, Kyoto 621-8555, Japan, [5]Department of Health and Sports Sciences, Kyoto Gakuen University, 1-1, Nanjo-Otani, Sogabe, Kameoka, Kyoto 621-8555, Japan, [6]Faculty of Nursing, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, Kyoto, 610-0395, [7]Graduate School of Comprehensive Human Sciences, University of Tsukuba, 3-29-1 Otsuka, Bunkyo-ku, Tokyo 112-0012

Background: Skeletal muscles contain a large volume of water that is classified into intracellular (ICW) and extracellular (ECW) water fractions. Nuclear magnetic resonance (NMR)-based biomarkers suggest that increased water T2 heterogeneities as well as elevated water T2 relaxation in the quadriceps occurs in the elderly when compared with young adults. However, NMR is difficult to apply to a large-scale study or a clinical setting for sarcopenia and frailty screening. Segmental bioelectrical impedance spectroscopy (S-BIS) is a unique tool used to assess the segmental ratio of ECW/ICW in the limbs. The aim of this study was to investigate the relationship between ECW/ICW in the upper leg segments and muscle strength or gait speed in the elderly.
Methods: We evaluated 405 community-living, elderly subjects aged between 65 and 90 years. ECW and ICW in the upper legs were assessed by S-BIS. Isometric knee extension strength (KES), gait speed, and skeletal muscle mass (SM) were measured. Correlation and multiple linear regression analyses were conducted with KES or gait speed as a dependent variable and ECW/ICW in the upper legs, age, sex, body mass index (BMI), and SM as independent variables.
Results: Thigh ECW/ICW was negatively correlated with KES and gait speed ($r = -0.617$ and -0.431, respectively, $p < 0.001$) and increased with age ($p < 0.001$). Thigh ECW/ICW was a significant predictor of KES and gait speed independent of age, sex, BMI, and SM.
Conclusions: Relative expansion of ECW against ICW in the thigh muscles is a factor in decreased muscle quality and a biomarker of muscle aging.

1-68

Association of new-onset diabetes mellitus in older people and mortality in Taiwan: a 10-year nationwide population-based study

Shang-Lin Chou[1], Ming-Yueh Chou[2,3], Chih-Kuang Liang[2,3], Liang-Kung Chen[3,4], Mei-Ju Chi[5]
[1]Department of Emergency Medicine, Fooyin University Hospital, Taiwan, [2]Center for Geriatrics and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [3]Aging and Health Research Center, National Yang Ming University, Taipei, Taiwan, [4]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, [5]Master Program in Long-term Care, College of Nursing, Taipei Medical University, Taipei, Taiwan

Backgound: Older patients with diabetes mellitus were at a higher risk of developing diabetic macro- and microvascular complications and cardiovascular diseases than younger diabetes mellitus patients. However, older diabetes mellitus people were very heterogeneous in clinical characteristics, diabetes mellitus-related complications and disease onset. This study aimed to evaluate the all-cause mortality rates and adverse health outcomes among new-onset diabetes mellitus in older people through a nationwide population-based study.
Methods: This was a retrospective cohort study by using National Health Insurance database in 2001-2011. Nationally representative sample of older people aged 65 years and older were sampled with propensity score-matched controls. All-cause mortality and adverse health outcomes were followed for 10 years.
Results: 45.3% in the diabetes mellitus cohort and 38.8% in the non- diabetes mellitus cohort died. The adjusted relative risk for mortality in the diabetes mellitus cohort was 1.23 (95%CI=1.16-1.30) for males and 1.27 (95%CI=1.19-1.35) for females. 8.9% of diabetes mellitus cohort and 5.8% of non- diabetes mellitus cohort developed cardiovascular diseases during the follow-up period and the adjusted relative risk for cardiovascular complication in the diabetes mellitus cohort compared to non- diabetes mellitus cohort was 1.54 (95%CI=1.36-1.75) for men and 1.70 (95%CI=1.43-2.02) for women. The adjusted relative risk for mortality in the hypoglycemia patients compared to non-hypoglycemia patients in diabetes mellitus cohort was 2.33 (95%CI=1.81-3.01) for men and 2.73 (95%CI=2.10-3.52) for women after adjustment for age, Charlson comorbidity index, acute coronary syndrome, respiratory disease, cancer, infectious disease and nervous system disease at baseline.
Conclusions: New-onset diabetes in older people was associated with increased risk of mortality, and hypoglycemia was an important marker in this association. Individualized care plans stratified by onset age, duration of disease, comorbidity, and functional status, as well as hypoglycemia avoidance, would be beneficial in the management of diabetes in older adults.

1-69

Frailty is a complex geriatric syndrome with multiple functional needs and wasting conditions

Li-Ning Peng, Liang-Kung Chen, An-Chun Hwang, Li-Kuo Liu
Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan, [2]Aging and Health Research Center, National Yang Ming University, Taipei, Taiwan

Objective: To evaluate the prevalence and associated functional needs for frailty among otherwise healthy community-dwelling middle-aged and elderly people in Taiwan
Design: a cross-sectional study
Setting: communities in I-Lan County of Taiwan
Participants: 1839 otherwise healthy community-dwelling people aged 50 years and older
Intervention: None
Measurements: Frailty defined by Fried's criteria, Charlson's comorbidity index (CCI), Functional Autonomy Measurement System

(SMAF), Center for Epidemiologic Studies Depression Scale (CES-D), Mini-Nutrition Assessment (MNA), Mini–Mental State Examination (MMSE), and Short Form-12 quality of life questionnaire

Results: Overall, 1839 subjects (mean age: 63.9±9.3 years, 47.5% males) participated in this study and men were more likely to have more education year, smoking and alcohol drinking habit. The prevalence of frailty was 6.8%, pre-frailty was 40.5% and 53.7% of all subjects were robust. Compared to subjects with different frailty status, age, education year, alcohol drinking habit, hypertension, diabetes mellitus, hyperlipidemia, CCI, walking speed, handgrip strength, score of SMAF, CES-D, MNA, MMSE, quality of life were significantly different between groups (P all$<$ 0.05). Older age, poorer physical function, poorer cognitive function, poorer nutritional status, more depressive symptoms, higher CCI and poorer quality of life were all independent associative factors for frailty.

Conclusions: Frailty was not merely a geriatric syndrome, but the combination of multiple geriatric syndromes. Further study is needed to evaluate the clinical benefits of integrated health promotion activities in the communities to reverse frailty and associated functional care needs.

1-70

Muscle power training for improved functional performance in older people: A systematic review and implications for pragmatic training interventions

Christopher Byrne[1], Charles Faure[2], David J. Keene[1], Sarah E. Lamb[1]
[1]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford; [2]Ecole Normale Supérieure de Rennes, Bruz, France

Background and aims: Muscle power is the physiological impairment most strongly associated with functional performance in older people. Interventions to improve muscle power involve resistance training with maximal intended movement velocity. The objectives of this review are to systematically review the effectiveness of power training (PT) intervention studies on both muscle power and physical function, and to identify pragmatic components of PT interventions.

Methods: We included PT intervention studies with both muscle power and functional performance as outcome measures with an age-matched comparative training group or non-exercising control group. We searched the MEDLINE database from 1996 to June week 3 2015. Search terms related to physiological impairments (e.g. strength, power, velocity), type of intervention (e.g. resistance training, exercise), population (e.g. aged, older), and study design (e.g. randomized control trial, clinical trial).

Results: We revealed 29 PT studies, characterised by short-term interventions (i.e. 8-16 weeks), small sample sizes, and incomplete reporting of interventions, resulting in less than one-in-five judged as having low risk of bias for random sequence generation and blinding of outcome assessment. Twelve studies compared PT to traditional (low velocity) resistance training, with nine reporting the superiority of PT for either muscle power or functional performance. Three studies compared PT load (i.e. low versus high) and revealed the efficacy of using low loads. A further fourteen studies demonstrated the efficacy of various PT methods including functional task training and low volume interventions.

Conclusions: Power training is superior to traditional resistance training for improving power and functional performance in older people. Low training load, low training volume, and simple functional training movements offer potential for the development of pragmatic PT interventions. We believe the area would benefit from larger and higher quality studies with a consideration of optimal long-term strategies and frail older populations.

1-71

Opposing activities of miR-542 and miR-422a on GDF-15 expression contribute to muscle wasting following cardiothoracic surgery

Richard G. Paul[1,2], Roser Farre-Garros[1], Michael I. Polkey[2], Paul R. Kemp[1], Mark J.D. Griffiths[2]
[1]National Heart and Lung Institute, Imperial College, London, UK, [2]NIHR Respiratory Biomedical Research Unit, Royal Brompton Harefield NHS Foundation Trust, London, UK

Introduction: Muscle wasting is a common co-morbidity of chronic obstructive pulmonary disease (COPD) and critical illness. However, wasting does not affect all people equally and there has been little success in the identification of patients at risk of muscle wasting. We have previously found that miR-542 and miR-424 were associated with disease severity and weakness in COPD. Conversely miR-422a was positively associated with strength in the patients but not different between patients and controls. Based on their predicted targets we hypothesised that miR-542 and miR-422a would associate with muscle loss in patients following cardiothoracic surgery and would have opposite effects on GDF-15 expression.

Methods: 40 patients undergoing high-risk cardiothoracic surgery with cardiopulmonary bypass underwent pre-operative rectus femoris biopsies and blood sampling. Muscle cross-sectional area (CSA) was assessed by ultrasound pre-operatively and at day 7 post-surgery. mRNA and microRNA expression in muscle were quantified by RT-PCR, GDF-15 protein in plasma by ELISA. The effects of the miRNAs in culture was analysed in HLCN-M2 cells.

Main Results: 52% patients of the developed showed significant muscle loss ($>$10%, wasters). Pre-surgery, miR-542 and miR-424 were associated with left-ventricular ejection fraction. miR-542-3p (1.9-fold, p=0.003), and miR-424 (4.2-fold, p=0.004) were higher in pre-operative muscle specimens of wasters compared to non-wasters, whilst miR-422a was lower (1.2-fold, p=0.018). Expression of these miRNAs correlated significantly with loss of rectus femoris CSA over time. Plasma GDF-15 concentration was significantly raised at all sampling time points in wasters compared to non-wasters. In vitro, miR-542 elevated GDF-15 expression and this effect was inhibited by co-transfection with miR-422a.

Discussion: Our data suggest pre-operative differences in muscle miRNA expression in wasters compared to non-wasters following cardiothoracic surgery. They also suggest that miR-542 is elevated by disease severity but the effects of this miRNA are opposed in some individuals by the activity of miR-422a.

1-72

A Phase 1 dose escalation study of ACE-083 in healthy volunteers: Preliminary results for a locally acting muscle therapeutic

Chad E. Glasser[1], Michael R. Gartner[2], Brian L. Boes[3], Scott Pearsall[1], Xiaosha Zhang[1], Jade Sun[1], Dawn M. Wilson[1], Ashley Bellevue[1], Monty Hankin[1], Matthew L. Sherman[1], Shuchi S. Pandya[1], Kenneth M. Attie[1]
[1]Acceleron Pharma, Cambridge MA, USA, [2]Celerion, Lincoln NE, USA, [3]Bryan Health, Lincoln NE, USA

Background: ACE-083 is an investigational protein therapeutic that acts as a ligand trap for myostatin (GDF8) and other negative regulators of muscle growth in the TGF-β superfamily. In wild-type mice and the MDX model of Duchenne muscular dystrophy, injection of ACE-083 into the gastrocnemius muscle led to localized muscle hypertrophy.
Methods: This is a single-center double-blind, placebo-controlled, dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ACE-083 in healthy, postmenopausal women. Five cohorts of 8 subjects each were randomized to ACE-083 (n=6) or placebo (n=2) administered as 2-4 injections into the right rectus femoris (RF) muscle: Cohorts 1-3 (50, 100, 200 mg) on Day 1, Cohorts 4-5 (100, 200 mg) on Days 1 and 22. MRI at baseline, 3, and 8 weeks post last dose determined muscle volume. Fixed and hand-held strength measurements were evaluated during treatment and follow-up.
Results: The difference in mean percent change in RF muscle volume from baseline between the injected right RF and the uninjected left RF at 3 weeks after the last dose in placebo was +0.6% compared to ACE-083 treated subjects in cohorts 1-5 of +1.2%, +2.8%, +4.2%, +6.2%, and +13.2% respectively. In Cohorts 2-5, RF volume remained increased though attenuated at 8 weeks after the last dose. Strength increases did not consistently correlate with muscle volume increases in these healthy subjects. All AEs were grade 1-2 and reversible. Myalgia was reported in 20% ACE-083 compared to 10% placebo treated subjects. Other frequent related AEs (≥15%) including injection site pain, injection site reaction, muscle twitching, and pain in extremity were similar in both groups.
Conclusions: Local administration of ACE-083 in the RF muscle was well tolerated and associated with dose-dependent increases in RF muscle volume. These findings support further studies of ACE-083 in a variety of muscle diseases, such as FSHD and DMD.

1-73

Effectiveness of comprehensive cardiac rehabilitation and useful biomarker for sarcopenia in patients with cardiovascular disease

Haruhito Harada[1], Hisao Ikeda[2], Hiroshi Niiyama[1], Yasuhiro Nishiyama[1], Atsushi Katoh[1], Noriko Yoshida[1], Hisashi Kai[1]
[1]Department of Cardiology, Kurume University Medical Center, Kurume, Japan, [2]Department of Physical Therapy, Faculty of Fukuoka Medical Technology, Teikyo University, Omuta, Japan

Background: Cardiovascular disease (CVD) is one of the causes of disease-related sarcopenia. European Working Group on Sarcopenia in Older People proposed nutrition, exercise training and medication for prevention and treatment of sarcopenia. Indeed, they are the same approaches with comprehensive cardiac rehabilitation (CCR). Additionally, the valuable diagnostic biomarker for sarcopenia has not been identified yet. Therefore, we investigated (1) the characteristics of, (2) the effect of CCR on, and (3) the biomarkers of sarcopenia with CVD.
Methods: We retrospectively studied 322 patients with CVD receiving CCR (age 72±12 years). Skeletal muscle index (SMI), physical performance, muscle strength, dietary intake and potential biomarkers (i.e. inflammatory and oxidative stress markers) were quantitatively evaluated before and after CCR. Correlation between the candidate biomarkers and diagnostic components for sarcopenia was investigated.
Results: Prevalence of sarcopenia was 28%. Sarcopenia group was older (78±8 years), lower nutritional condition, weaker muscle strength and lower physical performance than those of patients without sarcopenia. In role of nutrition, protein was the most independent nutrient for SMI. Exercise training significantly improved dietary intake, muscle strength and physical performance. In role of medication, statin was the most independent drug for SMI. Adiponectin and sialic acid were independent biomarkers for sarcopenia with CVD. Both adiponectin and sialic acid were higher in sarcopenia group. Adiponectin significantly correlated with diagnostic components of sarcopenia. The regression formula adopting adiponectin and sialic acid for sarcopenia diagnosis provided higher accuracy of ROC curve analysis.
Conclusions: These findings suggest that CCR is a useful strategy for prevention and treatment of sarcopenia and that adiponectin and sialic acid are useful diagnostic biomarkers for sarcopenia with CVD.

1-74

First in human allogeneic cell therapy after muscle trauma improves functional regeneration

Tobias Winkler[1,], Carsten F. Perka[2], Philipp von Roth[2], Alison N. Agres[3], Henning Plage[1], Bernd Preininger[4], Esther Lukasiewicz Hagai[5], Petra Reinke[6], Hans-Dieter Volk[7], Georg N. Duda[8]
[1]CMSC, JWI, BCRT, Charité - Universitaetsmedizin Berlin, Germany, [2]CMSC, BSRT, Charité - Universitaetsmedizin Berlin, Germany, [3]JWI, BCRT, Charité - Universitaetsmedizin Berlin, Germany, [4]CMSC, Charité - Universitaetsmedizin Berlin, Germany, [5]Pluristem Therapeutics Inc., Haifa, Israel, [6]Department for Nephrology, BCRT, Charité - Universitaetsmedizin Berlin, Germany, [7]Institute for Clinical Immunology, BCRT, Charité - Universitaetsmedizin Berlin, Germany, [8]JWI, BSRT, BCRT, Charité - Universitaetsmedizin Berlin, Germany

Insufficient muscle regeneration following trauma represents an unaddressed clinical need. On the basis of promising preclinical data, we evaluated safety and functional outcome following local placenta-derived mesenchymal like adherent stromal cell (PLX-PAD) transplantation using acute iatrogenic muscle damage after total hip arthroplasty (THA) as a model system.
Prospective, randomized, double blind, placebo-controlled phase I/II. 20 patients undergoing THA via lateral approach received transplantation (TX) of 300x10^6, 150x10^6 PLX-PAD or placebo into the gluteus

medius muscle (GM). Follow-up included safety, function, MRI and muscle biopsies.
No relevant AEs have been observed until 2 years FU. The primary efficacy endpoint, change of GM contraction moment after 26 weeks, showed a significant increase in the 150M group (p=0.0067) compared to placebo accompanied by an increase in muscle volume (p = 0.004). Interestingly, we could also observe a higher increase of contraction force after low dose treatment in contralateral, untreated muscles, compared to placebo. Change of contraction force and muscle volume in the 300M group showed a similar pattern as in the 150M group but was not statistically significant. Change of mean fiber diameters and regenerating myofiber count demonstrated a faster healing after cell TX. This is data from the first clinical study investigating allogeneic cell therapy for acute skeletal muscle injury. Although a limited number of patients were included in this trial, our results indicate a safe therapy with improved functional and structural outcome. This therapeutic concept could substantially improve patient outcomes in orthopedics, traumatology, and sports medicine after injuries to skeletal musculature. The force increase in non-treated musculature could indicate a possible systemic effect of the cells.

1-75

DHA-supplementation prior to fasting prevents muscle atrophy in mice

Christiane Deval[1,2], Frédéric Capel[1,2], Brigitte Laillet[1,2], Cécile Polge[1,2], Daniel Béchet[1,2], Daniel Taillandier[1,2], Didier Attaix[1,2], Lydie Combaret[1,2]
[1]Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, BP 10448, Clermont-Ferrand, INRA, UMR 1019, UNH, CRNH Auvergne, Clermont-Ferrand, France, [2]INRA, UMR 1213, URH, Saint Genes Champanelle, France

Background and aims: Muscle wasting prevails in numerous diseases (e.g. diabetes, cardiovascular and kidney diseases, COPD,…) and increases healthcare costs. A major clinical issue is to devise new strategies preventing muscle wasting. We hypothesized that a long-term docosahexaenoic acid (DHA) supplementation prior to fasting may preserve muscle mass in vivo.
Methods: Six-wk-old C57BL/6 mice were fed a DHA-enriched or a control diet for 8 weeks and then fasted for 48 h. The effect of DHA on i) muscle energy stores (glycogen, triglycerides (TG)), ii) muscle mass, and iii) Akt and AMPK signaling pathways involved in the control of protein and energy metabolism has been addressed. The regulation of the formation and the fate of lipid stores has been also evaluated.
Results: Feeding mice a DHA-enriched diet prior to fasting elevated muscle glycogen contents without any change in TG levels, reduced muscle wasting, blocked the 55 % decrease in Akt phosphorylation, and reduced by 30-40% the activation of AMPK, ubiquitination or autophagy. The DHA-enriched diet fully abolished the fasting induced-mRNA over-expression of the endocannabinoid receptor-1. Finally, DHA prevented or modulated the fasting-dependent increase in muscle mRNA levels for Rab18, PLD1 and perilipins, which determine the formation and fate of lipid droplets, in parallel with muscle sparing.
Conclusion: These data suggest that long-term DHA supplementation increased energy stores that can be efficiently mobilized, and thus preserved muscle mass in response to fasting through the regulation of Akt- and AMPK-dependent signaling pathways for reducing proteolysis activation. Whether a nutritional strategy aiming at increasing energy status may shorten recovery periods in clinical settings remains to be tested.

1-76

BIO101, a drug candidate targeting sarcopenic obesity through Mas receptor activation

Sophie Raynal[1], Anne-Sophie Foucault[1], Sanaa Ben Massoud[1], Waly Dioh[1], René Lafont[1,2], Stanislas Veillet[1]
[1]Biophytis, Romainville, France, [2]Sorbonne Universités, Université Pierre et Marie Curie, IBPS, 7 quai Saint Bernard, Paris, France

Background: The steroid hormone 20-Hydroxyecdysone (20E) plays a key role in insect development through nuclear ecdysone receptors (EcRs) and at least one membrane receptor. Although mammals lack EcR, 20E displays pharmacological effects on mammals: for example, it stimulates protein synthesis and is marketed as a physical performance enhancer. Based on its physiological effects on muscle mass, 20E presents an interest in the treatment/prevention of muscle pathologies, e.g. sarcopenia. However, the mechanism of action on mammals has not been elucidated. Thus, the goal of this study was to identify a receptor involved in 20E effects.
Methods: In vitro experiments were conducted in a mouse myoblast cell line using RT-qPCR for gene expression analysis and immunofluorescence for assessing muscle fiber size. Pharmacological molecules were used to modulate specific signaling pathways and a siRNA strategy was used to inhibit the molecular target. *In vivo*, C57Bl/6J mice were selected to study the impact of a chronic 20E treatment on muscle mass and on molecular markers.
Results: We documented an *in vitro* inhibitory effect of 20E on myostatin gene expression in association with muscle fiber enlargement. Experiments using protein-bound 20E established the involvement of a membrane receptor. Additionally, myostatin inhibition was reproduced with Angiotensin 1-7, the endogenous ligand of MAS and abolished by pharmacological inhibitors or by molecular invalidation of MAS receptor. *In vivo*, 20E oral treatment significantly increased protein content and decreased myostatin gene expression in *soleus* muscle, whereas several markers of myogenesis were enhanced.
Conclusion: 20E was shown to enlarge fiber size *in vitro* and protein amounts *in vivo*. These effects are associated with the inhibition of myostatin gene expression. Cellular signaling studies showed that 20E involves the activation of MAS receptor. These results led us to develop a 20E-based drug BIO101 to be assayed in a clinical trial on obese sarcopenic patients.

1-77

Diet-induced nonalcoholic fatty liver disease is associated with sarcopenia and decreased serum insulin growth factor-1

Claudio Cabello-Verrugio[1], Daniel Cabrera[2], Alex Ruiz[2], Pablo Quintero[2], Margarita Pizarro[2], Nancy Solis[2], Javiera Torres[3], Enrique Brandan[4], Francisco Barrera[2], Marco Arrese[2]

[1]Laboratorio de Biología y Fisiopatología Molecular, Departamento de Ciencias Biológicas, Facultad de Ciencias Biológicas & Facultad de Medicina., Universidad Andrés Bello, Santiago, Chile, Millennium Institute on Immunology and Immunotherapy, Santiago, Chile, [2]Department of Gastroenterology, Pontificia Universidad Católica de Chile, Santiago, Chile, [3]Department of Pathology, Pontificia Universidad Católica de Chile, Santiago, Chile, [4]Centro de Regulación Celular y Patología (CRCP), Centro de Regeneración y Envejecimiento (CARE), Laboratorio de Diferenciación Celular y Patología, Departamento de Biología Celular y Molecular, MIFAB., Pontificia Universidad Católica de Chile, Santiago, Chile

Background: decreased muscle mass or sarcopenia has been recently recognized as a risk factor for nonalcoholic fatty liver disease (NAFLD) but its mechanisms and consequences has not been tested. AIM: to explore if experimental NAFLD is associated to sarcopenia in mice and assess its association to functional changes and serum insulin growth factor-1 (IGF-1), a liver derived anabolic hormone.
Methods: C57/Bl6 mice were fed with a westernized diet (ALIOS-diet) and fructose in drinking water during 16 weeks. Weight gain, visceral fat, serum biochemical parameters, liver histology, and morphological and functional evaluation of skeletal muscle (gastrocnemius) were carried out. Muscle fiber cross-sectional area (CSA) was determined estimating the minimal Feret's diameter. In addition, we evaluated myosin protein levels by western blot as marker of muscle atrophy. Muscle strength was estimated by electro stimulation. IGF-1 serum levels were measured using a commercially available ELISA.
Results: The ALIOS diet induced significant weight gain and NAFLD with a significant increase in hepatic triglyceride content (23,97 ±7.9 mg/g liver vs. 2,47±1,5 mg/g liver in chow-fed mice, $p<0.05$), hepatic steatosis and inflammation as well as increased visceral fat. Muscle evaluation revealed that ALIOS diet-fed mice had a higher proportion of low-diameter (CSA 0-30 ⌠m) muscle fibers and a lower proportion of high-diameter (CSA 60-90 ⌠m) muscle fibers compared with chow-fed mice (figure: CSA 0-30 in red and CSA 60-90 in blue), which correlated with a decreased myosin protein levels. Functionally, isolated muscles from ALIOS diet-fed mice exhibited reduced muscle strength in electrophysiological studies. Finally, mice with NAFLD had reduced serum levels of IGF-1 (281.7±40 pg/ml vs. 366 ±30 pg/ml in chow-fed mice, p=0.04).
Conclusion: significant decreased muscle mass and muscle strength was found in experimental NAFLD. This may be related to decreased IGF-1 hepatic production and/ or the low-grade inflammatory milieu present in obesity and steatohepatitis.

1-78

Hypertension-induced diaphragm muscle weakness is prevented by high-intensity interval training in mice

Volker Adams, Tina Fischer, Sarah Werner, Juliana Drobner, Gerhard Schuler, T. Scott Bowen
Department of Internal Medicine and Cardiology, Leipzig University - Heart Center, Leipzig, Germany

Background and aims: Diaphragm muscle weakness, dyspnea, and fatigue are key features associated with chronic heart failure (CHF), but all can be attenuated by exercise training. Hypertension is a key risk for CHF, yet it remains unclear whether hypertension alone induces diaphragm muscle weakness. The present study, therefore, used a deoxycorticosterone acetate (DOCA)-salt hypertensive mouse model in combination with high-intensity interval training (HIIT) to assess the effects on diaphragm muscle function.
Methods: Hypertension was induced over 4 weeks by unilateral nephrectomy, subcutaneous DOCA pellet implantation (0.7 mg/d), and feeding saline water (1.05% NaCl). Mice were separated into three groups: 1) controls (n=11); 2) DOCA-salt (n=11); and 3) DOCA-salt with HIIT (n=15; 2 weeks of treadmill exercise). *In vitro* diaphragm muscle function, fiber size (histology), and protein expression (western blot) were quantified.
Results: Compared to controls, DOCA-salt mice had increased blood pressure independent of HIIT (149±15 vs. 186±14 and 187±12 mmHg, respectively). Diaphragm fiber bundles from DOCA-salt mice demonstrated greater weakness (~20%; $P<0.05$) and fatigability (~20%; P=0.05) compared to controls, yet these impairments were prevented by HIIT. Fiber cross-sectional area and markers of atrophy (i.e., MuRF1 and MAFbx) were not different between groups. However, a 35% reduction ($P<0.05$) in myosin heavy chain expression was seen in DOCA-salt mice that was not observed following HIIT, as compared to controls. Furthermore, HIIT mice had a significant increase in sarcomeric actin expression (~90%; $P<0.05$) compared to controls and DOCA-salt mice.
Conclusion: Diaphragm dysfunction induced by hypertension was prevented by HIIT, which normalized or increased key contractile proteins (i.e., myosin and actin). Overall, therefore, these findings suggest respiratory muscle weakness may be present in hypertension, which likely exacerbates early symptoms in patients who later develop CHF. However this impairment can be abolished by HIIT.

1-79

S-oxprenolol as a new drug for treatment of amyotrophic lateral sclerosis (ALS)

Cathleen Drescher[1], Sandra Palus[1], Vincenzo Musolino[2], Stefan D. Anker[1], Jochen Springer[1]
[1]Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany, [2]Institute of Research for Food Safety & Health (IRC-FSH), University of Catanzaro "Magna Graecia", Catanzaro, Italy

Amyotrophic lateral sclerosis (ALS) is caused by degeneration of upper and lower motoneurons resulting in weakness and muscle atrophy. Cachexia in ALS manifests itself in loss of body weight, especially skeletal muscle mass. The exact pathophysiology at ALS-associated cachexia is still unknown. Currently, only riluzole is approved for the treatment of ALS. Here, we tested novel therapeutic options in an internationally standardized and established model. Using male and female transgenic G93A mice, with a mutation in the gene encoding the superoxide dismutase (SOD1), the effects of different beta blockers (10mg/kg/d propranolol, n=28; 20mg/kg/d oxprenolol, n=28; 10 or 20mg/kg/d *R*-oxprenolol, n=29 and n=30, respectively; 10 or 20mg/kg/d, *S*-oxprenolol n=45 and n=28, respectively) on survival and disease progression in comparison to riluzole as a positive control (30mg/kg/d, n=28) and placebo (n=45) were

tested. The disease progression assessed using neurological scores determined by international SOPs from PRIZE4LIFE and „The Jackson Laboratory".
Survival is significantly improved at 10 and 20mg/kg/d *R*-oxprenolol (HR: 0.57, 95%CI: 0.35-0.93, p=0.0227; HR: 0.54, 95%CI: 0.34-0.88, p=0.013) and 20mg/kg/d *S*-oxprenolol (HR: 0.45, 95%CI: 0.27-0.73, p=0.0014) vs placebo while riluzole, propranolol and the racemate oxprenolol were not effective in comparison to placebo. The disease progression from the early phase to the later phase of ALS (score 1 to score 3) was significantly attenuated compared to placebo by treating with 20mg/kg/d *S*-oxprenolol (HR: 0.47, 95%CI: 0.28-0.81, p=0.0061) in contrast to riluzole, propranolol, oxprenolol and both doses of *R*-oxprenolol as well as the lower dose of *S*-oxprenolol where no positive effect was detected.
In summary, *S*-oxprenolol improves the survival and attenuates disease progression in a G93A mouse model of ALS.

1-80

A consistent and reproducible animal model to investigate skeletal muscle atrophy and recovery from atrophy

Andrew G. Fisher[1], Jonathan C. Jarvis[2], Judy Coulson[3]
[1]Human Anatomy Resource Centre, University of Liverpool, UK; [2]School of Sport and Exercise Science, Liverpool John Moores University, UK; [3]Institute of Translational Medicine, University of Liverpool, UK

Background & Aims: Several animal models induce skeletal muscle atrophy reflecting specific clinical causes of muscle wasting. However, these models have the added symptoms of the disease itself, which may complicate the investigation of muscle atrophy specifically. Gaining an understanding of muscle atrophy without the interference of a diseased state is fundamental in understanding the process of muscle wasting without confounding pathology. A model employing the use of tetrodotoxin (TTX) to block action potentials in nerves is an interesting alternative to the other models of disuse atrophy, such as denervation or limb casting.
Methods: A TTX nerve cuff implanted around the common peroneal nerve induced progressive disuse atrophy in rat dorsiflexor muscles *in vivo* over a period of 14 days. The absence of any histological signs of damage of the muscle fibres meant it was possible to block muscle activity for 14 days, and then reverse the blockade, allowing the same fibres to recover over the subsequent 7 days.
Results: The model produced a maximal 51% (+/-1%) loss in mass of the treated *Tibialis anterior* muscle compared to that in the untreated control limb. This loss in weight recovered significantly upon cessation of the block. Microarray analysis was used to compare genome-wide transcript changes following 3, 7 and 14 days of nerve blockade and 14 days of nerve block with 7 days of recovery. Key signalling pathways involved in the process of disuse atrophy were highlighted; including a 33-fold increase in Myog mRNA after 3 days nerve block.
Conclusions: The refinement of this animal model reveals an exciting and potentially productive avenue of research and ultimately the discovery of therapeutic treatments for skeletal muscle atrophy. Our results represent a starting point in the use of this model with potential for chemical or genetic intervention in the future.

1-81

A rat immobilization model based on cage volume reduction: a model for bed rest?

Enrica Marmonti[1], Sílvia Busquets[1,2], Míriam Toledo[1], Marina Ricci[1], Marc Beltrà[1], Victòria Gudiño[1], Francesc Oliva[3], José María López-Pedrosa[4], Manuel Manzano[4], Ricardo Rueda[4], Francisco J. López-Soriano[1,2], Josep M. Argilés[1,2]
[1]Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain, [2]Institut de Biomedicina de la Universitat de Barcelona, Barcelona, Spain, [3]Departament d'Estadística, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain, [4]Abbott Nutrition, Granada, Spain

Background and aims: In order to study disuse-induced changes in muscle and bone, as observed during prolonged bed rest in humans, an innovative model of muscle disuse for rodents is presented.
Methods: Basically, the animals are confined to a reduced space designed to restrict their locomotion movements and allow them to drink and eat easily, without generating any physical stress.
Results: The immobilization procedure decreased the body weight gain of the immobilized animals and induced a significant decrease of food intake.The reduced food intake was not a consequence of a stress condition induced by the model since plasma corticosterone levels - an indicator of a stress response - were not altered following the immobilization period. The animals showed a significantly decreased soleus muscle mass, grip force and cross-sectional area together with a decrease in bone mineral density. However, it is worth pointing out that, in terms of lifespan, the immobilization periods used here are far longer than those used previously with human studies.
Conclusions: The present model may potentialy serve to investigate the effects of bed-rest in pathological states characterized by a catabolic condition, such as diabetes or cancer.

2-01

Molecular pathways involved in the crosstalk between cytokines and mechanical cues in cancer cachexia

Alexandra Baccam[1,2], Martina Ramella[3], Francesca Boccafoschi[3], Mathias Mericskay[1], Zhenlin Li[1], Dario Coletti[1,2]
[1]Dept. of Biological Adaptation and Ageing B2A (CNRS UMR 8256 - INSERM ERL U1164 - UPMC P6), Pierre et Marie Curie University Paris 6, France, [2]DAHFMO Unit of Histology and Medical Embryology, and Interuniversity Institute of Myology, Sapienza University of Rome, Italy, [3]Dept. Of Health Sciences, University of Eastern Piedmont Avogadro, Novara, Italy

Cachexia is characterized by increased levels of pro-inflammatory cytokines, autophagy and proteolysis of sarcomeric myofibrils leading to impaired muscle fiber function. Satellite cells (SC) regeneration potential is also impaired in cachexia contributing to muscle wasting. Exercise training improves quality of life and survival of cancer patients. However, the molecular pathways implicated in the response

to physical activity are unknown. Exercise could act both endocrinologically by affecting the circulating factors responsible of muscle homeostasis (cytokines and myokines) or by inducing mechanostransduction in muscle cells. To dissociate these pathways *in vitro*, we treated C2C12 myoblast with cachectic mouse sera (CMS) or specific, recombinant pro-inflammatory cytokines (IL-6, TNF), assessing the effect on myogenic differentiation and on Pax7 expression. Our results showed that CMS or pro-inflammatory cytokines negatively affect myogenic differentiation, likely though Pax7 upregulation; however, recombinant cytokines don't fully mimic CMS effects. To investigate the crosstalk between humoral factors and mechanical cues C2C12 myoblasts were incubated in the absence or presence of CMS or recombinant cytokines, in the absence or presence of cyclic mechanical stretch by culturing the cells on extensible silicon membranes (Flexcell) in dynamic or static conditions. We observed that cytokine effects on myogenic differentiation could be counteracted by cyclic stretch, suggesting the latter rescues the negative effects of cytokines presents in CMS. Even though we cannot exclude that cyclic stretch affects myokine production by C2C12, it is likely that a pure mechanic effect activates a mechanotransduction pathway with pro-myogenic effects. We suggest that the positive effects of exercise on cancer patients could be due to a purely mechanical response by muscle SC. Studying the chemical and mechanical effects of cyclic mechanical stretch on Pax7 expression and identifying potential downtream effectors will highlight molecular pathways implicated in cachexia and in the potential cross-talk between mechanical cues and humoral factors.

2-02

The alternative RNA world: Alternative splicing in human skeletal muscle and implications to cancer cachexia

Ashok Narasimhan[1], Russell Greiner[2], Oliver Bathe[4], Cynthia Stretch[3], Vickie Baracos[3], Sambasivarao Damaraju[1]
Depts. of [1]Laboratory Medicine and Pathology, [2]Computing Sciences, [3]Oncology, University of Alberta, Canada, [4]Dept. of Oncology and Surgery, University of Calgary, Canada

Background: Alternative Splicing (AS) is a crucial intermediary regulatory mechanism between eukaryotic transcription and translation which contributes to proteome diversity (~25000 genes corresponding to ~100000 proteins). AS patterns manifest at several levels, e.g., tissue and developmental stage-specific manner. Skeletal muscle is reported to have the highest number of differentially expressed alternative exons. Dysregulated splicing mechanisms contribute to the pathogenesis of several diseases such as cancer and skeletal muscle related diseases such as duchene muscular dystrophy. However, the impact of dysregulated splicing mechanism in Cancer Cachexia (CC) remains unexplored at the whole genome level.
Aim: To identify differentially expressed-Alternatively Spliced Genes (D-ASGs) associated with CC.
Methods: 43 cancer patients were included, of which 18 (cases) exhibited weight loss $\geq$ 5% (13.25 ± 7.11) and 23 (controls) were weight stable in the preceding 6 months. Total RNA was isolated from muscle biopsies and ASGs were profiled using Human Transcriptome array (TA) 2.0. TA Console 3.0 was used to identify D-ASGs. Ingenuity Pathway Analysis (IPA) was used to identify canonical pathways for D-ASGs to gain functional insights.
Results: 175 D-ASGs were identified (86 up- regulated and 89 down-regulated) at a splice index of 1.5 (fold change equivalent) and $p<0.05$. The top 15 up-regulated D-ASGs were associated with actin cytoskeleton organization, autophagy and carbohydrate metabolism. The top 15 down-regulated D-ASGs were associated with lipid metabolism, Inflammation and translation respectively. Representative genes are: MYPN, CNN2, ATG2B, MAN2A1 (up-regulated) and PLA2G2A, IFRD1, EEF1D (down-regulated). IPA identified pathways such as PI3K/AKT signaling, GDNF family ligand-receptor interactions, IL-3 signaling as up-regulated and Glutamine biosynthesis, apoptosis and lipoate biosynthesis as down-regulated. Select D-ASGs will be validated using qRT-PCR. Independent studies will be carried out to replicate the findings.
Conclusions: The study premise may help identify new molecules and pathways that contribute to CC pathogenesis.

2-03

Micro players with macro roles - Next generation sequencing (NGS) profiling of microRNAs in human skeletal muscle and their sssociation with cancer cachexia

Ashok Narasimhan[1], Russell Greiner[2], Oliver Bathe[4], Cynthia Stretch[3], Vickie Baracos[3], Sambasivarao Damaraju[1]
Depts. of [1]Laboratory Medicine and Pathology, [2]Computing Sciences, [3]Oncology, University of Alberta, Canada, [4]Dept. of Oncology and Surgery, University of Calgary, Canada

Background: miRNAs (miRs) are small non-coding RNAs (18-22 nucleotides) and are considered as global regulators of gene expression (mRNA). MiRs have been implicated in several muscle wasting conditions such as myotonic dystrophy and duchene muscular dystrophy. However, a comprehensive profiling of miRs in Cancer Cachexia (CC) has not been attempted.
Aims: i) To profile miRs from skeletal muscle biopsies; (ii) To study association of miRs with the phenotype of CC; and (iii) To identify putative targets for miRs using TargetScan and validate in muscle tissue mRNA expression (n = 129) data set.
Methods: 43 cancer patients were identified of which 19 (cases) exhibited weight loss $\geq$ 5% (13.25 ± 7.11) and 24 (controls) were weight stable in the preceding 6 months. RNA isolated from muscle biopsies were sequenced using Illumina MiSeq platform. Differentially Expressed (DE) miRs and mRNAs were defined as those with a fold change of 1.4 and $p < 0.05$.
Results: A total of 781 miRs were expressed in the muscle and 82 miRs with read counts of >5 in 80% of samples were further interrogated. Seven miRs were DE (up-regulated) and were associated with CC. There is paucity of data in literature on miR-3184-3p and miR-1296-5p; whereas other miRs were shown to play a role in glucose metabolism (let-7d-3p), inflammation (miR-532-3p, miR-193b-5p), and mitochondrial energy metabolism (miR-423-5p, miR-345-5p). Reciprocal regulation of several target mRNAs (n = 20) were observed for the DE miRs. mRNAs regulated were Col1A1, CSF3; CLEC2L,

MASP1 (lectin family members); SCD (energy metabolism and obesity); PHIP (insulin signalling); VSNL1, PLXNC1 (calcium binding and immune regulation). Predicted targets (by TargetScan) for miR-1296-5p included CAMKV, ITCH, TNFRSF members 12A and 25. Select miRs are currently being validated using qRT-PCR.
Conclusions: miRs identified in this study have not been addressed in the context of CC and may be of value in developing targeted therapeutics.

2-04

Pancreatic tumor cell-derived factors induce NF-κB activation and activate the ubiquitin-proteasome system in cultured muscle cells

David P.J. van Dijk[1], Rianne D.W. Vaes[1], Steven W.M. Olde Damink[1], Cornelis H.C. Dejong[1], Annemie M.W.J. Schols[2], Sander S. Rensen[1], Ramon C. Langen[2]
[1]Department of Surgery, Maastricht University Medical Centre and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands, [2]Department of Pulmonology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

Background and aims: Muscle wasting is a hallmark of pancreatic cancer cachexia, causing significant morbidity and reduction of quality of life. NF-κB and the ubiquitin-proteasome system have been implicated in muscle wasting, but whether their activation results from tumor-derived factors remains to be established. We hypothesized that pancreatic tumor cells produce mediators that induce muscle atrophy and NF-κB activity in cultured muscle cells.
Methods: Differentiated murine C2C12 skeletal muscle cells containing a NF-κB luciferase reporter were incubated for 4h and 24h with conditioned medium (CM) from human pancreatic cancer cell lines (PK-45H, PANC-1, PK-1, and KLM-1) or human breast cancer cell lines (MCF7 and T47D) as non-cachectic controls. Transcript levels of the E3 UPS-ligases MuRF1 and atrogin-1 were assessed by qPCR. Myosin heavy and light chain levels were assessed using Western blot.
Results: CM of pancreatic cell lines PK-45H, PK-1, and KLM-1 induced NF-κB activation in differentiated muscle cells (1.5-fold, 2.9-fold, and 1.9 fold, $p<0.05$ respectively) whereas CM of the breast cancer cell lines did not. MuRF1 expression was increased after incubation with all pancreatic CM (PK-45 1.8-fold, PANC-1: 1.6-fold, PK-1: 1.7-fold, and KLM-1: 1.5-fold; $p<0.05$) and atrogin-1 expression was upregulated after incubation with medium of PANC-1, PK-1, and KLM-1 (1.5 fold, 1.7 fold, and 1.4 fold, $p<0.05$ respectively). Levels of type-1 heavy chain myosin and type-2 light chain myosin but not type 2 heavy chain myosin were reduced after incubation with medium of PANC-1 and PK-1 pancreatic cell lines.
Conclusion: Pancreatic cancer cell lines display variable muscle atrophy-inducing properties in contrast to non-cachectic breast cancer control cell lines, which may reflect different degrees of cachexia of the donor patient. Ongoing studies focus on replication of these findings using primary cell cultures of well-phenotyped cachectic and non-cachectic patients as well as identification of the responsible mediators.

2-05

Conditional gene targeting reveals an unexpected protective role of myeloid cells in cancer cachexia

Merve Erdem[1,2], Cathleen Drescher[3,4], Stephan von Haehling[3,4], Stefan D. Anker[3,4], Jochen Springer[3,4], Thorsten Cramer[1]
[1]Molecular Tumor Biology, Department of General Surgery, RWTH University Hospital, Aachen, Germany, [2]Molecular Cancer Research Center (MKFZ), Charité Medical University, Berlin, Germany, [3]Department of Innovative Clinical Trials, University Medical Centre, Göttingen, Germany, [4]Applied Cachexia Research, Department of Cardiology, Charité Medical University, Berlin, Germany

Background and aim: Cachexia is characterized by involuntary loss of skeletal muscle and body fat irreversible by nutritional interventions. Cachexia affects 30-80% of cancer patients and accounts for >20% of cancer-related deaths. While the molecular mechanisms of cancer cachexia are largely elusive, systemic inflammation is widely considered to be important in this setting. We sought to better understand the molecular pathogenesis of cancer cachexia in order to identify new targets for therapy. The transcription factor HIF1A, the principle mediator of the hypoxic response, was introduced as a pivotal regulator for myeloid cell function by us and others. Myeloid cell specific knock-out (KO) mice of HIF1A were crossed into the ASV-B background, a murine model for hepatocellular carcinoma (HCC).
Methods: Body weight and composition (fat and lean mass) were analyzed via NMR spectroscopy over time. As an indicator of wasting, proteasome-related and caspase enzyme activities were measured in muscle and heart tissue.
Results: ASV-B mice show progressive cachexia evidenced by loss of fat and lean mass during HCC development. Of note, the myeloid cell-specific loss of HIF1A resulted in further aggravation of this phenotype: KO mice displayed enhanced loss of body weight and fat mass as well as elevated activities of cachexia-associated enzymes in skeletal muscle.
Conclusions: Given the well-established role of inflammation for the pathogenesis of cachexia and the importance of HIF1A for myeloid cell function, these results are unexpected. The molecular nature of this observation is currently under investigation by us. In addition, we are addressing the clinically important question if HIF1A activators could be effective in the therapy of cancer cachexia.

2-06

Role of adiponectin receptor 1 and TNF-α in chronic heart failure-associated muscle adiponectin resistance and mitochondrial dysfunction.

Tahnee Sente[1,2], An M. Van Berendoncks[1,2], Erik Franssen[3], Vicky Y. Hoymans[1,2], Christiaan J. Vrints[1,2]
[1]Laboratory for Cellular and Molecular Cardiology, Antwerp University Hospital, Edegem, Belgium, [2]Cardiovascular Diseases, Department of Translational Pathophysiological Research, University of

Antwerp, Wilrijk, Belgium, [3]StatUa Center for Statistics, University of Antwerp, Antwerp, Belgium

Background and aims: Skeletal muscle metabolic alterations including adiponectin resistance and mitochondrial dysfunction are common features in chronic heart failure (CHF). We previously demonstrated that CHF patients are characterized by a functional adiponectin resistance at the level of the skeletal muscle. The purpose of the present study was to examine the role of AdipoR1 and TNF-α on adiponectin signalling and mitochondrial function in skeletal muscle.
Methods: Myoblast and myotubes cultures were initiated from muscle biopsies *(m. vastus lateralis)* of 10 CHF patients (LVEF; 31.30 ± 2.89%) and 10 control subjects. Control cultures were transfected with siAdipoR1 in the presence or absence of TNF-α.
Results: Adiponectin resistance was preserved *in vitro* in CHF myotubes, as evidenced by an increased adiponectin expression ($p = 0.058$) and downregulation of AdipoR1 ($p = 0.051$) and its underlying signalling pathway ($p < 0.05$). Upon siRNA-mediated silencing of AdipoR1, phosphorylated AMPK ($p = 0.033$) and AMPK activation were reduced. Dynamic high-resolution assessments of myoblast proliferation were evaluated using the xCELLigence RTCA and a delayed growth rate was observed ($p < 0.0001$). AdipoR1 was negatively correlated with proliferation ($r = -0.7319$, $p = 0.003$). Co-incubation with TNF-α (10ng/ml; 72h) decreased mRNA expression levels of genes involved in lipid (PPARα, ACADM), glucose (AMPK, HK2) and mitochondrial (FOXO3) metabolism ($p < 0.0001$). Immunohistochemistry and ELISA revealed a slightly increased presence ($p = 0.073$) and secretion of adiponectin ($p = 0.085$), respectively. In addition, an increased cellular senescence, as evidenced by SA-β-gal activity and p53 acetylation ($p < 0.05$) was apparent and accompanied by an increased secretion of IL-1β, IL-6, IL-10 and IFN-γ (Meso Scale Discovery; $p<0.05$). TNF-α partially restored the siAdipoR1 reduced myoblast proliferation ($p<0.001$).
Conclusion: Primary CHF muscle cells exhibited characteristics typical to *in vivo* skeletal muscles of CHF patients. Lack of AdipoR1 associated with inflammation impairs adiponectin signalling, mitochondrial function and disrupts muscle cell proliferation, probably contributing to skeletal muscle adiponectin resistance and muscle wasting in CHF.

2-07

Activation of AMP-activated protein kinase and stimulation of energy metabolism by the treatment of acetic acid in L6 myotube cells

Hitomi Maruta*, Yukihiro Yoshimura, Aya Araki*, Masumi Kimoto*, Yoshitaka Takahashi*, and Hiromi Yamashita*†
Department of Nutritional Science, Faculty of Health and Welfare Science, *Graduate School of Health and Welfare Science, Okayama Prefectural University, 111 Kuboki, Soja-shi, Okayama, Japan

Previously, we found that oral administered acetic acid had effects on the activation of AMP-activated protein kinase (AMPK) and on the expression of myoglobin and GLUT4 genes in skeletal muscle of Ostuka Long-Evans Tokushima Fatty (OLETF) rats, which exhibit hyper glycemic obesity with hyperinsulinemia and insulin resistance. It was appeared that acetic acid functioned as an agent for improving lipid metabolism in skeletal muscles. In this study, in order to investigate the regulatory role of acetic acid on energy metabolism in skeletal muscle cells, we examined the effect of acetic acid on the activation of AMPK as well as on gene and protein expressions of GLUT4 and myoglobin in L6 myotube cells.
L6 myoblasts were grown in DMEM containing 10%(v/v) FBS, 100 units/ml penicillin and 100ug/ml streptomycin at 37 °C in an atmosphere of 5% CO_2. The medium was changed to DMEM containing 2% (v/v) Horse serum for myotube differentiation. Acetic acid (0-0.5mM) was added to the differentiated L6 myotube cells. Acetic acid added in culture medium was taken up rapidly by L6 cells and AMPK was phosphorylated by the treatment of acetic acid. Acetic acid increased not only gene expressions of GLUT4 and myoglobin but also expressions of those proteins. Uptakes of Glucose and fatty acid by L6 cells were increased, while, triglyceride accumulation was lower in the cells that treated with acetic acid than those untreated control cells. Furthermore, it was shown an increase in gene and protein expression of myocyte enhance factor 2A (MEF2A), which is well known as a transcription factor that is involved with expression of myoglobin and GLUT4 genes, by the treatment of acetic acid. These results indicate that acetic acid would enhance glucose uptake and fatty acid metabolism through the activation of AMPK and increases of expression of GLUT4 and myoglobin.

2-08

Morphological indices and markers of signaling pathways in skeletal muscle of men with ethanol abuse

Boris S. Shenkman[2], Olga E. Zinovyeva[3], Tatiana L. Nemirovskaya[1, 2]
[1]Faculty of Basic Medicine, Lomonosov Moscow State University, Moscow, Russia.
[2]Institute of Bio-Medical Problems, RAS, Moscow, Russia, [3]I.M. Sechenov First Moscow State Medical University

Background and aims: A chronic alcoholic myopathy is the common form of skeletal muscle destruction in alcoholism. What is important in the development of the disease: the duration of alcohol abuse or the dose of the ethanol consumed?
Methods: The time course of chronic alcoholic myopathy was examined in 23 male patients (46.9 ± 1.5 years). The control group consisted of 7 healthy men. All patients were divided into 3 groups for the duration of alcohol consumption: 7.7 ± 0.6 (group 1, n = 9); 18.1 ± 1.2 (group 2, n = 7) and 31.3 ± 1.0 years (group 3, n = 7). A biopsy from m. vastus lateralis was taken. The average daily dose of alcohol was 16.1 ± 1.4 units of ethanol (1 unit = 10ml of pure ethanol).
Results: The clinical symptoms of myopathy, atrophy or transformation of muscle fibers (MF) were not observed in group 1, however, the level of p-p70S6k and p-p90 RSK was reduced ($p<0.05$) vs Control. The second group demonstrated the clinical symptoms of myopathy, the atrophy of type II MF ($p<0.05$), the shift of MF to a fast type ($p<0.05$) and the reduced activity of p-p70S6k and p-p90 RSK

($p<0.05$). In the third group we observed the clinical symptoms of myopathy syndrome, the atrophy of both types of MF ($p<0.05$), the shift of MF to a fast ($p<0.05$) and reduced activity of p-p70S6k and p-p90 RSK, ($p<0.05$). IGF-I level in plasma was significantly lower in the groups, 2,3 vs group without atrophy.

Conclusions: The duration of alcohol consumption is more important factor than the dosage to develop the myopathy symptoms. The involvement of different types of MF in the process of atrophy and the shift of fibers to the fast type depend on the alcohol abuse duration. The anabolic signaling pathways markers and IGF-1 reduced before noticed symptoms of myopathy.

Supported by Russian Science Foundation № 14-15-00392

2-09

Hypoxia sensitizes skeletal muscle to fasting-induced muscle atrophy and impairs AMPK/mTORC1 signaling

Ramon C.J. Langen[1,2], Chiel C. de Theije[1,2,†], Wout H. Lamers[1,3], S. Eleonor Köhler[1,3], Annemie M.W.J. Schols[1,2]

Maastricht University Medical Center+, Maastricht, Netherlands: [1]NUTRIM School of Nutrition and Translational Research in Metabolism, [2]Department of Respiratory Medicine, [3]Department of Anatomy & Embryology

Background and aims: Acute exacerbations in COPD are often associated with reduced food intake and hypoxemia, which may accelerate muscle wasting in these patients. This study addressed whether hypoxia sensitizes skeletal muscle to fasting-induced atrophy and affects protein turnover signaling.

Methods: Mice were kept under hypoxic (H) (8% oxygen) or normoxic conditions (21% oxygen) (N), or were pair-fed to the hypoxia group (pair-fed normoxic control, PN) for 12 days. Following an additional 24 hrs of fasting, muscle protein turnover signaling was assessed in the gastrocnemius muscle by RT-qPCR and Western blotting.

Results: Weight loss of the gastrocnemius muscle in response to fasting was greater in the hypoxic (H) than the normoxic (N) or pair-fed normoxic control (PN) groups. Conversely, the fasting-induced increase in expression of the ubiquitin 26S-proteasome E3 ligases (*Murf1*, *Atrogin-1*) and the autophagy-lysosomal degradation-related genes (*Bnip3, Map1lc3*B) and protein (LC3B) were attenuated in the H-group compared to the PN-group. MTORC1 activity was reduced by fasting under normoxic conditions but sustained under hypoxic conditions. Fasting-induced inhibition of mTORC1 was accompanied by reduced AKT1/TSC2 and AKT1/mTOR phosphorylation in the PN-group. Under hypoxic conditions, decreased AKT1/TSC2 and AKT1/mTOR phosphorylation did not match sustained mTORC1 activity. Fasting-induced activation of AMPK/TSC2 signaling correlated with the inhibition of mTORC1 activity in the PN-group. Conversely, no AMPK/TSC2 activation was observed under hypoxic conditions, which correlated with sustained mTORC1 activity.

Conclusion: Fasting-induced AMPK signaling is impaired under hypoxia and is associated with sustained mTORC1 activity, which may sensitize skeletal muscle to fasting-induced muscle atrophy.

This study was performed within the framework of the Dutch Top Institute Pharma, project T1-201.

2-10

Acute hypoxia reduces plasma myostatin independent of hypoxic dose

Bradley T. Elliott[1,3], Tatum S. Simonson[2], Stephen J. Getting[1], Derek Renshaw[3], Peter D. Wagner[2], Richard W.A. Mackenzie[1]

[1]Faculty of Science & Technology, University of Westminster, United Kingdom, [2]Division of Physiology, University of California San Diego, USA, [3]Centre of Applied Biological & Exercise Sciences, Coventry University, United Kingdom

Background: Muscle atrophy is seen ~ 25 % of patients with cardiopulmonary disorders, such as chronic obstructive pulmonary disorder and chronic heart failure. Multiple hypotheses exist for this loss, including inactivity, inflammation, malnutrition and hypoxia. Healthy individuals exposed to chronic hypobaric hypoxia also show wasting, suggesting hypoxia alone is sufficient to induce atrophy. Myostatin regulates muscle mass and may underlie hypoxic-induced atrophy. Our previous work suggests a decrease in plasma myostatin and increase in muscle myostatin following 10 hours of exposure to 12 % O_2.

Aims: To establish the effect of hypoxic dose on plasma myostatin concentration. Concentration of plasma myostatin following two doses of normobaric hypoxia (10.7 % and 12.3 % O_2) in a randomised, single-blinded crossover design (n = 8 lowlanders, n = 1 Sherpa), with plasma collected pre (0 hours), post (2 hours) and 2 hours following (4 hours) exposure.

Results: An effect of time was noted, plasma myostatin decreased at 4 hours but not 2 hours relative to 0 hours ($p = 0.01$; 0 hours = 3.26 [0.408] $ng.mL^{-1}$, 2 hours = 3.33, [0.426] $ng.mL^{-1}$, 4 hours = 2.92, [0.342] $ng.mL^{-1}$). No difference in plasma myostatin response was seen between hypoxic conditions (10.7 % vs. 12.3 % O_2). Myostatin reduction in the Sherpa case study was similar to the lowlander cohort.

Conclusions: Decreased myostatin peptide expression suggests hypoxia in isolation is sufficient to challenge muscle homeostasis, independent of confounding factors seen in chronic cardiopulmonary disorders, in a manner consistent with our previous work. Decreased myostatin peptide may represent flux towards peripheral muscle, or a reduction to protect muscle mass. Chronic adaption to hypoxia does not appear to protect against this response, however larger cohorts are needed to confirm this. Future work will examine tissue changes in parallel with systemic effects.

2-11

Microarray analysis of human skeletal muscle indicates that overnight preoperative TPN alters transcription of targets for miR-24.

Britt-Marie Iresjö, Cecilia Engström Mattisson and Kent Lundholm

Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

Rationale: We have previously reported that muscle IGF1/IGF-1 receptor mRNA expression is altered in skeletal muscle tissue 3 hours

after oral food intake in mice. Recent research indicates that local muscle IGF-1 expression can alter microRNAs such as miR-206 and miR-24, associated with muscle cell differentiation. In the present study we examined if provision of a "standard" total parenteral nutrition (TPN) regimen affects muscle mRNA expression of IGF-1/IGF-1 receptor in patients scheduled for surgery and if gene targets for miRNA may be altered. In addition, transcripts for Myosin heavy chains (MHC) were measured to reflect alterations in transcription of myofibrillar proteins.
Method: 22 patients, with a history of recent involuntary weight loss, received either a continuous standard peripheral TPN infusion (0.16 gN·kg^{-1} day^{-1}, 30 kcal·kg^{-1} day^{-1}) or saline infusion for 12 hours prior scheduled upper GI surgery. Biopsies from the rectus abdominis muscle were taken at start of operation. Relative mRNA expression of IGF-1, IGF-1 receptor and MHC isoforms were analyzed by Real-time PCR. RNA expression microarray analysis was performed with Agilent Sureprint G3, 8 x 60K arrays using one-color labelling. Gene set enrichment analysis (GSEA) was performed to find miRNA targets with altered expression.
Results: IGF-1 mRNA expression was similar between patient groups while IGF-1 receptor expression was significantly lower in the TPN group ($p<0.01$). MHC2A mRNA levels were significantly lower in TPN treated patients ($p<0.05$) while MHC1 and MHC2X levels were similar between groups. Microarray analysis indicated 136 mRNAs as differently expressed between TPN and Control patients. Four targets for miR-24 were found by GSEA search. All showed significantly decreased expression in muscles from patients on TPN infusion ($p<0.05$).
Conclusion: Provision of standard TPN for 12 hours before operation decreased IGF-1 receptor mRNA and several targets for miR-24 concomitant with alterations in MHC expression. These observations may be important in treatment of cachexia.

2-12

Muscle wasting induced by botulinum toxin in mice using measured by microcomputed tomography (microCT)

Helene Libouban[1], Nicolas Minier[1], Claude Guintard[1,2], Eric Aguado[1,2], Daniel Chappard[1]
[1]GEROM, IRIS-IBS Institut de Biologie en Santé, Angers, France, [2]UPSP BBTO CEx, ONIRIS, ENVN Nantes, Nantes, France

Background and aims: Muscle and bone mass are highly correlated and muscle impose large load on bone. Long term immobilization or prolonged exposure to microgravity induce a severe muscle wasting and bone loss. Muscle wasting that accompanied bone loss has been poorly investigated mainly due to the lack of appropriate analytical method to quantify muscle loss by microCT.
Methods: 21 female mice were spread into 7 groups. At day 0, 18 mice received Botulinum toxin (BTX) injection in the quadriceps to induce paralysis of the right hindlimb; the left contralateral side was used as control. Mice were sacrificed at 7, 14, 21, 28, 56 and 90 days post-BTX (3 mice/group). The 56 and 90 day periods correspond to the recovery of disuse because of reversible effect of BTX. The remaining group was not injected and sacrificed at day 0. Hindlimbs were immersed in a contrast agent solution containing $HgCl_2$ for muscle visualization in 3D by microCT allowing a morphometric analysis. Three parameters were calculated for the gastrocnemius, quadriceps femoris and plantaris muscles: area (mm^2) occupied by each muscle in 2D section, circularity and aspect ratio. 2 muscles were carefully dissected and weighed (gastrocnemius and quadriceps femoris).
Results: The area of gastrocnemius and of quadriceps were significantly lower in the paralyzed limb from 7 days; the decrease was maximum at resp. 21 days (-46.9%) and 28 days (−47.9%). No difference in geometric form parameters were found between the paralyzed and non-paralyzed limb. No modifications were observed for the plantaris muscle which was not influence by BTX injection. Similar results were obtained with the anatomical method. Significant correlations were obtained between area and weight for the gastrocnemius and quadriceps muscles ($r = 0.782$, $p < 0.001$).
Conclusions: The use of a specific contrast agent opens new perspective to better understand musculoskeletal relationships.

2-13

Aged mice with antioxidant deficiency show improved muscle quality after dietary intervention with whey protein and antioxidants

Miriam van Dijk[1], Francina Dijk[1], Annelies Bunschoten[2], Dorien van Dartel[2], Klaske van Norren[1,3], Stephane Walrand[4], Marion Jourdan[1], Sjors Verlaan[1], Yvette Luiking[1]
[1]Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, the Netherlands, [2]Department of Animal Sciences, Human and Animal Physiology, Wageningen University, Wageningen, the Netherlands, [3]Nutrition and Pharmacology, Wageningen University, the Netherlands, [4]Unite de Nutrition Humaine, INRA-UdA, Clermont-Ferrand, France

Background and aim: During ageing, muscle mass, strength and quality decline. Oxidative stress has been suggested to contribute to sarcopenia, and antioxidants (AOX) deficiencies are common with ageing. The aim was two-fold: 1) to investigate if low levels of dietary antioxidants had a negative impact on muscle function in mature mice and 2) to study if nutritional interventions with AOX and/or protein could improve it.
Methods: 18-months-old mice were fed an AOX-deficient (vitamin A/E 600/5 IU/kg, Se 0.04, Zn 2.5 mg/kg=LOWOX) or a casein-based AIN-93-M control diet (CTRL) for 7 months. During the last 3 months, the LOWOXmice were randomized to 4 nutritional interventions: a) continued LOWOX, b) supplementation with vitamin A/E 8000/600 IU/kg, Se 2, Zn 35 mg/kg (AOXmix); substitution of casein protein with leucine-enriched whey protein (PROT) or a combination of both (TOTAL). Parameters of sarcopenia (muscle mass, grip strength and *ex-vivo* function), muscle fatigue (*ex-vivo* exercise-protocol), general oxidative status (liver malondialdehyde (MDA)) and muscle mitochondrial dynamics were measured.
Results: After 7 months LOWOXmice displayed lower muscle strength and more muscle fatigue compared to CTRL. Compared to LOWOXmice, the PROTmice showed higher muscle power, grip strength and less muscle fatigue ($P<0.05$). AOXmixmice showed improved liver MDA, less muscle fatigue, improved grip strength and mitochondrial dynamics compared to LOWOXmice ($P<0.05$). The TOTAL group showed the combined effects of both interventions compared to LOWOXmice ($P<0.05$).

Conclusions AOX-deficiency negatively impacts muscle strength and fatigue, possibly due to impaired mitochondrial dynamics. Nutritional intervention with AOX and/or whey protein can play a role in improving muscle function in older subjects who are AOX-deficient.

2-14

Role of P63 in muscle wasting associated with cancer

Paula Abreu, Yannick von-Grabowiecki, Georg Mellitzer, Christian Gaiddon
U1113-Molecular mechanisms of the stress response and pathologies, Strasbourg, France

Cancer is a complex pathology in which the patient survival is not solely dependent on the tumor mass and/or metastases development. Increasing evidences point out the impact of the tumors and/or the therapies on the impairment of the intellectual faculties and muscle strength. Muscle fatigue and atrophy account for ± 20% of cancer death. Based on their role in cell differentiation, survival and metabolism, we investigated the role of the p53 family members in muscle atrophy. In particular, we investigated whether TAp63 regulates MuRF-1, an ubiquitin ligase important in muscle atrophy.
C2C12 myoblastic cells and muscle of TAp63-/- mice treated with the anticancer drug doxorubicin were analyzed by RT-qPCR and chromatin immunoprecipitation assays to identify a relationship between TAp63 and MuRF1.
Doxorubicin induces the expression of MuRF1, TAp63 and TAp73 in C2C12 cells and in muscles. Time course experiments with doxorubicin in wild type mice showed that Murf1 is mainly induced in an early stage of the atrophy process. Similar time course investigations in C2C12 cells showed that Tap63, Tap73 and Murf1 have an increase in the mRNA levels at the same time point. Overexpression of TAp63 induced MuRF1 expression. MuRF1 expression is decreased in C2C12 cells or in muscles when TAp63 is knockdown. However, the induction of MurF1 by doxorubicin is further induced by TAp63 silencing, which correlates with an inhibition of ΔNp63 expression.
TAp63 seems to be important to the basal expression of Murf1 but also have a modulator effect under stress caused by doxorubicin. Our work will contribute to characterize the interaction between p63 and Murf1 and to clarify the molecular pathways involved in muscle atrophy.

2-15

Hypoxia-induced muscle atrophy and impaired regulation of protein turnover are partially dependent on muscle GR signaling

Ramon C.J. Langen[1,2], Chiel C. de Theije[1,2,†], Wout H. Lamers[1,3], Judith J.M. Ceelen[1,2], J.J. Rob Hermans[4], S. Eleonor Köhler[1,3], Annemie M.W.J. Schols[1,2]
Maastricht University Medical Center[+], Maastricht, Netherlands: [1]NUTRIM School of Nutrition and Translational Research in Metabolism, [2]Department of Respiratory Medicine, [3]Department of Anatomy & Embryology, [4]Department of Pharmacology

Background and aims: Tissue hypoxia may contribute to muscle wasting in COPD. Hypoxemia induces skeletal muscle atrophy in mice, which in part can be attributed to a reduction of food intake. As increased glucocorticoid concentrations and glucocorticoid receptor (GR) signaling have been implicated in fasting-induced muscle atrophy, the aim of this study was to investigate whether hypoxia-induced muscle atrophy is GR dependent.
Methods: Muscle-specific GR knockout (mGRKO) mice and control mice were subjected to normoxia, normobaric hypoxia (8% oxygen) or pair-fed conditions to control for the hypoxia-induced reduction in food intake for 4 days. Muscle mass, fiber cross sectional area, and indices of protein synthesis and degradation signaling were determined in dissected muscle.
Results: Hypoxia and reduced food-intake resulted in an elevated corticosterone plasma concentration and an induction of GR-dependent gene expression (*Klf15*, *Glul* and *Foxo1*) in gastrocnemius muscle. GR deficiency prevented muscle atrophy in the pair-fed group but not in the hypoxic group. GR deficiency blunted elevated expression of autophagy-lysosomal degradation related genes (*Map1lc3B*, *Bnip3*) in both hypoxic and pair-fed conditions. Hypoxia-induced expression of the Ub 26S-proteasom E3 ligases (*Murf1*, *Atrogin-1*) was suppressed in the pair-fed group only. Based on phosphorylation of 4E-BP1 and S6, mTOR signaling was suppressed in response to reduced food intake, but surprisingly maintained following hypoxia. This deregulation of mTORC1 by hypoxia was GR-dependent and did not involve the established Akt/TSC2/mTOR axis or alterations in *Redd1* or *Klf15* expression.
Conclusion: Hypoxia-induced muscle atrophy is only partly attributable to muscle GR signaling. Moreover, GR signaling is responsible for impaired regulation of mTORC1 by hypoxia.
This study was performed within the framework of the Dutch Top Institute Pharma, project T1-201.

2-16

Identification and analysis of endogenous SUMOylated muscle proteins in mechanically ventilated diaphragms rat

Arvind Venkat Namuduri[1], Nicola Cacciani[1], Anne Konzer[2], Katarina Hörnaeus[2], Åsa Eriksson[2], Sara Bergström Lind[2], Lars Larsson[1], Stefano Gastaldello[1]
[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Analytical Chemistry, Dept. Chemistry-BMC and Science for Lab Laboratory, Uppsala University, Uppsala, Sweden

Mechanical ventilation is used in the Intensive Care Units to maintain sufficient pulmonary gas exchange in patients suffering from acute drug overdose, neuromuscular diseases, sepsis, and during surgery along with postsurgical recovery.
Although MV can be a life saving measure, a prolonged treatment results in the rapid development of the ventilator-induced diaphragmatic dysfunctions (VIDD) disease. The primary respiratory muscle dysfunction observed is a significant decrease in force-generating

capacity associated with a diaphragmatic oxidative stress condition. The major consequences of VIDD are: i. prolonging time to weaning patients from the ventilator, ii. increasing health care costs and iii. increase patient morbidity and mortality.

Post-translational modification by attachment of the Small Ubiquitin-related Modifier (SUMO) to a specific lysine is one of the most common regulatory protein changes in eukaryotic cells. SUMO conjugation and deconjugation is a very dynamic and sensitive equilibrium that can easily be disturbed by endogenous and exogenous stressor both in cellular and in complex organ tissues like muscle.

In this study our goal was to identify and characterized, the endogenous SUMOylated muscle proteins from control and from 6 hours to 13 days mechanically ventilated diaphragms rat. Immuno-SUMO1-2-3 complexes were isolated by specific anti-SUMO1 and anti-SUMO2/3 monoclonal antibodies generated from hybridoma cell lines and coupled to protein G-agarose beads. Conventional Mass-Spectrometry and bioinformatics tools were adopted to identify the SUMO protein complexes.

Finally, we provided an endogenous muscle SUMO1 and SUMO2/3 proteome of a healthy respiratory muscles rat including a classification of the SUMO related proteins according to their biological function and also a list of potential muscle proteins that become a SUMO target during MV treatment.

Further studies on these new identified proteins along the intervention will provide the knowledge necessary for the development of a pharmacological approach that can prevent VIDD and reduce the incidence of weaning problems.

2-17

Mitochondrial depletion and MAPKs activation are associated with the occurrence of muscle loss and fatigue: a potential mechanism for chemotherapy-associated cachexia

Andrea Bonetto

Department of Surgery, IU Simon Cancer Center and Indiana University School of Medicine, Indianapolis, IN, USA

Cachexia is defined by increased fatigue and loss of muscle function resulting from muscle and fat depletion, and affects the majority of cancer patients with no effective treatments. Previous studies suggest that chemotherapy itself may contribute to cachexia. For example, cancer patients affected with sarcopenia show reduced survival and increased susceptibility to severe chemotherapy-associated toxicity. The purpose of this study was to investigate the mechanism(s) associated with chemotherapy-related effects on body composition and muscle function. We examined commonly used chemotherapeutics such as 5-fluorouracil (5-FU), irinotecan, leucovorin, paclitaxel and gemcitabine. We found that these treatments cause cytotoxicity and dose-dependent muscle fiber wasting in murine C2C12 myotubes. In addition, CD2F1 mice that were administered FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI (5-FU, leucovorin, irinotecan) or gemcitabine/paclitaxel for up to 5 weeks showed transient toxicity and reduced food intake. These mice also exhibited marked decreases in skeletal muscle content consistent with reduced whole body muscle strength. Fat tissue was also severely depleted (up to 63%). EMT analysis also revealed a marked depletion in muscle mitochondrial content in the mice that received chemotherapy. Using LC/MS-protein quantitative analysis of skeletal muscle from mice administered chemotherapy, we observed modulation of several proteins associated with mitochondrial homeostasis/biogenesis. Interestingly, ERK1/2/MAPK and p38/MAPK signaling pathways were significantly up-regulated, potentially suggesting a causative relationship with enhanced oxidative stress. These findings suggest that chemotherapy may play a causative role in the occurrence of muscle loss and fatigue, possibly by enhancing oxidative stress and promoting the activation of MAPK-dependent muscle atrophy. Further studies are required to isolate the mechanisms that drive chemotherapy-dependent muscle depletion. Future investigations will clarify whether pharmacologically increasing muscle mass or inhibiting MAPK activation reduces chemotherapy-related cachexia, thereby providing potential pharmacological targets to improve efficacy and tolerance of anticancer drugs.

2-18

Specific post-translational modifications of the slow myosin isoform associate with dysfunctional contraction of skeletal muscle in old age

Meishan Li[1,2], Hannah Ogilvie[1,2], Konstantin Artemenko[3], Jonas Bergquist[3], Lars Larsson[1,2]

[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Department of Clinical Neuroscience, Clinical Neurophysiology, Karolinska Institutet, Stockholm, Sweden, [3]Department of Chemistry - Biomedical Centre, Analytical Chemistry, Uppsala University, Uppsala, Sweden

Background and aims: The impaired muscle function in old age is secondary to both quantitative and qualitative changes of skeletal muscle and is referred to as *sarcopenia.* The quantitative decrease in muscle mass has been studied widely, but the qualitative changes that affect muscle function are less known. The aims of the present study are to investigate the effects of aging on the function of the β/slow (type I) myosin isoform and to identify the associated aging-specific post-translational modifications (PTMs).

Methods: Skinned single muscle fibers expressing type I myosin isoform from young (6 months) and old (28 months) female Fisher 344 rats were prepared. Single fiber contractile measurements, single fiber *in vitro* motility assays, and mass spectrometry analyses were used to evaluate contractile function and to identify aging-specific PTMs.

Results: At the muscle fiber level, cross sectional area (CSA, 667 ± 53 vs. 928 ± 49 μm^2), specific tension (ST, 20.8 ± 7.1 vs. 26.3 ± 6.5 N/cm^2) and maximum velocity of unloaded shortening (V_0, 0.54 ± 0.06 vs.0.59 ± 0.06 ML/s) were significantly decreased in the old vs. young rats ($P<0.05$). At the protein level, motility speed was significantly slower in the old vs. young rats (0.59 ± 0.08 vs. 0.72 ± 0.10 μm/s) ($P<0.05$). The force index, on the other hand, did not differ between old and young rats. Three aging specific PTMs were identified, i.e., oxidation of Phe436 and carbonylation of Trp438 located in the myosin motor domain and deamidation of gln1854 in the rod region.

Conclusions: The aging-related decline in contractile speed at the muscle cell and motor protein level were associated with specific PTMs in the β/slow myosin isoform. However, the unchanged force-

generation capacity of myosin at the motor protein level and the decreased force-generating capacity at the muscle fiber level suggest quantitative rather than qualitative changes in contractile proteins.

2-19

Effects of 11b-HSD1 inhibitor on the muscle atrophy induced by the glucocorticoid excess

Michiyoshi Hatanaka, Ryo Yoshimoto, Ayumi Kato, Toru Yanagimoto, Hideo Yukioka
Discovery Research Laboratory for Innovative Frontier Medicines, Shionogi & Co., Ltd., Osaka, Japan

Background: Sarcopenia and cachexia are muscle wasting syndromes associated with many chronic diseases, such as congestive heart failure, cancer and chronic obstructive pulmonary disease. While mechanisms are complex, these conditions are often accompanied by elevated glucocorticoid levels. A growing body of evidence demonstrates that glucocorticoid signaling is a major mediator of muscle atrophy. The activity of glucocorticoid is modulated by two enzymatic activities that interconvert cortisol to cortisone. 11beta-hydroxysteroid dehydrogenase1 (11b-HSD1) converts cortisone that does not activate glucocorticoid receptor to cortisol that activate glucocorticoid receptor. The evidences that 11b-HSD1 is present and biologically active in human skeletal muscle suggest the possibility of 11b-HSD1 activity inhibition in the skeletal muscle as a novel therapeutic option for the muscle atrophy under the glucocorticoid excess condition. In this study, we have investigated the possibility by using a newly synthesized small molecule 11b-HSD1 inhibitor, compound H, in our laboratory and a novel muscle atrophy model mice induced by the glucocorticoid excess.
Results: Compound H is a highly potent and selective 11β-HSD1 inhibitor. Compound H treatment significantly inhibited cortisone mediated Atrogin and MuRF1 mRNA expression in C2C12. Also, significant inhibition of 11b-HSD1 activity in the muscle tissue homogenate was observed. Implantation of cortisone pellet to mice increased the plasma cortisone and cortisol levels. Moreover, the body weight, the skeletal muscle weight and the grip force was significantly decreased in 9 days after the implantation of pellet. Single oral administration of Compound H to mice inhibited 11β-HSD1 activity in the skeletal muscle in a dose-dependent manner. Daily administration of compound H ameliorated the decrease of the body weight, the skeletal muscle weight and the grip force significantly in the muscle atrophy model mice.
Conclusions: These results demonstrated that inhibition of 11β-HSD1 with compound H can suppress the muscle atrophy induced by the glucocorticoid excess.

2-20

Mouse cachectic skeletal muscle anabolic response to acute and chronic eccentric contractions.

Justin P. Hardee[1], Song Gao[1], Dennis K. Fix[1], Brandon N. VanderVeen[1], Kimbell L. Hetzler[1], James A. Carson[1,2]
[1]Integrative Muscle Biology Laboratory, University of South Carolina, Columbia, SC, [2]Center for Colon Cancer Research, University of South Carolina, Columbia, SC, USA

While cancer cachexia disrupts the regulation of muscle protein turnover, it is less certain if suppressed protein synthesis in cachectic muscle can respond to increased use. Eccentric muscle contractions (ECC) can induce growth that is associated with activated mTORC1 signaling. This study's purpose was to determine if cachexia suppressed the acute and training response of skeletal muscle to eccentric contractions. Acute muscle protein synthesis activation post-contraction and the training effect on myofiber growth were examined in cachectic mice. The acute study examined eccentrically contracted tibialis anterior (TA) muscle 3h post-contraction from cachectic male ApcMin/+ mice (N = 5; 15% bw loss). The second experiment examined repeated ECC training in male ApcMin/+ mice initiating cachexia (N = 9; 7% body weight loss), which performed 7 bouts of ECC over 2-wks. TA cross-sectional area (CSA) was examined in type IIA, IIX, and IIB fibers. In both experiments the left TA performed ECC while the right TA served as intra-animal control. C57BL/6 (WT) mice served as controls. Cachexia decreased TA muscle mass, mTORC1 signaling, and protein synthesis when compared to WT controls. Cachexia did not inhibit the acute ECC induction of mTORC1 signaling and protein synthesis, but protein synthesis remained significantly suppressed compared to WT. In the second study ApcMin/+ mice body weight decreased during training (11% loss from peak). Cachexia decreased control TA muscle mass and the CSA of all fiber-types examined. In contrast, ECC increased TA muscle mass and the CSA of all fiber-types in the cachectic mouse. Although cachexia suppresses muscle anabolic signaling, these data demonstrate that cachectic muscle retains the capacity to adapt to increased use related to growth stimulating eccentric contractions. Additionally, multiple bouts of ECC can initiate myofiber growth of all fiber-types during the progression of cachexia. Muscle contraction may have therapeutic potential to attenuate muscle mass loss with cancer cachexia.

2-21

Tumor-derived microvesicles: new players in cancer-induced muscle wasting

Fabrizio Pin[1,2], Riccardo Ballarò[1], Fabio Penna[1], Marc Beltrà Bach[1], Denis C. Guttridge[2], Paola Costelli[1]
[1]Department of Clinical and Biological Sciences, Experimental Medicine and Clinical Pathology Unit, University of Torino, Torino, Italy, [2]Human Cancer Genetics Program Department of Molecular Virology Immunology and Medical Genetics, The Ohio State University, Columbus (OH), USA

Rationale: Cancer cachexia is a debilitating syndrome characterized by skeletal muscle wasting, impairment of myogenesis and metabolic abnormalities, mediated, partially at least, by humoral factors. In this regard, tumor-derived microvesicles (MVs), circulating particles containing proteins, mRNAs and microRNAs, likely contribute to cancer-induced muscle wasting (1).
Methods: MVs were isolated by differential ultracentrifugation from the conditioned medium of LLC (Lewis Lung Carcinoma) or C26 (colon adenocarcinoma C26) cells, and were quantified by a NanoSigth apparatus. MVs were added to the culture medium of C2C12 myotubes for 24 h. The effects on protein turnover and energy metabolism were assessed.

Results: C2C12 myotubes exposed to MVs do not show changes in the mRNA expression of Atrogin-1, MuRF-1 and myosin heavy chain (MyHC). By contrast, mRNA levels of the mitochondrial biogenesis promoter PGC-1α and Cytochrome C (CytC) are reduced, while those of BNIP3, involved in mitochondrial degradation, are increased. Oxygen consumption in MV-treated myotubes is decreased while lactate levels are increased. Reduced CytC protein levels can be observed also in MV-treated differentiating C2C12 myoblasts. The involvement of mitochondria in myogenesis is supported by results obtained on PGC1α-overexpressing mice, where myogenic precursors, more abundant than in wild-type animals, lead to myotubes increased in both number and size in comparison to those obtained from wild-type progenitors.
Conclusions: These results show that while MVs do not affect protein turnover in C2C12 myotubes, at least as assessed by mRNA expression of Atrogin-1, MuRF-1 and MyHC, they modulate energy metabolism, likely reducing mitochondrial mass and function, possibly resulting also in impaired myogenesis. On the whole, MV-induced alterations could contribute to muscle wasting during cancer cachexia.
1) He WA[1], Calore F, Londhe P, Canella A, Guttridge DC, Croce CM. Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proc Natl Acad Sci U S A. 2014 Mar 25;111 (12):4525-9.

2-22

Inactivation of USP19 prevents muscle wasting upon fasting by improving protein synthesis and modulating insulin, glucocorticoid and MEF2C signaling pathways

Erin Coyne[1], Samer Jammoul[2], Nathalie Bedard[2], Kezhuo Zhang[3], Linda Wykes[4], Robert S. Sladek[2,3], Simon S. Wing[1,2]
[1]Dept. of Biochemistry, [2]Dept. of Medicine, [3]Dept. of Human Genetics, [4]School of Dietetics & Human Nutrition, McGill University and Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Background and aims: USP19 deubiquitinating enzyme is induced in skeletal muscle atrophying in response to cancer and many other catabolic conditions in mice and its expression correlates with that of atrogin-1 and MuRF1 in skeletal muscle in patients with lung or gastrointestinal cancer. Mice lacking USP19 are protected against glucocorticoid or denervation atrophy due to suppression of proteolytic systems. Since anorexia is an important feature of cachexia, we also explored whether USP19 KO mice are protected against fasting induced atrophy.
Methods: WT and USP19 KO mice were fed or fasted for 48 hours. Rates of protein synthesis, expression of markers of proteolytic systems, microarray analyses of gene expression were analyzed in the skeletal muscles. Insulin stimulated signaling was also assessed in WT and KO mice.
Results: Upon fasting, KO mice lost less muscle mass than WT mice. Muscle grip strength was also enhanced in fasted KO mice. In contrast to what was observed in glucocorticoid induced atrophy, protein synthesis rates were higher in muscle of fasted KO mice compared to fasted WT mice whilst markers of proteolytic systems were not significantly changed. The increase in muscle myostatin expression seen upon fasting in WT mice was completely inhibited in KO mice. Insulin stimulated phosphorylation of Akt and p70-S6kinase were increased in KO muscle compared to WT muscle. Analysis of gene expression and glucocorticoid receptor levels were consistent with altered responses to glucocorticoid and MEF2C signaling in the KO muscles.
Conclusions: Loss of USP19 suppresses proteolysis upon glucocorticoid stimulation, but enhances protein synthesis upon fasting. Since both increased stress and anorexia are features of many cachectic states, these beneficial effects of inhibition of USP19 on both protein synthesis and degradation may be particularly useful in preventing loss of muscle mass and function.

2-23

Effects of exercise and blocking activing receptor ligands on the redox status and unfolded protein response of mdx mouse

Jaakko Hentilä[1], Ayhan Korkmaz[2], Konstantinos G. Papaioannou[1], Reija Autio[3], Arja Pasternack[4], Urho M. Kujala[5], Olli Ritvos[4], Heikki Kainulainen[1], Mustafa Atalay[2], Juha J. Hulmi[1,6]
[1]University of Jyväskylä, Department of Biology of Physical Activity, Neuromuscular Research Center, University of Jyvaskyla, Finland, [2]Institute of Biomedicine, Physiology, University of Eastern Finland, Kuopio, Finland, [3]Department of Signal Processing, Tampere University of Technology, Tampere, Finland, [4]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Finland, [5]Department of Health Sciences, University of Jyväskylä, University of Jyväskylä, Finland, [6]Department of Physiology, Faculty of medicine, University of Helsinki, Finland

Background and aims: Oxidative stress is the state of imbalance between oxidants and antioxidants levels and disruption of redox control of cellular events. It is closely related to endoplasmic reticulum (ER) stress and unfolded protein response (UPR). Although oxidative stress contributes to the pathophysiology of Duchenne Muscular Dystrophy (DMD), little is known about the UPR in DMD. Myostatin/activin blocking and exercise are promising therapy candidates for muscle wasting diseases. Therefore, the aim of the study was to investigate the effects of muscular dystrophy, myostatin/activing blocking and exercise on these various cellular stress states.
Methods: The combined and independent effects of soluble activin receptor ligand blocker (sActRIIB-Fc) and 7 weeks of voluntary wheel running on oxidative and ER stress and UPR were investigated in gastrocnemius muscle of mdx mice, a model for DMD.
Results: Many, but not all pathways of ER stress/UPR were upregulated in mdx mice ($P<0.05$). Oxidized (GSSG) and reduced (GSH) forms of glutathione were increased in mdx when compared to wild-type mice together with decreased grip strength and hanging wire endurance. Exercise, especially in sActRIIB-Fc-administered mdx mice increased protein carbonyls accompanied by increased GSSG/GSH suggesting increased oxidative stress. This was seen without altering endogenous antioxidant capacity (GSH and enzyme activities of glutathione peroxidase and reductase). sActRIIB-Fc, however, increased some (GRP78 and TxNIP), but not all of the ER stress/UPR markers.
Conclusions: Altered antioxidant metabolism was observed in dystrophic mice accompanied by elevation of many UPR biomarkers.

Exercise independently and combined with sActRIIB-Fc administration resulted in elevated oxidative stress that dystrophic mice could not fully rescue with endogenous antioxidants. Finally, sActRIIB-Fc administration may increase UPR, but this needs further studies.
This work was supported by Academy of Finland grant No. 137787.

2-24

Blocking activin receptor ligands prevents doxorubicin-induced cachexia and blunted muscle protein synthesis

Juha J. Hulmi[1,2], Tuuli A. Nissinen[1], Joni Degerman[3], Markus Räsänen[3], Satu Koskinen[4], Arja Pasternack[5], Olli Ritvos[5], Riikka Kivelä[3]
[1]Department of Biology of Physical Activity, Neuromuscular Research Center, University of Jyväskylä, Jyväskylä, Finland, [2]Department of Physiology, Faculty of medicine, University of Helsinki, Helsinki, Finland, [3]Wihuri Research Institute and Translational Cancer Biology Program, University of Helsinki, Biomedicum Helsinki, Finland, [4]LIKES Research Center for Sport and Health Sciences, Jyväskylä, Finland, [5]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland

Background and aims: Doxorubicin is a widely used and effective anthracycline chemotherapy drug. However, it causes cardiotoxicity and also a few negative effects on skeletal muscle as well. As a result, cancer treatment might actually worsen cancer-induced cachexia and consequently the prognosis of the disease. Inhibiting myostatin/activin signaling is known to increase muscle size. This pathway blockade by soluble activin receptor IIB (sActRIIB-Fc) has also prolonged survival in cancer, even of animals in which tumor growth is not inhibited. It is not known, however, whether blocking this pathway affects chemotherapy-induced muscle wasting.
Methods and results: Four-week period with two-week doxorubicin administration (4 x 6 mg/kg intraperitoneally (2x/wk)) into C57BL/6 mice decreased body mass, muscle mass, lean mass and fat mass measured by DXA and tissue weighing ($P<0.05$). Another experiment, showed that the decreased muscle and fat mass was observed already at 2 weeks. Doxorubicin administration also resulted in decreased muscle fiber cross-sectional area of tibialis anterior muscle. However, 1-2 x / wk (5 mg/kg) intraperitoneal administration of sActRIIB-Fc completely prevented the body and muscle mass as well as fiber size decrease by doxorubicin. This was accomplished even though the feed intake was even further decreased by sActRIIB-Fc increasing fat tissue loss. To understand the mechanisms for muscle results, mice were sacrificed acutely after single sActRIIB-Fc and doxorubicin administration. Doxorubicin decreased muscle protein synthesis and sActRIIB-Fc completely blocked this response. This was accompanied by increased mTORC1 signaling (elevated p-rpS6 and p-S6K1) by sActRIIB-Fc, but was unchanged by doxorubicin. This suggests that doxorubicin and sActRIIB-Fc are not affecting same pathways regulating muscle mass.
Conclusions: These results show that blocking ActRIIB signaling pathway is a promising strategy to prevent chemotherapy induced muscle wasting.
This work was supported by Academy of Finland grant No. 275922.

2-25

Transgenic models of cardiac cachexia and cardiac effects of muscular atrophy

Valentina Sala[1], Stefano Gatti[2], Simona Gallo[2], Daniella Cantarella[3], Enzo Medico[2], Antonio Ponzetto[1], Tiziana Crepaldi[2]
[1]Dept. of Medical Sciences, University of Turin, Italy, [2]Dept. of Oncology, University of Turin, Italy: [3]IRCCS-Candiolo, Candiolo (TO), Italy

Background and aims: Cachexia is a common feature of heart failure and is associated with poor prognosis, increased mortality, unfavourable response to treatment and poor quality of life. Moreover, evidences indicate that cachexia itself has cardiac implications. Because of the difficulties in generating clinical trials for cardiac cachexia, well-characterized animal models are needed to explore the aetiological flow from triggers to disease. This could enable clinicians to identify new therapeutically targetable entities.
Methods: The Hepatocyte Growth Factor and its tyrosine-kinase receptor c-Met are involved in many physio-pathological processes, including heart and skeletal muscle growth. To investigate the effects of a sustained activation of Met signalling, we generated two transgenic mouse models with tetracycline-suppressible expression of Tpr-Met, the constitutively active form of Met. Tpr-Met expression was addressed specifically to cardiac or skeletal muscle, by means of αMHC and MCK promoters, respectively.
Results: αMHC-Tpr-Met mice revealed as a model of heart failure with early exordium and high penetrance: these mice develop a concentric hypertrophy, which rapidly progresses into congestive heart failure and cardiac cachexia. Cardiac and skeletal muscles from cachectic mice were analysed, and altered pathways/candidate messenger mediators secreted by the heart were highlighted, which could contribute to muscle wasting. Notably, the suppression of Tpr-Met expression and downstream signalling reversed cardiac hypertrophy and prevented the cachectic outcome.
Next, with MCK-Tpr-Met mice, we generated a transgenic model of skeletal muscle wasting, which also shows atrophy of the cardiac muscle.
Conclusions: Congestive heart failure and cachexia may be linked by a reciprocal causal relationship. The study of αMHC/MCK-Tpr-Met transgenic models might be useful for the identification of molecules responsible for heart-to-skeletal muscle cross-talk and vice versa; indeed, identifying early targets for therapeutic intervention against this pathogenic loop is a fundamental goal to delay wasting.

2-26

Acupuncture plus low-frequency electrical stimulation (Acu/LFES) attenuates diabetic myopathy by enhancing muscle regeneration

Xiaonan Wang
Renal Division, Emory University School of Medicine Atlanta, GA, USA
Aim: Mortality and morbidity are increased in patients with catabolic diseases such as diabetes. Previously we discovered that exercise has

the ability to thwart the detrimental effects caused by catabolic diseases. Unfortunately, patients with severe diseases are usually unable to consistently exercise. We hypothesized that Acu/LFES will mimic exercise and prevent diabetes-induced muscle loss.

Methods: Streptozotocin (STZ) was used to induce diabetes in mice. The mice were then treated with Acu/LFES for 15 minutes daily for 2 weeks. Acupuncture points were selected according to the WHO Standard Acupuncture Nomenclature guide. The needles were connected to an SDZ-II Electronic acupuncture device delivering pulses at 20Hz and 1mA.

Results: Western blot and mRNA expression were used to analyze the change of myogenesis proteins. Expressions of MyoD (proliferation marker), myogenin (differentiation marker) and eMyHC (differentiation and fusion marker) were significantly decreased in diabetic muscle vs. control muscle. The suppressed levels in diabetic muscle were reversed by Acu/LFES. These protein levels were also upregulated in healthy mice. Immunohistochemistry revealed that Acu/LFES stimulates satellite cell migration into myofibers within 24 hours promoting myogenesis. At day-2, central nuclei, indicating new muscle cells, are apparent. At day-3 the decrease of central nuclei indicate satellite cell fusion with myofibers.

Conclusion: We conclude that Acu/LFES is effective in counteracting diabetes-induced skeletal muscle atrophy, in part by stimulation of myogenesis.

Funding: NIH/NIAMS: R01 AR060268

2-27

Vitamin D regulates muscle strength: Grip strength in vitmain D deficient and vitamin D receptor (VDR) knockout mice

Jenny E. Gunton[1], Christian M. Girgis[1], Peter J. Houweling[1], Kuan Minn Cha[1], Roderick Clifton-Bligh[2]

[1]Westmead Millennium Institute, University of Sydney, Australia, [2]University of Sydney, Australia

Background: Vitamin D deficiency has been associated with muscle weakness, pain, atrophy and falls. Serum vitamin D levels predict muscle strength, age-related decline in muscle mass and function; i.e. sarcopenia. However with the many confounders, it has been unclear whether vitamin D directly affects muscle function.

Methods and Results: Using 2 models; vitamin D receptor knockout (VDRKO) mice and mice with diet-induced vitamin D deficiency (D-def), we examined grip strength and muscle weights. Both groups of mice and their respective controls were fed high-calcium high-phosphate diets to prevent defects in those minerals. Serum calcium and phosphate did not differ in the groups of mice ($p>0.4$). VDRKO and D-def mice were significantly weaker than their respective controls, and the weakness progressed with age. VDRKO mice were 43% weaker and VDR-het mice were 30% weaker adjusted for weight than their controls at 7 weeks of age. At 14 weeks, they were 48% weaker and 40% weaker (all $p<0.005$).

D-def mice were also weaker than their controls. After 7 weeks, they were 15% weaker and after 10 weeks of diet they were 25% weaker ($p<0.05$ for both).

Muscles from VDRKO mice were significantly smaller than their WT littermates (8-25% reduction depending on the muscle, $p<0.005$). No muscle weight differences were seen in the D-def mice.

In summary, deletion of VDR dose-dependently decreases grip strength in mice, and vitamin D deficiency also causes pronounced weakness. Deletion of VDR is also associated with loss of muscle mass, the second hallmark of sarcopenia. Together these findings suggest that vitamin D does play an important role in muscle function and sarcopenia.

2-28

MEK inhibition rescues cancer cachexia by preserving muscle mass through a tumor extrinsic pathway

Erin E. Talbert[1, 2], Jennifer Yang[1,3], Gregory B. Lesinski[1,4], Denis C. Guttridge[1,2,3]

[1]Arthur G. James Comprehensive Cancer Center Cancer Cachexia Program, [2]Department of Molecular Virology, Immunology, and Medical Genetics, [3]Molecular, Cellular, and Developmental Biology Program, [4]Department of Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio 43210, USA

Cachexia is a debilitating co-morbidity of cancer characterized by involuntary weight loss. Patients with gastrointestinal cancers are particularly susceptible to weight loss, including the loss of skeletal muscle. A recent clinical trial revealed that cholangiocarcinoma patients treated with the MEK inhibitor Selumetinib gained weight and skeletal muscle mass, implying that MEK inhibition is anti-cachectic. To gain insight into this finding, we treated mice bearing Colon-26 (C-26) tumors with MEK162, a MEK1/2 inhibitor in clinical trials for solid tumors. Similar to the cholangiocarcinoma trial data, MEK162 had poor anti-tumor activity, yet was efficacious in preventing weight loss and muscle wasting. Further, MEK162 is not simply an anabolic agent, as muscle mass of non-tumor-bearing mice was not increased by MEK162 treatment. To confirm that the effect of MEK162 on lean muscle was unrelated to alterations in the tumor, we created a MEK162-resistant C-26 cell line (C-26R). MEK162 spared body weight and skeletal muscle in mice with C-26R tumors, confirming that MEK inhibition prevents cachexia through a tumor-extrinsic mechanism. Although such results are encouraging, successful anti-cancer therapy will need to treat both host tissues and malignant cells. Indeed, consistent with MEK resistance, we observed that C-26R cells exhibited a compensatory activation of the PI3K/Akt pathway. Therefore, we dosed C-26 bearing mice with a combinatorial therapy of MEK162 and the PI3K/Akt inhibitor, buparlisib. Compared to treatment with buparlisib alone, which significantly decreased tumor growth but was unable to rescue cachexia, the combination of MEK162 and buparlisib had a pronounced anti-tumor activity and rescued body weight loss and muscle wasting. Combination treatment likely prevented tumor growth via increased cytotoxic T and decreased immune suppressor cells. In summary, results show MEK162 is an anti-cachectic compound that should be considered as a potential partner for anti-tumor therapies in cancers with negative effects on skeletal muscle.

2-29

Four component (4C) body composition and REE in children with end stage liver disease (ESLD)

Eirini Kyrana[1], Jane E. Williams[2], Jonathan C.K. Wells[2], Anil Dhawan[1]
[1]Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, [2]Childhood Nutrition Research Centre, UCL Institute of Child Health, London, United Kingdom

Background: Cachexia has been described in adults with liver disease. These are results of a larger ongoing study of cachexia in children with ESLD. The 4C model is the gold standard for *in vivo* differentiation of fat and fat free mass.
Methods: The 4C model uses the following equations:
FM= (2.747 X BV) – (0.710 X TBW) + (1.460 X BMC) – (2.050 X WT) (1)
FFM= WT- FM
FM: fat mass, BV: body volume (by BOD POD), TBW: total body water (by deuterium stable isotope), BMC: body mineral content (by DXA scan), WT: weight and FFM: fat free mass.
REE was measured by indirect calorimetry and compared to the predicted REE as per *Henry 2005* equations. Hypermetabolism was REE of >120% of predicted REE.
Results: Five children with ESLD (3F:2M) awaiting liver transplant had their body composition measured.

Conclusion: 4 of 5 patients had z-scores for FFM lower than their z-scores for BMI and FM, indicating a reduction in muscle mass. 3 of 5 patients were hypermetabolic. In spite of reassuring BMIs, this hypermetabolism could place them at risk for future weight loss and wasting.
1. Wells JC, Fuller NJ, Dewit O, et al. Four-component model of body composition in children: density and hydration of fat-free mass and comparison with simpler models. Am J Clin Nutr 1999;69(5):904-12.

Table 1 Body composition data

ID	Weight (kg)	Weight z-score	Height (cm)	Height z-score	BMI	**BMI z-score**	FM (kg)	**FM z-score**	FFM (kg)	**FFM z-score**
1	31.8	−0.02	154.6	2.67	13.3	**−2.22**	4.77	**−1.33**	27.03	**0.33**
2	21.7	1.02	112.4	0.38	17.1	**1.13**	7.93	**1.8**	13.77	**−1.33**
3	33.4	−0.14	131.2	−1.55	19.4	**0.88**	6.83	**1**	26.57	**−0.67**
4	21.8	−2.16	119.6	−2.54	15.24	**−0.57**	3.99	**−0.67**	17.8	**−2**
5	59.01	0.42	167.4	0.71	21.1	**0.09**	18.9	**0.56**	40.1	**−0.33**

Table 2 REE of patients

ID	REE/preREE	(REE-preREE)/ preREE %	REE/Kg	REE/FFM
1	1572/1179	**33.30%**	49.4	**58.15**
2	1166/986	**18.30%**	53.7	**84.68**
3	1455/1102	**32%**	43.7	**54.75**
4	1284/1010	**27.10%**	58.9	**72.1**
5	1503/1534	**-2%**	25.47	**37.47**

2-30

Evaluation of weight loss over time in cats with chronic kidney disease

Lisa M. Freeman, Marie-Paul Lachaud, Sean Matthews, Linda Rhodes, Bill Zollers
Tufts Cummings School of Veterinary Medicine, Department of Clinical Sciences, North Grafton, USA

Background and aims*:* Thin body condition, weight loss, and muscle loss are common in pet cats with naturally-occurring chronic kidney disease (CKD). However, the time course and progression of weight loss before and after diagnosis have not been thoroughly evaluated. Therefore, the purpose of this retrospective analysis was to describe the weight loss experienced by cats with CKD before and after diagnosis.
Methods*:* Pet cats with CKD from 6 US veterinary practices for which International Renal Interest Society (IRIS) stage was available were eligible. Only those with age, date of CKD diagnosis, and body weight measurements available in the 3 years before and after diagnosis were included in the analysis.
Results*:* A total of 569 cats, with a mean age at diagnosis of 14.5 ± 2.8 yrs, were evaluated (55.5% females and 44.5% males). Cats were categorized at diagnosis as IRIS Stage 1 [n=34 (6%)], Stage 2 [n=345 (61%)], Stage 3 [n=141 (25%)], and Stage 4 [n=49 (9%)]. Median body weight at diagnosis was 4.2 kg (range, 1.6-9.9 kg). Cats lost a median of 8.9% of body weight in the 12 months before diagnosis, but weight loss was already present 3 years before diagnosis and accelerated after diagnosis of CKD. Cats below median body weight (4.2 kg) at the time of diagnosis had a significantly shorter survival time compared to cats >4.2 kg at diagnosis ($P<0.0001$).
Conclusions*:* Weight loss can be detected in cats before diagnosis of CKD, accelerates after diagnosis, and is associated with survival. Like people, pet cats develop cachexia and sarcopenia and may be useful natural animal models for achieving a better understanding of the development and treatment of these important syndromes.

2-31

Slowness and weakness are associated with complexity of care among older men living in the veterans retirement community in southern Taiwan: A cross-sectional study

Ming-Yueh Chou[1,2], Tzu-Ya Huang[1,3], Chih-Kuang Liang[1,2], Liang-Kung Chen[2,4]
[1]Center for Geriatrics and Gerontology, Kaohsiung Veterans General Hospital, [2] Aging and Health Research Center, National Yang Ming University, [3]Departments of Family Medicine, Kaohsiung Veterans General Hospital, [4]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital

Aim*:* To evaluate the association between walking speed, handgrip strength and the complexity of care among older people living in the retirement community.

Methods: All residents of Gangshan Veterans Home, a veterans retirement community in southern Taiwan, were invited for study. The overall care needs of these residents were evaluated by the Chinese version of Minimum Data Set (MDS) nursing home version 2.1, and Resident Assessment Protocol (RAP) triggers were generated for each resident as care problems. Slowness was defined as the casual gait speed ≤0.8 m/s during 6-meter walk and weakness was defined as the handgrip strength less than 26 kg according to the consensus of the Asian Working Group for Sarcopenia.
Results: Overall, 292 residents (mean age 83.69 ± 4.68 years, all males) participated in this study. Adjusted for age and multimorbidity, we found that slowness was significantly associated several RAP triggers, including the cognitive loss ($P = 0.043$), communication ($P < 0.001$), urinary incontinence ($P = 0.035$), psychosocial well-being ($P = 0.019$), mood states ($P = 0.007$), activities ($P = 0.001$), falls ($P = 0.022$), psychotropic drug use ($P < 0.001$) and a greater sum of RAP triggers (5.41 ± 2.51 *vs* 3.65 ± 1.77, $P < 0.001$). On the other hand, weakness was significantly associated with the delirium ($P = 0.006$), cognitive loss ($P < 0.001$), rehabilitation needs ($P = 0.005$), mood states ($P = 0.024$), activities ($P = 0.018$), psychotropic drug use ($P = 0.042$) and a greater sum of RAP triggers (5.28 ± 2.63 *vs* 3.92 ± 1.82, $P < 0.001$).
Conclusion: Slowness and weakness were associated with higher burden of care and some specific care needs among older residents living in the veterans retirement community. Further intervention study is needed to explore the potential to reduce the complexity of care by improving slowness and weakness.

2-32

Pressure ulcers and cachexia in patients with acquired brain injury

Tiziana Montalcini[1], Rosa Terracciano[1] Marta Moraca[1], Sebastiano Serra[2], Maria Girolama Raso[2], Francesco Rossi[2], Walter G. Sannita[2], Giuliano Dolce[2], Rocco Savino[1], Arturo Pujia[1]
[1]Pole of Innovation, health technology - Biotecnomed, University Magna Grecia, Catanzaro, Italy, [2]S.Anna Neurological Institute, Crotone, Italy

Background and aim: The association between malnutrition and pressure ulcers is well established in a variety of setting. Furthermore, now it is well accepted that malnourished patients most frequently have inflammation and that the nutritional status is not the only one influencing changes in the nutritional parameters. Currently none investigation was conducted in patients with long-term consequences of the acquired brain injury. Thus, the aim of this study was to investigate the association between nutritional status and pressure ulcers formation in Minimal Conscious State patients as consequences of the acquired brain injury and on the eventual role of cachexia.
Methods: In this prospective, observational study of 5-months duration, a 30 patients sample admitted to a Neurological Institute was evaluated. Anthropometric parameters like mid-arm circumference and mid-arm muscle circumference and nutritional parameters as serum albumin and blood hemoglobin concentration were assessed.
Results: As expected, at univariate and logistic regression analysis, mid-arm circumference, mid-arm muscle circumference, hemoglobin and albumin resulted inversely associated with pressure ulcers. Analysis by t-test revealed that patients having pressure sores had the lower mid-arm circumference and mid-arm muscle circumference ($p = 0.03$ and $p = 0.02$ respectively), haemoglobin, albumin and transferrin despite the higher caloric intake in comparison to those without pressure ulcers. The area under the ROC curve for albumin to predict sores was 0,76 (SE = 0,09; p = 0,029; lower limit 0.57, higher limit 0.94).
Conclusion: Albumin is a prognostic index in patients with the long term consequence of acquired brain injury. Since the higher caloric intake and the lower mid-arm circumference in patients having pressure sores in comparison to those without pressure ulcers and on the base of the concept that albumin and haemoglobin could be affected by a variety of factors, our finding suggests a link between cachexia and pressure ulcers rather than underfeeding.

2-33

Oxidative stress, proteasomal degradation and autophagy: targets for the anti-atrophic effect of angiotensin-(1-7) in cachexia induced by lipopolysaccharide

Claudio Cabello-Verrugio[1,3], Juan Carlos Rivera[1,3], Johana Abrigo[1,3], Maria Gabriela Morales[1,3], Felipe Simon[2,3]
[1]Laboratorio de Biología y Fisiopatología Molecular, [2]Laboratorio de Fisiología Integrativa, Facultad de Ciencias Biológicas, Universidad Andrés Bello, Santiago, Chile, [3]Millennium Institute on Immunology and Immunotherapy, Santiago, Chile

Background: the skeletal muscle is a fundamental tissue that performs functions such as movement, displacement and respiration. Lipopolysaccharide (LPS) can impaires muscle function and produces cachexia, causing a fast and severe loss of mass and muscle strength. Among the molecular mechanisms involved in muscle wasting are the oxidative stress, proteasomal degradation of myofibrillar proteins and autophagy. Angiotensin-(1-7) [Ang-(1-7)], a peptide of the non-classical axis of Renin Angiotensin System, has be-neficial effects in skeletal muscle via its receptor Mas.
Aim: a) To evaluate the effect of Ang (1-7) on the LPS-induced atrophy in mice and skeletal muscle cells. b) To determine the mechanisms involved in muscle wasting induced by LPS.
Methods: C57BL/10J mice were exposed to LPS in absence or presence of Ang-(1-7). Muscle strength, fiber diameter, myosin levels and markers of proteosomal system (atrogin-1 and MuRF-1) and autophagy (LC3II, Bnip, BnipL, Gabarap and Atg7) were determined. Reactive oxygen species (ROS) were detected in muscles sections and cells using DCF fluorescent probe.
Results: Our results shown that Ang-(1-7) recovers the decreased muscle strength, fiber diameter and MHC levels in tibialis anterior of mice. In addition, we observed that Ang-(1-7) prevents the increment of atrogin-1, MuRF-1, LC3II and BnipL induced by LPS in mice. Ang-(1-7) also decreased the increment of ROS in skeletal muscles from mice treated with LPS. Studies in vitro using C2C12 cells, shown similar effects of Ang-(1-7) corroborating that the anti-atrophic

properties of this peptide in skeletal muscle is produced by decrease of proteosomal degradation, autophagy and oxidative stress.
Conclusions: The mechanisms through Ang-(1-7) prevents cachexia induced by LPS involve the inhibition of autophagy and proteasomal degradation of myofibrillar proteins, also as the prevention of the oxidative stress. Funding: Association-Francaise Contre Les Myopathies AFM #16670; FONDECYT #1120380, 1121078; IMII #P09-016-F; UNAB DI-741-15/N.

3-01

Bimagrumab protects mice from cancer cachexia and provides an additional survival benefit in the presence of active anti-cancer treatments

Shinji Hatakeyama, Serge Summermatter, Marie Jourdain, Stefan Melly, Giulia C. Minetti, David J. Glass, Estelle Lach-Trifilieff
MusculoSkeletal Diseases, Novartis Institutes for Biomedical Research

Cachexia affects the majority of patients with advanced cancer and is associated with reduced treatment tolerance, response to therapy, quality of life and life expectancy. To date, there is no effective therapy available to treat cachexia. Several members of the transforming growth factor beta superfamily including myostatin and Activin are involved in pathological muscle wasting conditions such as cancer cachexia. Bimagrumab is a neutralizing antibody against the Activin type II receptors (ActRII); it prevents binding of ligands such as myostatin and Activin to the ActRII receptors. The aim of this study was to evaluate interactions between ActRII blockade and anti-cancer agents, since cachectic patients with advanced cancer often receive anti-cancer agents as a first line therapy. Bimagrumab was evaluated in a mouse colon cancer cachexia model, in combination with cisplatin as a standard classical cytotoxic agent or with everolimus, a new generation molecular-targeted agent against mammalian Target of Rapamycin (mTOR). ActRII blockade delayed cancer cachexia either alone or in combination with cisplatin or everolimus and, more importantly, both combination therapies slowed down time-to-progression. No deleterious interaction between ActRII blockade and anti-cancer agents was observed. Therefore, co-treatment of chemotherapy with bimagrumab might constitute a promising new approach to alleviate chemotherapy- and cancer-related wasting conditions and extend survival rates in cachectic patients.

3-02

Capecitabine dosing using skeletal muscle index (SMI) and lean body mass (LBM) may be superior to body surface area (BSA)

Julia Sun[1], Alastair I. Ilich[2], Christina A. Kim[3], Grace G. Wong[2], Sunita Ghosh[1], Melanie Danilak[2], Karen E. Mulder[1], Jennifer L. Spratlin[1], Carole R Chambers[4], Michael B Sawyer[1]
[1]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada, [2]Pharmacy, Cross Cancer Institute, Edmonton, AB, Canada, [3]Cancer Care Manitoba, Winnipe, MB, Canada, [4]Tom Baker Cancer Centre, Calgary, AB, Canada

Background and aims: The capecitabine dose used to treat colorectal (CRC) and breast cancer (BC) is calculated using BSA. Capecitabine dose is 1250 mg/m^2 in CRC and 1000 mg/m^2 in BC. Using BSA to calculate dose does not consider body composition. We hypothesize that differences in capecitabine dose between CRC and BC patients (pts) is due to body composition differences between males (M) and females (F), not cancer type. We hypothesize females dosed at 1250 mg/m^2 have a higher capecitabine dose/SMI than males, and dose reductions for dose-limiting toxicity (DLT) would lead to M and F CRC pts receiving the same capecitabine dose/SMI.
Methods: This is a retrospective study of stage II and III CRC pts treated with adjuvant capecitabine from 2008-2012. Collected demographics included age, stage, gender, height, weight, and performance status. Capecitabine doses at cycles 1 and 3 were documented. SMI was calculated using pre-treatment CT scans.
Results: 183 pts (101 M, 82 F) were identified. Females received a higher starting capecitabine dose compared to Ms based on SMI. Mean capecitabine/SMI dose was 5107.4 mg/cm^2/m^2 (SD 1113.8) for Fs compared to 4711.9 mg/cm^2/m^2 (SD 870.6) for Ms ($p = 0.009$). At cycle 3, Fs still had a higher dose of 3875.1 mg/cm^2/m^2 (SD 1663.5), although it was not statistically significant from their M counterparts at 3691.6 mg/cm^2/m^2 (SD 1629.5) ($p = 0.4580$).
Conclusions: Females received higher capecitabine doses/SMI than Ms at the CRC 1250 mg/m^2 dose. This is in keeping with our previous study that showed F CRC pts on adjuvant capecitabine experience more DLTs compared to Ms. After adjusting capecitabine doses for DLTs, M and F CRC pts received the same cape dose/SMI. This suggests SMI may be more useful than BSA when adjusting capecitabine doses.

3-03

A selective angiotensin-II receptor 2 agonist C-21improves outcome in cancer cachexia

Masaaki Konishi[1], Cathleen Drescher[1], Sandra Palus[1], Junichi Ishida[1], Andrew JS. Coats[2], Stefan D. Anker[1], Jochen Springer[1]
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]Monash University, Australia and University of Warwick, UK

Angiotensin-II has been shown to be up-regulated in catechetic states and mediates its actions via AT1 and AT2 receptors. Angiotensin-II binds with equal affinity to both receptors, but because of the predominant expression of the AT1 receptor, angiotensin-II predominantly elicits AT1 mediated responses. Recently, it has been described that the AT2 receptor acts in anti-proliferative, anti-inflammatory, anti-fibrotic and anti-apoptotic ways. These features are in contrast to what is usually associated with RAS activation, such hypertension, inflammation, fibrosis and end-organ damage, all of which are mediated by the AT1 receptor. Using the Yoshida hepatoma model, the effect of a selective AT-2 agonist (C-21 at 0.2 mg/kg/d; $n = 15$) on survival, body weight and body composition was tested in 200g male Wistar rats vs placebo. At 0.2mg/kg/day C-21

significantly improved survival vs placebo (n = 44): HR: 0.45 95%CI: 0.22-0.92, p = 0.0275. Rats showed no difference in baseline body weight. Loss of body weight was attenuated by 0.2 mg/kg/d C-21 (−28 ± 10g) compared to untreated tumor-bearing animals (−50 ± 2g). Food intake and spontaneous activity were significantly improved compared to placebo (both $p < 0.05$). This indicates an improved quality of life. Heart weight was improved by C-21. The weights of the mixed fiber type muscle gastrocnemius, the fast fiber type EDL and the slow fiber type soleus were all higher compared to placebo (all $p<0.01$). Both white and brown fat were improved by 0.2 mg/kg/d C-21 (both $p<0.05$). The preservation of both muscle and fat mass as well as the improved quality of life and survival makes C-21 an interesting candidate for cancer cachexia.

3-04

The combination of weight loss grade, performance status, and Glasgow Prognostic Score contribute to survival discrimination in advanced cancer patients at risk for cachexia

Lisa Martin[1], Pierre Senesse[2], Ioannis Gioulbasanis[3], Kent Lundholm[4], Ingvar Bosaeus[5], Anne Voss[6], Chris Deans[7], Ken Fearon[7], Federico Bozzetti[8], Vickie Baracos[1]

[1]University of Alberta, Edmonton, Alberta, Canada, [2]Institut du Cancer de Montpellier, Montpellier, France, [3]Larissa General Clinic 'E Patsidis', Larissa, Greece, [4]Institute of Clinical Sciences, Gothenburgh University, Gothenberg, Sweden; [5]Sahlgrenska University Hospital, Gothenburg, Sweden, [6]Abbott Nutrition, Abbott Laboratories, Columbus, Ohio, USA, [7]School of Clinical Sciences and Community Health, University of Edinburgh, Royal Infirmary, Edinburgh, United Kingdom, [8]University of Milan, Milan, Italy

Background: Cancer cachexia is suggested to represent a continuum that spans early clinical signs such as limited weight loss (WL, precachexia), proceeding to varying degrees of WL and inflammation, culminating in severe WL associated with poor performance status (PS) and short survival.

Purpose: To determine if inflammation as assessed by the Glasgow Prognostic Score (GPS), and ECOG performance status (ECOG PS) can discriminate advanced cancer patients with varying survival across the recently defined BMI-WL Grades.[2]

Methods: BMI-WL grades, GPS, and ECOG PS assessments were recorded on patients with advanced cancer, and entered into a multivariable analysis controlling for age, sex, and cancer site. Patients were stratified according to these assessments and median survivals were determined.

Results: N=2,656 advanced cancer patients were included. Median overall survival was 7.6 months (95% CI 7.1-8.1). BMI-WL grades, GPS, and ECOG PS independently predicted overall survival ($p<0.001$). Stratifying patients according to BMI-WL Grade, GPS and ECOG-PS offered prognostic information spanning from patients with no manifestation of cachexia (e.g. BMI-WL grade 0-1, PS 0-1, GPS 0, N=248, 23.5 months, Table) to patients with severe WL, poor PS and inflammation (BMI-WL Grade 4, PS 3-4, GPS 2, 2.0 months). Importantly, compared to patients with no apparent manifestation

Table 1 Estimated median survival, using the Kaplan-Meier method, in months for advanced cancer patients stratified by BMI-WL Grades, ECOG PS, and GPS

		ECOG PS 0–1				ECOG PS 2(N=780)				ECOG PS 3–4 (N=455)			
		11.4 months (95% CI 10.5–12.3)				5.2(4.6–5.8)				3.3(2.8–3.8) P,<0.001*			
	Over all Survivor	GPS 0	GPS 1	GPS 2	P–value	GPS 0	GPS 1	GPS 2	P-value	GPS 0	GPS 1	GPS 2	P-value
BMI-WL Grade 0–1													
N	654	248	113	55	<0.001†	45	57	43	<0.001†	16	26	54	<0.015†
Median Survival	11.5 (10.0–13.0)	23.5[a]	15.2[b,c]	4.4[d,e]		13.5[a]	5.9[b,c]	3.5[d]		12.2[a]	6.2[a]	2.5[b]	
(95% CI)	720	19.5–27.5	9.1–21.3	2.4–6.4		8.4–18.6	3.5–8.3	1.7–5.3		3.5–20.9	4.3–8.1	0.7–4.3	
BMI-WL Grade 2–3													
N	1249	345	237	126	<0.001†	95	137	114	<0.001†	27	73	95	<0.001†
Median Survival	8.2 (7.5–8.9)	15.8[b]	10.3[c]	4.4[d,e]		9.3[a,b]	5.5[c]	3.5[c,d]		6.8[a]	5.3[a,b]	1.6[c]	
(95% CI)	1355	13.3–18.3	8.5–12.1	3.2–5.6		6.3–12.3	3.3–7.7	2.8–4.2		3.5–10.1	3.7–6.9	0.9–2.3	
BMI-WL Grade 4													
N	753	98	99	108	<0.001†	57	95	133	<0.001†	24	64	75	<0.046†
Median Survival	4.5 (4.0–5.0)	15.3[c]	6.1[d]	3.6[c]		7.7[a,b]	4.9[c]	2.8[d]		4.5[a]	3.0[b]	2.0[c]	
(95% CI)	829	6.2–10.8	4.6–7.6	3.1–4.1		6.3–9.1	3.9–5.9	2.1–3.5		2.6–6.4	2.1–3.9	1.4–2.6	
		17.7 (15.3–20.1)	9.6 (8.1–11.1)	3.9 (3.2–4.6)	<0.001†	9.4 (7.1=11.7)	5.1 (4.3–5.9)	3.4 (2.8–4.0)	<0.001†	6.8 (4.1–9.5)	4.3 (3.3–5.3)	1.9 (1.3–2.5)	<0.001†
P-value	<0.001*	<0.001‡	<0.001‡	0.214‡		0.137‡	0.167‡	0.261‡		0.041‡	0.128‡	0.322‡	

BMI-WL Grades, Body Mass Index adjusted Weight Loss Grades (see reference 2 Martin et al for description of categories)
ECOG PS, Eastern Cooperative Oncology Group Performance Status
GPS, Glasgow Prognostic Score: score 0, CRP <10 mg/L, Albumin ≥ 35/L; Score 1, CRP <10 mg/L OR Albumin < 35g/L; score 2, CRP ≥ mg/L and Albumin, 35g/L
Comparisons between median survival curves with Mantel-Cox log rank tests:
*P-value for overall comparison of estimated median survival within a single diagnostic criteria: BMI-WL grades only, ECOG PS only
†P-value for overall comparison of estimated median survival within each stratification of BMI-WL Grade and ECOG PS by GPS (read left to right)
‡P-value for overall comparison of estimated median survival within each stratification of GPS and ECOG PS by BMI-WL grade (read top to bottom)
[a,b,c,d,e]represent significant differences ($P < 0.05$) in median survival within the following ECOG PS stratification: 0–1, 2, and 3–4

of cachexia, the presence of either BMI-WL Grade ≥2 (survival 8.5 to 15.8 months), reduced PS ≥2 (12.2 to 13.5 months) or GPS 1 (15.2 months) immediately associated with reduced survival ($p<0.05$). Patients with any combination of 2 or 3 of BMI-WL≥2, PS ≥2, and GPS≥1 have consistently shortened survival.

Conclusion: A combination of BMI-WL grades, PS, and GPS consistently stratifies advanced cancer patients in to very different survival groups, and could be considered as diagnostic criteria for cachexia. Our hope is to continue adding patients to this analysis through collaboration and continue investigating these relationships as well as other important features of cachexia such as dietary intake and body composition.

3-05

Inclusion criteria for cancer cachexia clinical trials: CT-defined skeletal muscle loss versus weight loss

Eric J. Roeland[1], Sandahl H. Nelson[1], Ashleigh D. Campillo[1], Sean F. Heavey[1], Joseph D. Ma[2], Carolyn Revta[1], Andrea Gallivan[3], Vickie E. Baracos[3]

[1]University of California, San Diego School of Medicine, La Jolla, California, USA, [2]University of California, Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, California, USA, [3]University of Alberta, Edmonton, Alberta, Canada

Background and aims: Cancer cachexia is defined by skeletal muscle loss, with or without fat loss (Fearon et al 2011); however, inclusion on cachexia clinical trials requires a defined weight loss (WL) over time rather than muscle loss. We hypothesized that cross-sectional imaging may reveal cachexia otherwise obscured by fat mass changes.

Methods: Retrospective analysis of longitudinal CT scans was performed in metastatic colorectal cancer (mCRC) patients screened for a cachexia trial requiring ≥5% WL over prior 6 mos. CT images were analyzed for total muscle and fat cross-sectional areas (cm^2) at the 3rd lumbar vertebra coinciding with the WL time period (Lieffers et al 2009). Logistic regression was used to test differences between patients with <5% vs ≥5% WL. Random intercept regression was used to evaluate significant trends in CT measures over time.

Results: 42 mCRC patients were screened and 3(7%) enrolled. Patients were excluded for comorbidity/contraindication 14(33%), >20% WL 4 (9.5%), and <5% WL 19(45%). The <5% WL subset had a mean of 6.7 CTs (SD = 2.67) and 9% (SD = 5.4, min = 0%, 25th percentile = 4.9%) mean max muscle loss, while simultaneously losing muscle ($p = 0.002$) and gaining visceral adipose ($p = 0.007$). The ≥5% WL subset had a mean of 7.5 CTs (SD = 4.5) and 20% (SD = 10.0, min = 5.2%, 25th percentile = 10.6) mean max muscle loss. Greater max muscle loss increased the odds of being in the ≥5% WL subset (OR=1.19, 95% CI:1.06,1.33). This group also had a significant decrease in visceral adipose over time ($p<0.001$). Redefined inclusion criteria of ≥5% muscle loss would have included 14 of 19 patients excluded because of <5% WL.

Conclusions: Defining cancer cachexia as WL over time may be limited as it does not capture body composition changes and hinders trial accrual. Cross-sectional CT body composition analysis may improve early detection of muscle loss and improve trial accrual.

3-06

Cardiac muscle wasting in patients with cancer cachexia

Anush Barkhudaryan[1], Nadja Scherbakov[2,3], Jochen Springer[4], Wolfram Doehner[2,5]

[1]Clinic of General and Invasive Cardiology, University Clinical Hospital № 1, Yerevan, Armenia, [2]Center for Stroke Research CSB, Charité - Universitätsmedizin Berlin, Germany, [3] German Centre for Cardiovascular Research (DZHK), partner site Berlin, Germany, [4]Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Göttingen, Germany, [5]Department of Cardiology, Charité - Universitätsmedizin Berlin, Germany

Background: Cachexia is a severe complication of cancer which adversely affects the course of the disease and is associated with high rates of mortality. Patients with cancer manifest symptoms, such as fatigue, shortness of breath and impaired exercise tolerance which are typical clinical signs of chronic heart failure (HF). The aim of this study was to evaluate cardiac muscle wasting in cancer patients.

Methods: We retrospectively enrolled 177 cancer patients, including 58 lung, 60 pancreatic and 59 gastrointestinal (GI) cancers and 42 healthy controls. Cancer cachexia (CC) was defined based on clinical and/or pathological diagnosis, body mass index (BMI) <20.0 kg/m^2 and/or edema-free body weight loss of 5.0% during the previous year or less. The pathology reports were analysed for BMI, heart weight (HW), left and right ventricular wall thicknesses (LVWT and RVWT). The analysis of clinical data included recording of biochemical abnormalities and medication data of study patients.

Results: CC was detected in 54 (30.5 %) patients. Patients with CC had a significantly lower HW than noncachectic subjects (363.1 ± 86.2 vs. 447.0 ± 128.9 g, $p<0.001$) and control group (412.9 ± 75.8 g, $p<0.05$). BMI correlated with HW in patients with GI cancer ($r = 0.44$, $p<0.001$), lung cancer ($r = 0.53$, $p<0.0001$) and pancreatic cancer ($r = 0.39$, $p<0.01$). Furthermore, BMI correlated with LVWT ($r = 0.32$, $p<0.05$) and RVWT ($r = 0.34$, $p<0.05$) in patients with GI cancer and with LVWT in patients with lung cancer ($r = 0.29$, $p<0.05$). Cancer patients differed from controls with regard to patients' cardiovascular medication, whereas no difference was detected between cachectic and noncachectic groups. Cancer treatment was significantly prevalent in cachectic patients than in noncachectic subjects.

Conclusion: Body weight loss in patients with lung, pancreatic and GI cancers is accompanied by a decrease in HW. The diagnostic evaluation of heart function and monitoring of cancer therapy are recommended for prevention of cardiac complications in patients with cancer.

3-07

Loss of skeletal muscle mass during neoadjuvant chemotherapy is related to a decreased survival in ovarian cancer patients

Iris J.G. Rutten[1,2], David P.J. van Dijk[3,4], Roy F.P.M. Kruitwagen[1,2], Regina G.H. Beets-Tan[2,5], Steven W.M. Olde Damink[3,4], Toon Van Gorp[1,2]

[1]Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, The Netherlands, [2]GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands, [3]Department of General Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands, [4]NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands, [5]Department of Radiology, Maastricht University Medical Centre, Maastricht, The Netherlands

Background and aims: Malnutrition, weight loss and muscle wasting (sarcopenia) are common amongst women with advanced ovarian cancer and have been associated with adverse clinical outcomes and survival. Our objective is to investigate overall survival (OS) related to changes in skeletal muscle (SM) for patients with advanced ovarian cancer treated with neoadjuvant chemotherapy and interval debulking.

Methods: Ovarian cancer patients (n = 123) treated with neoadjuvant chemotherapy and interval debulking in the area of Maastricht (the Netherlands) between 2000 and 2014, were included retrospectively. Surface areas of SM and adipose tissue were defined on computed tomography at the level of the third lumbar vertebra. Low SM at baseline and SM changes during chemotherapy were compared with Kaplan Meier curves and Cox-regression models were applied to test predictors of OS.

Results: Median OS for patients who lost SM (n = 83) was 916 ± 99 days, which was significantly different from median OS for patients who maintained or gained SM (n = 40), which was 1431 ± 470 days (p = 0.004). Loss of SM was also a significant predictor of OS in multivariable Cox-regression analysis (hazard ratio 1.773 (95%CI: 1.018–3.088), p = 0.043). Low baseline SM did not influence survival.

Conclusions: Patients with ovarian cancer have a worse survival when they lose skeletal muscle during neoadjuvant chemotherapy. Evaluation of low skeletal muscle at a specific time point is not prognostic for OS. External and prospective validation of these findings is imperative. Nutritional, pharmacological and/or physical intervention studies are necessary to establish whether tissue deterioration can be prevented to prolong ovarian cancer survival.

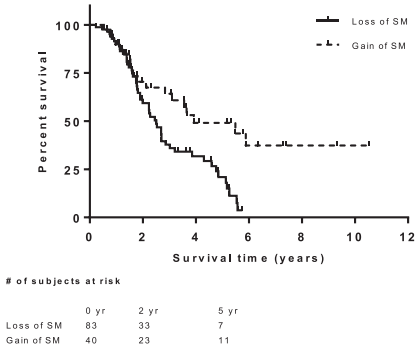


Figure 1 Survival proportions: Changes in skeletal muscle Kaplan Meier curve comparing overall survival between loss of skeletal muscle (>2% decrease per 100 days) and maintenance or gain of skeletal muscle (any increase or ≤2% decrease per 100 days), p-value = 0.004. *SM = skeletal muscle*.

3-08

Challenges in recruiting into a current randomized controlled trial in refractory cancer cachexia

Joanne Reid[1,2], David Scott[1], Sam Porter[1,2]

[1]School of Nursing and Midwifery, Queen's University Belfast, Medical Biology Centre, Belfast, UK, [2]All Ireland Institute of Hospice and Palliative Care, Ireland

Introduction: Cancer cachexia is defined it as a multi-factorial syndrome characterised "by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support"[(1)] (p. 8). Refractory cachexia refers to the 'stage where reversal of weight loss seems no longer possible' [(1)] (p. 8) and the majority of patients at this stage will be receiving palliative care. Previous research in this area has demonstrated the holistic impact of the syndrome.[(2-5)] In the absence of a recognized treatment solution, an evidence-based psycho-educational DVD health care intervention has been developed for this patient cohort and their family members by a team of researchers and healthcare staff in Northern Ireland.

Intervention: This research is funded by the All-Ireland Institute of Hospice and Palliative Care and will be evaluated in a randomized controlled trial with a palliative cancer population who have refractory cachexia.[(6)] The team's experience thus far highlights the inherent difficulties in conducting research with this client group. Refractory cancer cachexia is rarely acknowledged or diagnosed due to a lack of clear clinical diagnostic guidelines and local protocols for clinical management and this has hindered identification of potential participants. Indeed previous research has demonstrated the lack of clinical awareness of this syndrome among health care professionals.[(7)]

Conclusion: There is a clear need for the urgent development of evidence based guidelines to aid in the education, diagnosis and management of refractory cancer cachexia. Such guidelines will undoubtedly provide the clinical diagnostic criteria necessary to assist healthcare professionals in identifying refractory cachexia and allow them to respond appropriately. This in turn will make it easier to identify and recruit appropriate patients for future studies in palliative care.

3-09

Role of mechanical cues on physical activity-mediated rescue of muscle homeostasis in cancer cachexia

Nissrine Daou[1], Eva Pigna[2], Viviana Moresi[2], Sergio Adamo[2], Mathias Mericskay[1], Zhenlin Li[1], Dario Coletti[1,2]

[1]Dept. of Biological Adaptation and Ageing B2A (CNRS UMR 8256 - INSERM ERL U1164 - UPMC P6), Pierre et Marie Curie University, Paris, France, [2]DAHFMO Unit of Histology and Medical Embryology, and Interuniversity Institute of Myology, Sapienza University of Rome, Italy

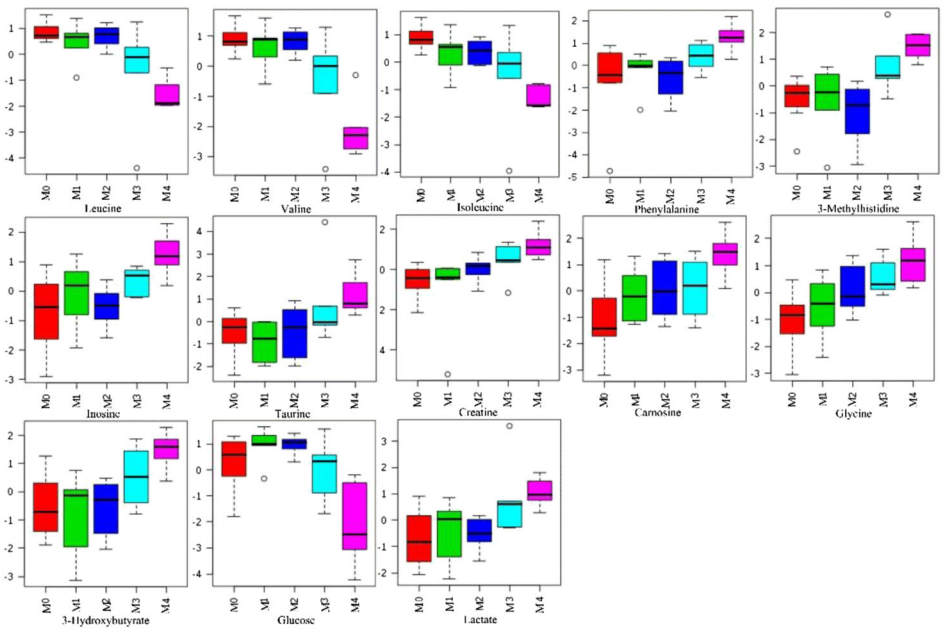
Aim and methods: To counteract muscle wasting by physical activity, control and C26 colon carcinoma bearing mice (C26-mice) were hosted in wheel-equipped cages.
Results: We observed that exercise rescued body weight (BW), muscle mass and fiber cross-sectional area in C26-mice, counteracting the hallmarks of cancer cachexia. Since wheel running is a voluntary activity, variations in running distance (RD) among mice occurred. This allowed us to correlate the RD and the final BW of C26-mice and to find that there is a dose-dependent effect of exercice on the BW rescue in these animals. With the aim of finding the mechanisms underlying the beneficial effects of exercice, we quantified the number of myonuclei and found that the observed rescue occurs in the absence of major changes in the number of nuclei per fiber. This suggests that exercise activates fiber-specific responses, independently from the incorporation of additional nuclei (possibly deriving from recruited cells). To assess whether the exercise-mediated muscle mass rescue depends on mechanical (muscle contraction) or on endocrinological (changes in the level of humoral factors) cues, we denervated one hindlimb for each mouse: in this way, we obtained denervated, immobilized muscles exposed to the humoral factors of exercised mice and we measured the effects on the Tibialis muscle fibers size comparing it to the contralateral muscle. Our preliminary results indicate a slight rescue in the denervated muscle mass upon exercise in C26-mice, suggesting that both humoral factor and mechanical cues are important and each one contributes to exercise-mediated rescue of muscle homeostasis. Since Serum Response Factor (a mechanotransduction-activated transcription factor) expression is downregulated in cachexia, we are currently investigating its expression and activation upon exercise.
Conclusion: In conclusion, mechanical cues contribute to physical activity-mediated rescue in cachexia at least in part throught mechanotransduction.

3-10

Integrated analysis of serum and muscle metabonomics reveals metabolic pathway reprogramming during cancer cachexia in a dynamic mouse model

Yang Quan-Jun[1], Yang Gen-Jin[2], Wan Li-Li[1], Huo Yan[1], Yu Qi[1], Han Yong-Long[1], Li Bin[1], Lu Jin[1], Peng-Guo Chen[1], Li Jie[1], Guo Cheng[1]
[1]Department of Pharmacy, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China, [2]School of Pharmacy, Second Military Medical University, Shanghai, China

Background: Cancer cachexia is a multifactorial metabolic syndrome characterized by an ongoing loss of body weight and lean body mass resulting from increased protein catabolism and decreased protein synthesis. Metabolic dysfunction is the primary cause of muscle atrophy, and metabolic profile prompts the potential biomarker for the early detection and underlying metabolic mechanism of muscle atrophy. Herein, we studied dynamic metabolic profiles in serum and intact muscle to reveal metabolite hubs and altered pathways in cancer cachexia.
Methods: The intact gastrocnemius muscle was evaluated using high-resolution magic angle spinning (HR-MAS) NMR spectroscopy. A dynamic metabolic model was established using C26 colon carcinoma-bearing mice sacrificed at continuous time points from procachexia to the refractory cachexia period. The data were integrated and analyzed, and the altered pathways were determined using MetPA.
Results: Forty-three distinguishing metabolites were found to be altered significantly in the serum, and thirteen metabolites were altered in the gastrocnemius muscle during the dynamic progression of cancer cachexia. The metabolic profile of intact gastrocnemius muscle with HR-MAS spectra reveal distinct metabolic hubs, including increasing



The relative changes in the muscle metabolites from non-cachexia to severe cachexia. M1 to M4 represent the groups from day 9 to day 21 (every three days), and M0 is the control group.

phenylalanine, 3-methylhistidine, inosine, taurine, creatine, carnitine, glycine, 3-hydroxybutyrate, and lactate, as well as decreaseing leucine, valine, isoleucine, and glucose. When integrated the metabolites identified in the serum and intact muscle, five metabolic features of cachexia were identified: low blood glucose and lipids, high ketone bodies, decreased branched-chain amino acids, increased neutral amino acids and elevated amino acid intermediates.
Conclusion: The present study revealed five metabolic pathway reprogramming that occur during cancer cachexia. The metabolic hubs provided potential biomarkers for the early detection of cachexia and indicated the underlying metabolic mechanisms of muscle atrophy.

3-11

Cancer and cachexia: role the ANGPTL-4

Nelson IP Neto[1], Lila M Oyama[1], Valter T Boldarine[1], Ana Claudia L Hachul[1], Marilia Seelaender[2], Paulo SM Alcantara[3], Jose P Otoch[3], Flavio Tokeshi[3], Claudia M Oller do Nascimento[1]
[1]Physiology, Escola Paulista de Medicina, UNIFESP, São Paulo, SP, Brazil, [2]Cancer Metabolism Research Group, Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Brazil, [3]Department of Clinical Surgery, University Hospital, University of Sao Paulo, Sao Paulo, Brazil

Introduction: The Angiopoeitin-like 4 (ANGPTL-4) is expressed in several tissues such as adipose tissues, liver, intestines, and a variety of tumours (Kersten, 2005; Yoon *et al*, 2000; Tan *et al*, 2012). It has been implicated as an important factor involved in energy homoeostasis, redox regulation, angiogenesis, development of cancer and cachexia, and development of metastasis and inflammation; however, the studies are still incomplete and often contradictory (Zhu *et al*, 2012). Inflammatory factors, such as IL-1b and IL-6 or hypoxia alone, increased ANGPTL4 protein levels.
Methods: Population enrolled in this study was 121 patients divided in control patient (n=43), patient with cancer without cachexia (n=36) and patient with cancer and cachexia (n=42). The study was approved by the Ethics Research Committee (972.914). Samples of plasma, tumour, mesenteric adipose tissue, peritumoral adipose tissue were removed for determination of ANGPTL-4 IL-6, IL-10, IL-1beta, IL-15, TNF-alpha, MCP1 and VEGF concentration. The cytokines and proteins were measured by ELISA.
Results: ANGPTL-4 plasma concentration was high in cancer cachexia group than the control and cancer without cachexia. The content of ANGPTL-4 in all tissues studied was similar among groups. The ANGPTL-4 did not correlated with cytokines and proteins content in Mes adipose tissue. However, it was detected a positive correlation between ANGPTL-4 and IL-10 and VEGF in TAPT. Also, IL-6, IL-15 and MCP-1 tumor content correlated positively with ANGPTL-4 tumour concentration.
Conclusion: These previously results suggested that ANGPTL-4 has an important role in cancer associated with cachexia. Also, it was demonstrated that this protein correlated positively with pro-inflammatory cytokines, especially in tumour, which suggested that ANGPTL4 could be involved on the development of proinflammatory microenvironment tumour conditions, which could worsen the clinical state of patients with cancer-cachexia.

3-12

The habenula as a link between the homeostatic and hedonic pathways in cancer anorexia-cachexia: a pilot study

Maria Maldonado, Kaylah Curtis, Humsini Viswanath, Ramiro Salas, Jose M. Garcia
MEDVAMC/Baylor Coll Med, Houston, TX, USA

Importance: Despite being a major cause of suffering and mortality in cancer patients, little is known about the brain mechanisms involved in cancer anorexia and cachexia (CAC). Anorexia in this setting may be due to alterations in homeostatic pathways that control the hormonal milieu, and/or the hedonic pathways that control the rewarding value of food consumption.
Objective: To test the hypothesis that the homeostatic and hedonic pathways are abnormally connected in CAC patients.
Design: We used resting state functional connectivity in human brain imaging to study three areas that we hypothesized may be relevant: the hypothalamus (homeostatic), the nucleus accumbens (hedonic) and the habenula (possible link between the other two) in a sample of 13 cancer patients and 13 healthy controls.
Setting: Tertiary care referral center.
Participants: Individuals with histological diagnosis of incurable cancer (solid tumor), an European Cooperative Oncology Group (ECOG) performance status of 0-2, and presence of CAC as defined as involuntary weight loss of at least 5% of the pre-illness body weight over the previous 6 months and non-cancer controls.
Main Outcome Measure: Resting state functional connectivity in selected brain regions.
Results: The resting state functional connectivity between the habenula and the hypothalamus and between the habenula and the nucleus accumbens were significantly decreased in CAC patients when compared to controls after adjusting for BMI.
Conclusions and Relevance: Our data suggests that the habenula is a link between the homeostatic and hedonic pathways and that this link is weaker in cancer cachexia-anorexia. This data opens the door to the study of possible therapies against CAC, by providing a brain circuit that may be targeted by pharmacological or other types of therapy.
This study was funded by a MEDVAMC Seed grant (JG, RS), VHA MERIT grants (BX000507 to JG, CX000174 to JG, and CX000994 to RS) and the NIA T32AG000183 and AG040583 to JG. Funding was also provided by the American Federation of Aging Research via the Medical Student Training in Aging Research program to MM, and the McNair Medical Institute to RS.

3-13

Effect of doxorubicin on cardiac muscle subsarcolemmal and intermyofibrillar mitochondria

Ashley J. Smuder[1], Andreas N. Kavazis[2], Scott K. Powers[1]
[1]Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA, [2]School of Kinesiology, Auburn University, Auburn, AL, USA

Background and aims: Doxorubicin (DOX) is an anticancer anthracycline used in the treatment of a broad spectrum of malignancies. However, clinical use of DOX is highly limited by cumulative and irreversible cardiomyopathy that occurs following DOX treatment. The pathogenesis of DOX-induced cardiac muscle dysfunction is complex. Mitochondria have repeatedly been implicated as the main target of DOX-induced toxicity as a result of the dose-dependent increase in the mitochondrial concentration of DOX. In this regard, cardiac muscle possesses two distinct populations of mitochondria based on their composition and biochemical properties. Subsarcolemmal (SS) mitochondria are localized just below the sarcolemma, whereas intermyofibrillar (IMF) mitochondria are found between myofibrils. Mitochondria in both regions exhibit subtle differences in biochemical properties, giving rise to differences in respiration, lipid composition, enzyme activities and protein synthesis rates.
Methods: To test the hypothesis that acute DOX administration has distinct effects on cardiac muscle mitochondria subpopulations, SS and IMF mitochondria were isolated from the hearts of female Sprague-dawley rats 48 hours after either saline (control) or DOX administration.
Results: Acute DOX administration results in a higher rate of mtPTP pore opening (Vmax) in both SS and IMF mitochondria, but time required to reach Vmax was only reduced in the IMF mitochondria. DOX-induced mitochondrial reactive oxygen species production was increased in both cardiac mitochondria subpopulations. However, mitochondrial coupling was only reduced in the DOX treated IMF mitochondria compared to control animals.
Conclusions: DOX-induced cardiotoxicity results in differential adaptations to SS and IMF mitochondrial phenotype, with the IMF mitochondria appearing to be more susceptible to DOX treatment.

3-14

System biology approach to dissect human cancer cachexia pathways impairing muscle regeneration

H. Alexander Ebhardt[1], Simone Degen[3], Valentina Tadini[3], Alain Schilb[3], Lirong Huang[1], Heinz Koeppl[4], Estelle Triffilieff[3], Michaela Kneissel[3], Ruedi Aebersold[1,2], Carsten Jacobi[3]
[1]Department of Biology, Institute of Molecular Systems Biology, ETH Zürich, Zürich, Switzerland, [2]Faculty of Science, University of Zürich, Zürich, Switzerland, [3]Novartis Institutes for BioMedical Research Basel, Novartis Pharma AG, Basel, Switzerland, [4]Department of Electrical Engineering and Information Technology, TU Darmstadt, Darmstadt, Germany

Cancer cachexia has been defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass and adipose tissue, body weight loss that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia affects the majority of patients with advanced cancer and is associated with a reduction in treatment tolerance, response to therapy, quality of life and duration of survival.
One major aspect of the disease is a systemic inflammation which led to long-term activation of inflammation pathways effecting skeletal muscle. Muscle wasting is the result of a combination of an imbalance between synthetic and degradative protein pathways together with increased myocyte apoptosis and decreased regenerative capacity.[1]
To further understand the underlying mechanism of the impaired regeneration we are currently analyzing the age related effects in an in vitro system using human skeletal muscle cells of different aged donors under normal and disease mimicking conditions (e.g. TNFa, conditioned media from human cancer cells) with the goal to elucidate which stage of myogenesis is impaired in cachexia. Our experiments were based on comparing myogenesis of untreated to cytokine treated primary human skeletal myoblasts from fetal and 83 year old donors.
Global proteome changes of myogenesis were quantified by LC-MS/MS (MS2 quantification: SWATH-MS). Protein arrays were used for in-depth analysis of selected phospho-epitopes. Proteomics data was further confirmed using immuno-staining and phenotypic characterization of established myogenesis markers. Meta-analysis of these datasets clearly demonstrated impairment of myogenesis and uncovered novel markers for precise classification of myogenesis and cachexia. The data obtained from Fetal myocytes will be compared to the myogenesis of an 83 year old primary donor.

Reference

1. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. 2014. Cancer cachexia: understanding the molecular basis. *Nature reviews Cancer* **14**: 754-762.

3-15

Solid Ehrlich tumor model reproduces functional and biological conditions of tumor-induced cachexia

Fernando T. Frajacomo[1], Camila Padilha[1], Paola Cella[1], Renan Nogueira[1], Flavia A. Guarnier[2], Felipe Moura[1], Rubens Cecchini[2], Rafael Deminice[1]
[1]Department of Physical Education, State University of Londrina. Londrina, Parana, Brazil, [2]Department of Pathological Sciences, State University of Londrina. Londrina, Parana, Brazil

Background and aims: Well-characterized animal tumor models of cancer cachexia are warranted to mimic specific underlying human disease. However, a critical evaluation of functional and biological adaptations in experimental tumor-models is lacking. We aimed to investigate whether solid Ehrlich carcinoma reproduces functional and biological conditions of tumor-induced cachexia in mice.
Methods: Ehrlich tumor cells [(1 x 10^6 viable cells in 100μL volume, Tumor group (T)] or vehicle control [Sham group (S)], were subcutaneously transplanted into the right flank in young female Swiss mice. As functional analysis, tumor growth, food intake and forelimb grip strength were taken periodically. Fat content and muscle weight were measured once after euthanized. As biological markers, we assessed plasma creatine kinase (CK), lactate dehydrogenase (LDH), and tumor necrosis factor alpha (TNF-α). The open field test was used to assess locomotor and behavior mice deficits.
Results: Our functional analysis demonstrated that tumor burden group reduced handgrip strength ($P < 0.05$), aside from critically

reduced parametrial fat pads ($P < 0.001$). Tumor growth reached 9.76% of body weight at 28 days after tumor cells implantation. Biological parameters reveled a significant increase in plasma CK ($P < 0.05$), LDH ($P < 0.001$) and TNF-α ($P < 0.05$) compared with S group. However, food intake, gastrocnemius e soleus weight and open field parameters did not change.

Conclusions: Our data elucidated that solid Ehrlich tumor model is feasible and effective to reproduce functional and biological conditions of tumor-induced cachexia. Hence, this model encourages future studies using different therapeutic approaches to unveil the pathways that regulate fat loss and skeletal muscle dysfunction associated with cancer cachexia.

3-16

The activation of the SDF1/CXCR4 pathway in muscle retards atrophy during cancer cachexia

Giulia Benedetta Martinelli[1], Davide Olivari[1], Laura Talamini[1], Stewart H. Lecker[2], Linda Ottoboni[3], Andrea Resovi[4], Raffaella Giavazzi[1], Luigi Cervo[5], Rosanna Piccirillo[1]

[1]Department of Oncology and [5]Neuroscience, IRCCS - Mario Negri Institute for Pharmacological Research, Milan, Italy, [2]Beth Israel Deaconess Center, Boston, MA, USA, [3]San Raffaele Scientific Institute, Milan, Italy, [4]Department of Oncology, Tumor Angiogenesis Unit, IRCCS - Mario Negri Institute for Pharmacological Research, Bergamo, Italy.

Cancer cachexia is a life-threatening syndrome that affects most patients with advanced cancers and involves severe body weight loss, with rapid depletion of skeletal muscle. No effective treatment is available.

We analyzed microarray datasets to identify a subset of genes whose expression is specifically altered in cachectic muscles of Yoshida hepatoma-bearing rodents, but not in those with diabetes, disuse, uremia or fasting. By Ingenuity Pathways Analysis, we found three genes belonging to the CXCR4 pathway downregulated only in muscles atrophying because of cancer: *SDF1*, *PAK1* and *ADCY7*. Consistently, we show that the expression of all *SDF1* isoforms declines also in Tibialis Anterior from cachectic mice bearing colon adenocarcinoma or renal cancer and drugs with anti-cachexia properties such as sunitinib restore it. Overexpressing genes of this pathway (i.e. *SDF1* or *CXCR4*) in cachectic muscles increases the fiber area by 20%, partially protecting them from wasting. The mechanisms behind this muscle preservation during cachexia include both reduced degradation of long-lived proteins, by either SDF1α or SDF1β on atrophying myotubes, and increased protein synthesis, mainly by SDF1α. However, inhibiting CXCR4 signaling with the antagonist AMD3100 does not affect protein homeostasis in atrophying myotubes, whereas normal myotubes treated with AMD3100 display decreased diameter in a time- and dose-dependent manner, until a plateau. This further confirms the involvement of a saturable pathway (i.e. CXCR4).

Overall, these findings support the idea that activating the CXCR4 pathway in muscle suppresses the deleterious wasting associated with cancer.

3-17

Causative role of MEF2c in pre-cachectic downregulation of muscle structural genes and muscle atrophy in tumor-bearing mice

Sarah M. Judge[1], Rachel L. Nosacka[a], Daniel Delitto[2], Jose G. Trevino[2], Andrew R. Judge[1]

[1]Department of Physical Therapy and [2]Department of Surgery, University of Florida, FL, USA

The initiating mechanisms of cancer-induced muscle atrophy and weakness remain largely unknown. Any initiating mechanism must be changed early during the progression of cancer cachexia, and data from our lab demonstrate that several muscle structural genes are downregulated in the skeletal muscle of Colon-26 (C26) tumor bearing mice at time points which precede and parallel the progression of cancer cachexia. Included among the downregulated genes are Myocilin (*Myoc*), Kyphoscoliosis peptidase (*Ky*), and Myomesin3 (*Myom3*), which are involved in maintaining the structural integrity of the DAPC, the sarcomeric Z-disc and the M-line, respectively. These genes are downregulated in C26 tumor-bearing mice 14, 18 and 26 days post-C26 inoculation, timepoints which correspond to pre-, moderate, and severe cachexia. Importantly, we further establish that these genes are similarly downregulated in muscle biopsies from cachectic pancreatic cancer patients, as well as their mouse avatars, (i.e. mice implanted with pancreatic tumor xenografts surgically resected from these patients). Analysis of the promoter regions of the structural genes downregulated in these models identified conserved binding motifs for myocyte enhancing factor-2 (MEF2), which we further establish is decreased at the mRNA and protein level prior to the onset of muscle wasting in our C26 mouse model of cachexia. To test whether maintenance of MEF2c expression can prevent the downregulation of muscle structural genes and muscle atrophy, we injected mice with rAAV9-tMCK-*Mef2c* (or control vector) at the time of C26 tumor cell inoculation and harvested muscles 18 and 26 days later. In these muscles the cancer-induced downregulation of *Myoc*, *Ky* and *Myom*3, and muscle fiber atrophy was inhibited. These findings demonstrate a common transcriptional downregulation of several key muscle structural genes in response to tumor burden in mice and patients, and further identify a causative role of MEF2C in this downregulation as well as in muscle fiber atrophy.

3-18

Effects of LLC tumoral secretory products in co-culture system on adipocyte differentiation

Magno A. Lopes[1], Felipe S. Henriques[1], Felipe O. Franco[1], Luana G. Leal[1], Juliana C.Vieira[1], Kaltinaitis B. Santos[1], Pamela V. Knobl[1], Sidney B. Peres[2], Miguel L. Batista Jr[1]

[1]Laboratory of Adipose Tissue Biology, Integrated Group of Biotechnology, University of Mogi das Cruzes, Mogi das Cruzes, São Paulo, Brazil, [2]Department of Physiological Sciences, State University of Maringá, Maringá, Paraná, Brazil

Background and aims: Cancer cachexia is a multifactorial syndrome with an unknown etiology. The main symptom is the progressive reduction of the body weight. Recently, down-regulation of adipogenic and lipogenic genes were demonstrated to be early affected during cachexia progression in adipose tissue (AT), resulting in AT remodeling. However, the possible influence of the tumor secreted proteins in adipocyte differentiation has not been addressed. Thus, the aim of this study was to evaluate in a co-culture system the influence of the LLC tumoral cells in 3T3-L1 adipogenic capacity.
Methods: 3T3-L1 cells were plated ($2x10^4$, *n*=3). The tumor cell LLC (Lewis Lung Carcinoma) was plated in a co-culture Transwell system ($1x10^4$) two days before the adipogenesis induction (day -2). On day 0, medium inductor of differentiation (MID) was added to the co-culture. The cells were harvested at different stages of the adipocyte differentiation, i.e., days 0, 2, 4 and 8 *(time-course study)*. Afterwards, the gene expression of classical adipocyte markers (qPCR for C/EBP-beta, C/EBP-alpha, PPAR-gamma, perilipin, adiponectin, pref-1 and FABP4) and Oil Red-O staining for lipids accumulation performed.
Results: The co-culture of LLC tumor cells in the presence of 3T3-L1 caused a 33% reduction in lipids accumulation, suggesting that secretory tumor cells products may affect adipogenesis. Once established that LLC cells in co-culture impaired adipogenesis, the next step was to evaluate the behavior of some major adipogenic genes, on day 0, 2, 4 and 8. Interestingly, a very early (day 2) down-regulation of PPAR-gamma, perilipin was detected, followed by terminal (day 4 and 8) down-regulation of C/EBP-alpha, adiponectin and FABP4.
Conclusion: Overall, our results suggest that LLC secretory products impair adipocyte differentiation in a co-culture system; seemingly LLC cells are able to influence the initial expression of the PPAR-gamma in 3T3-L1 cells and as a consequence inhibit the whole adipogenic program.

3-19

A role of adrenal hormones on cancer-associated cachexia

Lucía-T. Díez Córdova[1], Michele Petruzzelli[2], Marko Poglitsch[3], Erwin F. Wagner[1]
[1]Spanish National Cancer Research Center (CNIO-ISCIII), Madrid, Spain, [2]Oncology Department, Addenbroke´s Hospital, Cambridge, UK, [3]Attoquant diagnostic, Vienna, Austria

Cancer-associated cachexia (CAC) is a life-threatening wasting syndrome affecting a large fraction of cancer patients. Limited therapeutic options are available and the underlying molecular mechanisms are not well understood. Using mouse models and cancer patient samples, we previously reported that WAT browning is an early event and a key feature of Cancer-Associated- Cachexia (1).
Adrenal hormones, particularly Aldosterone, are important for the pathogenesis of cardiovascular disease-associated cachexia. A genetically engineered mouse model, K5-SOS, which develops skin tumor–associated cachexia was employed to investigate the contribution of adrenal hormones to CAC. Increased mRNA expression of the receptors for two adrenal hormones, Aldosterone and Corticosterone, were measured in muscle and adipose tissue from K5-SOS mutant mice. Serum samples from pre-cachectic and cachectic K5-SOS mice were analyzed by Liquid-Chromatography-Mass-Spectrometry. Importantly, increased levels of Corticosterone and Aldosterone were detected in both pre-cachectic and cachectic mice, when compared to littermate controls. Furthermore, when analyzing the intermediate peptides of the Renin-Angiotensin-Aldosterone system (RAAS), consistently higher levels of Angiotensin II and Angiotensin 1-5 were measured in sera from pre-cachectic and cachectic mice. These results suggest an overall activation already at the pre-cachectic stage of the RAAS, as well as the Hypothalamic-Pituitary-Adrenal (HPA) axis, as the main regulators of adrenal hormone secretion. While further experiments are needed to define the contribution of the RAAS pathway and the HPA axis, these alterations may represent a novel and therapeutically relevant early event in CAC.

(1) Petruzzelli, M. et al. *A switch from white to brown fat increases energy expenditure in cancer-associated cachexia.* Cell Metabolism. Sep 2;20(3):433-47 (2014)

3-20

Counteracting intestinal dysbiosis with a synbiotic approach reduces cachexia and increases lifespan in leukemic mice

Laure B. Bindels[1], Audrey M. Neyrinck[1], Sandrine P. Claus[2], Caroline I. Le Roy[2], Corinne Grangette[3], Bruno Pot[3], Inés Martinez[4], Jens Walter[4,5], Patrice D. Cani[1,6], Nathalie M. Delzenne[1]*
[1]Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium, [2]Department of Food and Nutritional Sciences, University of Reading, Reading, United Kingdom, [3]Lactic Acid Bacteria and Mucosal Immunity, Centre for Infection and Immunity of Lille, INSERM U1019-CNRS UMR 8204, Institut Pasteur de Lille, Université Lille Nord de France, Lille, France. [4]Department of Agricultural, Food & Nutritional Science, University of Alberta, Edmonton, Alberta, Canada, [5]Department of Biological Sciences, University of Alberta, Edmonton, Alberta, Canada, [6]Walloon Excellence in Life sciences and BIOtechnology (WELBIO), Louvain Drug Research Institute, UCL, Brussels, Belgium

Background and aims: Cancer cachexia is a multifactorial syndrome that includes muscle wasting and inflammation. Since gut microbes influence host immunity and metabolism, we investigated the role of the gut microbiota in the therapeutic management of cancer and associated cachexia.
Methods: We used two mouse models of cancer cachexia (acute leukaemia, BaF model, or subcutaneous transplantation of colon cancer cells, C26 model). Caecal microbiomes were analyzed using 16S rDNA sequencing, H^1-NMR metabolomics analyses were performed on the portal serum, and muscle atrophy, cancer cell proliferation and gut barrier function were assessed using RT-qPCR.
Results: A community-wide analysis from two mouse models of cancer cachexia identified common microbial signatures, including decreased *Lactobacillus* spp. and increased *Enterobacteriaceae* and *Parabacteroides goldsteinii*/ASF519. This microbial signature was not a consequence of the decreased food intake. Building on this

information, we administered a synbiotic containing inulin-type fructans and live *Lactobacillus reuteri* 100-23 to leukemic mice. A new sequencing analysis revealed that, among others, this treatment restored the *Lactobacillus* population and reduced the *Enterobacteriaceae* levels. The treatment improved many of the features associated with cancer and cachexia, such as muscle atrophy, hepatic cancer cell proliferation and lifespan. Cancer cachexia was also associated with alterations of the gut barrier function. Administration of the synbiotic treatment restores the expression of antimicrobial proteins controlling intestinal barrier function and gut immunity markers. Finally, the synbiotic treatment did not impact the metabolomics imprinting of energy demand linked to the development of cancer and cachexia.

Conclusions: In summary, this set of experiments provides evidence that the development of cancer outside the gut can impact intestinal homeostasis and the gut microbial ecosystem and that a symbiotic intervention, by targeting some alterations of the gut microbiota, confers benefits to the host, improving lifespan and reducing cancer cell proliferation and cachexia.

3-21

Proposal for detailed classification of the Glasgow Prognostic Score 2

Miura Tomofumi[1], Amano Koji[2], Tatsuya Morita[3], Yoshihisa Matsumoto[1], Takashi Hama[4]

[1]Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2] Department of Palliative Medicine, Osaka City General Hospital, Osaka, Osaka, Japan, [3]Palliative and Supportive Care Division, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan, [4]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Osaka, Japan

Background: The Glasgow Prognostic Score (GPS) 2 predicts a poor prognosis for patients in the palliative care setting. GPS 2 was recognized as refractory cachexia, that is, a poor prognosis within three months, and resistance to anti-cancer therapy. However, some patients with refractory cachexia might benefit from nutritional and anti-inflammatory therapy. The present study proposes a detailed classification of GPS 2.

Methods: Patients (n = 844; female, 39%; mean age, 70 y) who were referred to palliative care for the first time and had not received anti-cancer treatment, were enrolled in this sub-analysis of this validation study of the Japan Prognostic assessment tool. Patients in GPS 2 were assigned to groups with high or low CRP based on a cut-off of CRP 40 mg/L. Background, symptoms, activities of daily living (ADL), laboratory data, and survival were compared between the two groups.

Results: The group with high CRP levels had a higher frequency of a poor PS, liver metastasis, appetite loss, edema, fatigue, weight loss within one month, low muscle power, a need for assistance to accomplish ADL, a high white blood count, a low lymphocyte count, hypoalbuminemia and low transthyretin ($p < 0.05$). The median survival for the groups with high and low CRP was 18 and 31 days, respectively (95% confidence interval [CI]: 16 – 21 vs. 25 - 36 days, $p < 0.001$).

Conclusion: A classification of the GPS 2 based on a CRP cut-off of less than 40 mg/L detected a population with a median survival of $>$ 30 days and having a relatively better condition. This new classification might become a new definition of refractory cachexia and a new criterion for use in clinical trials of patients with cancer in the palliative care setting.

3-22

Cancer cachexia assessment in a specialist palliative care inpatient unit

Eimear Loftus[1], Shane Lyng[1], Louise O'Halloran[1], Cliona M. Lorton[1,2], Brenda O'Connor[1,3], Pauline Uí Dhuibhir[1,3], Lucy Balding[2], Stephen Higgins[2] , Norma O'Leary[2], T. Declan Walsh[1,2,3]

[1]School of Medicine, Trinity College Dublin, College Green, Dublin, Ireland, [2]Our Lady's Hospice & Care Services, Dublin, Ireland, [3]UCD School of Medicine and Medical Sciences, University College Dublin, Belfield, Dublin, Ireland

Background and aims: Cancer cachexia is associated with poor quality of life, increased cancer treatment morbidity and reduced survival. Accurate assessment enables appropriate nutritional intervention. Multiple barriers to cachexia assessment exist in the palliative setting. The aim of this study was to examine current practice in a specialist palliative care unit (SPCU) and whether cachexia is accurately assessed, based on the international consensus definition of cancer cachexia (Fearon et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489-495).

Methods: Unified healthcare records of consecutive cancer admissions to the SPCU from September 2014 to February 2015 were retrospectively reviewed. Documentation of anorexia, catabolic drivers (C-Reactive Protein; CRP), functional status (Palliative Performance Scale; PPS), weight and weight change was sought as per the 2011 consensus. The symptom subsection (12 questions) of the Patient-Generated Subjective Global Assessment (PG-SGA) was used as a validated tool to record symptoms. Outcome of admission (death/discharge) was recorded. Statistics were generated with Microsoft Excel.

Results: 214 admissions were reviewed. Anorexia was documented in 68% (n = 135). Median CRP was 47.8mg/L (range:0.6-456 mg/L). Median PPS was 40% (range:10-80%). Weight was documented in 19% (n = 41). 13% (n = 27) were asked about weight change; 95% (n = 25) of them reported weight loss. Weight loss was quantified in 8 cases. The word "cachectic" was applied to 47 admissions. Median number of symptoms was 3 (range:0-7 of 12 potential). 23% (n = 49) were discharged home.

Conclusions: Nutritional assessment was neither comprehensive nor routine despite a high prevalence of abnormalities consistent with cachexia. Anorexia was common. Weight evaluation was infrequent. Symptom burden was high and inflammatory markers elevated. Almost one quarter of patients were discharged and might have benefited from intervention. Screening tools and education are needed to prompt recognition and appropriate management of cancer cachexia in the palliative care setting.

3-23

Multi-frequency phase angle for prognostication of survival in cancer patients at an outpatient palliative care clinic

Lindsey Pimentel, Rony Dev, David Hui, Eduardo Bruera
Department of Symptom Control & Palliative Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Phase angle is a novel nutritional marker and has been found to have prognostic significance. Compared to the traditional single frequency bioelectrical impedance analysis (BIAs), multi-frequency BIAs can determine phase angle at different frequencies. However, the prognostic utility of multi-frequency phase angle has not been determined. In this retrospective study, we determined the association of multi-frequency phase angle with overall survival in patients with advanced cancer.
Methods: We included all patients with advanced cancer who had an outpatient palliative care consultation. Multi-frequency BIAs assessed resistance and reactance on both sides of the body at 3 frequencies (5 kHz, 50 kHz and 250 kHz), providing 6 phase angle measures. Survival analysis was conducted with Kaplan Meier curves and Log rank test.
Results: Among 353 patients, the median age was 58 (range 21-90), 163 (46%) were female, and 234 (66%) were White. The most common cancer diagnoses were gastrointestinal (N=112, 32%), breast cancer (N=47, 13%) and head and neck cancer (N=46, 13%). The median overall survival was 262 days (95% confidence interval 207-350 days). The median phase angle for 5 kHz, 50 kHz and 250 kHz were 2.3 θ, 4.4 θ, 4.2 θ on the right, and 2.0 θ, 4.2 θ and 4.1 θ on the left, respectively. For all 6 measures, a lower phase angle was significantly associated with poorer overall survival.
Conclusions: Phase angle represents a novel objective prognostic factor in outpatient palliative cancer care setting, regardless of frequency and body sides.

3-24

Elevated C-reactive protein level is associated with accumulated symptom burden and activity of daily living disability in advanced cancer patients receiving palliative care

Koji Amano[1], Isseki Maeda[2], Tatsuya Morita[3], Mika Baba[4], Tomofumi Miura[5], Takashi Hama[6], Ichiro Mori[7], Nobuhisa Nakajima[8], Tomohiro Nishi[9], Hiroya Kinoshita[10]
[1]Department of Palliative Medicine, Osaka City General Hospital, Osaka City, Japan, [2]Department of Palliative Medicine, Graduate School of Medicine, Osaka University, Suita City, Japan, [3]Palliative and Supportive Care Division, Seirei Mikatahara General Hospital, Hamamatsu City, Japan, [4]Department of Palliative Care, Saito Yukoukai Hospital, Ibaragi City, Japan, [5]Department of Palliative Medicine, National Cancer Hospital East, Kashiwa City, Japan, [6]Palliative Care Team, Osaka Medical Center for Cancer and Cardiovascular Disea ses, Osaka City, Japan, [7]Gratia Hospital Hospice, Mino City, Japan, [8]Department of Palliative Medicine, Graduate School of Medicine, Tohoku University, Sendai City, Japan, [9]Kawasaki Comprehensive Care Center, Kawasaki Municipal Ida Hospital, Kawasaki City, Japan, [10]Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa City, Japan

Background: The association between C-reactive protein (CRP) level, symptoms, and ADL in advanced cancer patients is unclear.
Methods: This multicenter prospective cohort study consisted of 2426 patients and 1702 patients of them were eligible for the current analysis. They were divided into four groups: low- (CRP $<$ 1 mg/dl), moderate- (1 = $<$ CRP $<$5 mg/dl), high- (5 = $<$ CRP $<$ 10 mg/dl) and very high-CRP (10 mg/dl = $<$ CRP). Laboratory data, symptoms, activities of daily living (ADL), and manual muscle testing (MMT) results were obtained at baseline. The proportions of symptoms, ADL disabilities, and three categories of MMT were investigated. Adjusted mean numbers of symptoms and ADL disability were calculated after adjustment by using generalized linear models. The impact of CRP level on the accumulation of symptoms and ADL disabilities was tested by analysis of covariance.
Results: Rates of positivity for symptoms and ADL disabilities increased with increasing CRP level. Those of anorexia, fatigue, and weight loss were 89.8%, 81.0%, and 79.2%, respectively, and over 70% of patients received assistance for bathing, dressing, going to the toilet, and transfer in the very high-CRP group. The grade of MMT deteriorated with increasing CRP level. Regarding symptoms, significantly higher adjusted means than in the low-CRP group were observed in the moderate-, high-, and very high-CRP groups ($P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Regarding ADL disabilities, they were observed significantly more in the very high-CRP group ($P < 0.001$). The accumulation of symptoms and ADL disabilities significantly increased with increasing CRP level ($P < 0.001$ and $P = 0.002$, respectively).
Conclusions: Associations between CRP level, symptoms, and ADL were observed in advanced cancer patients receiving palliative care.

3-25

Integration between supportive care and medical oncology for better recognition and treatment of cachexia in cancer patients at home

Francesco Matozzo, Monica Campanelli, Germana Gavioli, Cristina Simonato, Korenza Tesoriati, Daniele Martinelli
Department of Palliative Care "*Carlo Poma*" Hospital-Mantova, Italy

Introduction: The cancer cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. Prior to reaching its refractory phase, cachexia is not completely irreversible; hence, the potential difference in cachexia therapy is that early intervention during active adjuvant or palliative cancer therapy is the better setting to develop treatment rather than when the patients has become likely refractory to anticachexia treatment (*end of life care*).

Aims: recognize and classify the cancer patients in according to the severity of the cachectic syndrome.
Methods: It is designed an evaluation form incorporating clinical, functional and biochemical parameters in order to adequately identify and treat patients at home with cancer cachexia. This evaluation form includes six sections: Personal data (**I**). Diagnosis of malignancy (reporting the presence or absence of metastasis) (**II**). Anthropometric values: total involuntary weight loss, body mass index, anorexia, Correct Arm Muscle Area (CAMA), handgrip strength, SARC-F screen for sarcopenia (**III**). Prognosis: <3 months, 3-6 months, 6-9 months (**IV**). Blood test (**V**). The last section identifies the three stages of cachexia in according to the different data collected. *Precachexia*: 6-9 months expected survival, weight loss $\leq$ 5%, anorexia and metabolic change. *Cachexia*: 3-6 months expected survival, weight loss $>$ 5% or BMI <20 and weight loss $>$ 2% or sarcopenia and weight loss $>$ 2%. *Refractory Cachexia*: <3 months expected survival, criteria responsive to the diagnosis of cachexia, no response to anticancer treatment, inappropriate artificial nutrition, SARC-F $\geq$4, hypercatabolism (**VI**).
Results: 20 patients were enrolled, 12 males and 8 females (a mean age of 72) with a newly discovered histologically confirmed malignancy. All patients were assisted by Palliative Home Care Service of the "Carlo Poma" Hospital *in simultaneous care* with medical oncologist. The patients declared *off therapy* were ruled out. Precachexia was identified, approximately, in 25% of patients, cachexia in 55% of patients, refractory cachexia in 20% of patients. Data collection was easy to perform and such staging system was beneficial to decide the type of treatment in order to improvement to therapy or survival.
Conclusion: The cancer cachexia is an insidious syndrome that not only has a dramatic impact on patient quality of life, but also is associated with poor response to chemotherapy and decreased survival. The aim of improvement in tolerance to therapy or survival imply intervention at the earliest possible indication that cachexia has started to develop, or even preventative intervention in patients who can reasonably be expected to develop it (*precachexia*).

3-26

Swimming training attenuates muscle and fat mass atrophy-induced in LLC tumour-bearing mice

Luana G. Leal[1], Camila Ueda[1], Felipe S. Henriques[1], Franco O. Franco[1], Victor A. Correa[1], Kaltinaitis B. Santos[1], Magno A. Lopes[1], Pamela V. Knöbl[1], Claudio S. Shida[2], Miguel L. Batista Jr[1]
[1]Laboratory of Adipose Tissue Biology, Integrated Group of Biotechnology, University of Mogi das Cruzes, Mogi das Cruzes, São Paulo, Brazil, [2] Department of Biomedical Engineering, Federal University of Sao Paulo, Sao Jose dos Campos, São Paulo, Brazil

Background and aims: Cancer cachexia (CC) is a multifactorial syndrome. The majority of CCpatients experience wasting characterized by muscle loss with or without fat loss. Recently, physical exercise has been suggested as an efficient therapeutic intervention for the cachexia symptoms by promoting increases in strength, endurance and skeletal muscle hypertrophy. However, there is no evidence to clearly support the role of swimming training (ST) in preserving lean and fat mass loss. The purpose of this study was to verify the effects of swimming training in the muscle and adipose tissue of tumor-bearing mice.
Methods: Males C57Bl/6 mice (n=38), were subcutaneously inoculated with 300μl ($3{,}5x10^6$) of Lewis Lung Carcinoma (LLC) cells or vehicle-saline. The animals were randomly divided into a sedentary control (SCO), training control (TCO), sedentary tumor-bearing (STB) and training tumor-bearing (TTB) groups. The swimming training was consisted of 30 minutes, 5-times/week, during 4 weeks. After 28 days, animals were sacrificed and gastrocnemius and soleus muscles, subcutaneous adipose tissue (scAT) were dissected. The morphological and morphometric analyses were done by light microscopy and the gene expression (mTORC, p70, Murf-1 and Atrogin-1) by qPCR.
Results: ST was able to restore the soleus atrophy in 17% ($p<0.05$) in the TTB when compared with the STB. However, qPCR analysis for hypertrophic and atrophic genes showed no difference between groups. ST effect showed similar findings in scAT mass. SCAT was affected by tumor, showing atrophy in 44% ($p<0.05$), while ST revert this decrease demonstrating an increase of 85% in scAT mass (STB versus TTB, $p<0.05$). scAT adipocyte diameter was 26% smaller in STB when compared with TTB ($p<0.05$), and ST was also able in restore such atrophy in 36%($p<0.01$).
Conclusion: The swimming training demonstrated to be effective in attenuate the skeletal muscle and fat mass atrophy induced by cancer cachexia.

3-27

The impact of patient sex and supervised exercise training on change in exercise capacity in cancer cachexia

Tamara Windholz, Mary Kanbalian, Thi Tran, Tara Swanson, Leo Culhane, Thomas R. Jagoe
McGill Cancer Nutrition Rehabilitation Program, Segal Cancer Centre, Jewish General Hospital, Montreal, Quebec, Canada

Background and aims: Exercise has broad potential value in management of cancer cachexia but the optimum method of training and expected effects on exercise outcomes are unclear. To investigate this we analysed the results of exercise testing performed in patients attending a multidisciplinary clinic specializing in cancer cachexia.
Methods: *A retrospective analysis of patients with advanced (stage III/IV) cancer attending the McGill Cancer Nutrition Rehabilitation program clinic at the Jewish General Hospital (CNR-JGH).* Six-minute walk test distance (6MWT) and exercise category were recorded at each of the first three clinic visits (V1,V2,V3). Change in 6MWT from baseline was compared between males and females and between each of 3 different exercise categories: None, Unsupervised, Supervised.
Results: 405 patients attended V1 of which the majority were doing no exercise (78% None, 19% Unsupervised). 350/405 (86%) performed 6MWT at V1. 6MWT at V1 was higher in males (mean(SD) male 375(152)m vs female 321(129)m, $P<0.001$), but improvement in 6MWT V1-V2 (mean(SD) 5.6(2.6) weeks) and V1-V3 (mean(SD)

11.6(3.5) weeks) was only seen in females (e.g. V1-V3 mean(SD) 6MWT change: males vs females, 29(113)m vs 74(101)m, P=0.03). Patients undertaking both supervised and unsupervised exercise had significant improvements in 6MWT between V1-V2 compared with no training. However, by V3 only those participating in supervised exercise group (N=47(27%)) had significantly improved compared with no training (N=58(33%)). Mean (SD) change in 6MWT V1-V3: Supervised vs None: 88(110)m vs -6(100)m, P = 0.002. When sex and exercise category were combined in a two-way ANOVA, change in 6MWT at V3 for those undertaking supervised exercise remained significantly greater than for no training (P=0.006).
Conclusions: Marked improvements in exercise function can be achieved in patients with cancer cachexia. In the program offered at the CNR-JGH increases in exercise capacity are greater in females and in those participating in supervised exercise training.

3-28

The timing of standard exercise training affects the therapeutic benefits for advanced cancer patients undergoing treatment

Brandy Vanderbyl[1], Michelle J. Mayer[1], Caryn Nash[1], Anh-Thi Tran[2], Tamara Windholz[1], Tara Swanson[1], Gonar Kasymjanova[2], R. Thomas Jagoe[2]
[1]McGill Cancer Nutrition Rehabilitation Program, Segal Cancer Centre, Jewish General Hospital, Montreal, Quebec, Canada, [2]McGill Cancer Nutrition Rehabilitation Program and Peter Brojde Lung Cancer Centre, Segal Cancer Centre, Jewish General Hospital, Montreal, Quebec, Canada

Background and aims: Patients with advanced cancer frequently experience anxiety, depression and poor quality of life (QOL), as well as physical symptoms such as fatigue and weakness. Exercise may help control these symptoms but the optimal training prescription is still not clear. To investigate this we performed a study comparing Qigong (QG) and standard exercise therapy (SET) in patients with advanced stage lung (NSCLC) and gastrointestinal (GI) cancers.
Methods: A randomized, cross-over study was performed targeting patients with advanced NSCLC and GI cancers receiving or eligible for chemotherapy. Each intervention involved supervised QGor SET twice-weekly for six weeks. Psychological functioning, QOL, symptoms and physical functioning were assessed (HADS, FACT-G, ESAS, Simmond's test battery) before and after each intervention period. Changes in outcomes were analysed by two-way ANOVA using intervention type and order.
Results: 19 patients completed both interventions. Comparing interventions revealed no difference between QG or SET on change in anxiety or depression scores (HADS) or QOL (FACT-G). However, SET treatment was significantly better at improving feelings of strength ($P<0.05$) and 6MWT distance (P=0.02). The order in which interventions were performed had a significant impact on the improvement in certain symptoms (sleep quality, breathlessness; $P<0.05$), QOL (P=0.008) and 6MWT (P=0.008). In all cases, the beneficial effects of the exercise interventions were less or even absent during the second interval.
Conclusion: Our results show that QG and SET are equivalent in their impact on many aspects of emotional/psychological function in cancer patients. However SET leads to greater improvements in exercise capacity and some symptoms. The impact of order, and the reduced improvement in exercise function with SET in the second interval is surprising. These results may indicate that the functional benefits from exercise interventions are more evident when used early in the patients' trajectory but these findings deserve further study.

3-29

Whole body vibration training in prevention of cancer cachexia during allogeneic haematopoetic stem cell transplantation: a RCT

Tobias S. Kaeding[1,2], Marcel Frimmel[3], Florian Treondlin[3], Justin Hasenkamp[3]
[1]Institute of Sports Science, Carl von Ossietzky University of Oldenburg, Germany, [2] Department of Rehabilitation- and Sports Medicine, University Medical Center Göttingen, Germany, [3]Clinic for Hematology and medical Oncology Department of Stem Cell Transplantation, University Medical Center Göttingen, Germany

Background: The usually during a carcinosis occurring physical inactivity, effects of the tumor and respective therapies lead to the genesis of cancer cachexia and a considerable reduction of the physical capacity [1,2,3,4]. Poor physical capacity impairs the quality of life and limits the effectiveness of the therapy [1,5,6]. There is evidence that whole body vibration training (WBVT) is a safe and effective intervention in therapy and prevention of sarcopenia [7,8,9]. Sarcopenia and cancer cachexia are different in main characteristics but share some metabolic pathways and mediators [4]. Therefore, we assumed that WBVT might be a safe and effective intervention for the prevention of cancer cachexia in patients undergoing allogenic hematopoietic stem cell transplantation (HSCT).
Methods: 26 patients were randomly assigned to an intervention group (INT (n= 13)) or a control group (CON (n= 13)). All patients received conventional physical therapy during their hospitalization, only patients in INT additionally received a progressive WBVT on every other day. An isokinetic measurement of the muscular strength of the lower extremities was carried out before and after treatment.
Results: No unwanted side-effects were detected. Despite lack of significant differences between the groups after treatment, we found trends of positive effects of the intervention in maximum torque at 180°/s extension (p=0.07) and at 300°/s extension (p=0.09). The maximum torque at 180°/s extension in CON was reduced from 81.9 Nm +/-28.54 to 73.9 Nm +/-24.5, whereat in INT it raised from 78.1 Nm +/-37.72 to 88.6 Nm +/-36.39. At 300°/s extension the maximum torque in CON was reduced from 75.85 Nm +/-31.42 to 66.5 Nm +/-28.02 and raised in INT from 78.11 Nm +/-37.72 to 88.59 Nm +/-36.39.
Conclusions: WBVT can be implemented safely as a supportive therapy for patients undergoing an allogeneic HSCT and possibly is an effective option for the prevention of cancer cachexia.

3-30

A multidisciplinary rehabilitation program targeting patients with cancer cachexia improves quality of life even in advanced stage disease

Monica P. Parmar Calislar[1], Mary Kanbalian[2], R. Thomas Jagoe[2,3]
[1]McGill Cancer Nutrition Rehabilitation Program, Segal Cancer Centre, Jewish General Hospital & Ingram School of Nursing, McGill University, Montreal, Quebec, Canada, [2]McGill Cancer Nutrition Rehabilitation Program, Segal Cancer Centre, Jewish General Hospital, Montreal, Quebec, Canada, [3]Department of Medicine, McGill University, Montreal, Quebec, Canada

Background and aims: Prior results suggested overall well-being was only minimally improved in patients attending our multi-disciplinary program for cancer cachexia, despite stabilization of body weight. We used a cachexia-specific quality of life (QoL) tool to study profile of changes in QoL in a second cohort of patients with advanced cancer.
Methods: A retrospective analysis of patients with advanced (stage III/IV) cancer, over the first three visits to the McGill Cancer Nutrition Rehabilitation program at the Jewish General Hospital (CNR-JGH) was conducted. The total score of the FAACT QoL tool and 5 individual sub-scales, as well as the trial outcome index (TOI, comprised of the Physical (PWB), Functional (FWB) and Anorexia-cachexia (ACS) subscales), were assessed.
Results: 405 patients were included at baseline with mean weight loss of 10% over the preceding 6 months. The majority (84%) of patients had an ECOG score of $\geq$2 and overall median survival from time first visit was 37 weeks. FAACT scores were collected at each visit with $<$10% missing data at each time point. Total FAACT, TOI, PWB and ACS subscales increased consistently and progressively over each visit interval. After 3 visits mean (SD) increase of 7.7(15.8) in TOI ($P<0.001$) and 4.1(9.1) in ACS ($P<0.001$) over 11.6(3.5) weeks was found. The improvements in QoL achieved the threshold for clinically significant change (e.g., $>$ 3 points for ACS subscale), but the main effects were limited to the ACS and PWB domains.
Conclusions: Patients attending the CNR-JGH program report better QoL largely due to improvements in ACS and PWB. The profile of improvements in QoL observed may simply reflect the impact of the primary interventions targeting nutritional and physical functional goals. However, further efforts to address poor emotional and social functioning in cachexia may be warranted, to maximize overall success of cachexia interventions and improvements in QoL.

3-31

Tumour contribuition to cachexia-related inflammation in cancer patients

Joanna D.C.C. Lima[1], Emídio M. Matos-Neto[1], Raquel G. Figuêredo[1], Katrin Radloff[1], Rodrigo X. Neves[1], Linda Maximiano[2], Flávio Tokeshi[2], José Pinhata Otoch[2], Paulo S.M. Alcantara[2], Marília Seelaender[1]
[1]Cancer Metabolism Research Group, University of Sao Paulo, Brazil, [2]Department of Clinical Surgery, University of Sao Paulo, Brazil

Background: Cancer cachexia is a syndrome characterised by reduction of adipose tissue, skeletal muscle mass and by metabolic imbalance. It is believed to result from the interaction between the host's cells and the tumour, yielding systemic inflammation. Aim: To establish whether the pattern of tumour cytokine secretion is correlated with cachexia.
Methods: Volunteers diagnosed with colon/rectum carcinoma, and not undergoing pharmacological treatment were recruited at the University Hospital and divided, after obtainment of the informed consent, into two groups: Weight-stable cancer (WSC n=17) and cachectic cancer (CC n=18). Cachexia was diagnosed as in Evans *et al*. (2008). Tumour tissue cytokine expression was analysed with Luminex xMAP and is expressed as median [1st quartile; 3rd quartile].
Results: No correlation between cachexia and tumour stage was found (p=0.781). The pro-inflammatory cytokine IL-1B expression was higher in CC, as compared with WSC (WSC: 3.723 [1.68;25.59]; CC: 16.08 [3.61;87.37]; p=0.041); while IL-8 showed a tendency to be higher in CC (WSC: 375.8[83.71;1175];CC:1926[160.6;2886] p=0.084). Tumour IFN-γ, IL-6, IL-17A expression was not significantly different between the groups. TNF-α and TNF-β were not different in CC, compared with WSC, yet a tendency for increased TNF-α content in CC was observed (WSC: 0.4190 [0.206; 1.309]; CC:1.296 [0.443;2.56] p = 0.062; WSC:1.824 [0.832;3.763]; CC:2.959[1.091; 5.859] p = 0.229, respectively). Protein concentration of anti-inflammatory interleukin IL-10 was not different between the groups (WSC: 0.606 [0.209; 1.49]; CC: 0.427 [0.107; 2.82] p = 0.965), while that of IL-13 was lower in CC in relation to WSC (WSC: 11.49 [4.761; 28.55]; CC: 3.139[1.582; 7.06] p = 0.013). Correlation analysis demonstrated positive relationship between IL-1β/TNF-α (p=0.006, r = 0.714) and between IL-1β/IL-8 ($p<0.0001$, r=0.842). IL-1B content was similarly correlated with IL-10 and IL-13 levels (p = 0.041, r = 0.471 and p = 0.015, r = 0.545, respectively.)
Conclusions: Patients with tumours with higher pro-inflammatory cytokine expression capacity (IL-1B, IL-8, TNF-α) are more prone to developing cachexia.

3-32

Regulation of hepatic cardiolipin metabolism by TNFα: implication in cancer cachexia

Laure Peyta[1], Michelle Pinault[1], Caroline Goupille[1], Stephan Chevalier[1], Jean-François Dumas[1], François Maillot[1], Grant M. Hatch[2], Pascal Loyer[3], Stephane Servais[1]
[1]University of Tours-INSERM UMR1069 Nutrition Growth and Cancer, Tours, France, [2]Department of Pharmacology and Therapeutics, Biochemistry and Medical Genetics, Faculty of Health Sciences, Center for Research and Treatment of Atherosclerosis, DREAM Children's Hospital Research Institute of Manitoba, University of Manitoba, Canada, [3]Inserm UMR S-991, Foie, Métabolismes et Cancer, CHU Pontchaillou, Rennes, France

Cardiolipin (CL) content accumulation leads to an increase in energy wasting in liver mitochondria in a rat model of cancer cachexia in which tumor necrosis factor alpha (TNFα) is highly expressed. In this study we

investigated the mechanisms involved in liver mitochondria CL accumulation in cancer cachexia and examined if TNFα was involved in this process leading to mitochondrial bioenergetics alterations. We studied gene, protein expression and activity of the main enzymes involved in CL metabolism in liver mitochondria from a rat model of cancer cachexia and in HepaRG hepatocyte-like cells exposed to 20 ng/ml of TNFα for 12 h. Phosphatidylglycerolphosphate synthase (PGPS) gene expression was increased 2.3-fold ($p<0.02$) and cardiolipin synthase (CLS) activity decreased 44% ($p<0.03$) in cachectic rat livers compared to controls. CL remodeling enzymes monolysocardiolipin acyltransferase (MLCL AT-1) activity and tafazzin (TAZ) gene expression were increased 30% ($p<0.01$) and 50% ($p<0.02$), respectively, in cachectic rat livers compared to controls. Incubation of hepatocytes with TNFα increased CL content 15% ($p<0.05$), mitochondrial oxygen consumption 33% ($p<0.05$), PGPS gene expression 44% ($p<0.05$) and MLCL AT-1 activity 20% ($p<0.05$) compared to controls. Finally, SiPGPS cells demonstrated no effect of TNFα on CL content in HepaRG cells. These above findings strongly suggest that in cancer cachexia, TNFα induces a higher energy wasting in liver mitochondria by increasing CL content via upregulation of PGPS expression.

3-33

Turnover of triglycerides in cancer cachexia adipocyte: Possible role of immune-metabolism modulation

Felipe S. Henriques[1], Pamela V. Knobl[1], Felipe O. Franco[1], Rogerio L. Sertié[2], Sidney B. Peres[3], Rodrigo X. Neves[2], Kaltinaitis B. Santos[1], Fabio B. Lima[2], Marilia C. Seelaender[2], Miguel L. Batista Jr[1]

[1]Laboratory of Adipose Tissue Biology, Integrated Group of Biotechnology, University of Mogi das Cruzes, Mogi das Cruzes, São Paulo, Brazil, [2]Cancer Metabolism Research Group, Institute of Biomedical Sciences, University of Sao Paulo, São Paulo, Brazil, [3]Department of Physiological Sciences, State University of Maringá, Paraná, Brazil

Background and aims: Cancer cachexia is a multifactorial syndrome characterized by systemic inflammation, body weight loss, and atrophy of white adipose tissue. In such disease, adipose tissue (AT) is recognized to play a pivotal role in whole-body lipid and glucose homeostasis through metabolic control by various immunological mechanisms. Inflammatory mediators as TNF-α, which is of the markers of advanced cachexia, contribute to the condition since they may stimulate local lipolysis. However, there is little information regarding the mechanisms triggering the inflammatory response in AT, especially during cancer cachexia development.

Methods: Male Wistar rats, 8 weeks old, subcutaneously inoculated with 1 mL (2×10^7) of Walker 256 tumor cells (TB) or vehicle-saline (C). Samples from mesenteric AT (MeAT) depots and blood were collected at day 0, 4, 7 and 14 and metabolic alterations were evaluated by lipolysis and lipogenesis, on day 4 and 14 from isolated adipocytes. The inflammatory profile was determined by immunohistochemistry for CD11b and CD68 and treatment of isolated adipocyte with TNF-α (100 ng/mL) for 2 hours were assessed.

Results: Adipocyte lipolysis showed an increase of 6-fold on day 14 observed only in basal stimulation in TB compared to the control. HSL Phospho-Ser^{563} levels increased of 5.6-fold on day 14 in TB group. 1-[^{14}C]-glucose to fat acid incorporation decreased on day 14 in TB when compared to C on day 14. CD11b and CD 68 were positively marked on day 14. TNFα induced-lipolysis increased 84 % in TB group on day 14 when compared with C cells.

Conclusion: In the present study we demonstrated time-dependent changes at metabolic and inflammatory parameters in MeAT. This change was followed by a TNF-α induced lipolysis in adipocytes from cachectic rats and suggests that targeted immunomodulatory interventions may be beneficial during cachexia development.

Financial Support: FAPESP (2010/51078-1) and CAPES.

3-34

Inflammation in different adipose tissue depots during human cancer cachexia

Katrin Radloff[1], Daniela M.R. Riccardi[1], Emidio Matos-Neto[1], Raquel G. Figuêredo[1], Joanna D.C.C Lima[1], Michele J. Alves[1], R.X. Neves[1], L. Maximiano[2], Flávio Tokeshi[2], José P. Otoch[2], Paulo S. M. Alcantara[2], Marília Seelaender[1]

[1]Cancer Metabolism Research Group, University of Sao Paulo, Brazil, [2]Department of Clinical Surgery, University of Sao Paulo, Brazil

Background: Systemic inflammation and loss of fat mass are hallmarks of cancer cachexia. Adipose tissue is capable of pronounced synthesis of inflammatory molecules.

Aim: To investigate inflammatory pathological changes in different adipose tissue depots in cancer cachexia.

Methods: Volunteers were recruited after signing the informed consent form at the University Hospital. Patients subjected to incisional hernia surgery were included in the control group (Control), while gastrointestinal carcinoma patients were divided into weight-stable cancer (WSC) group and cachectic cancer group (CC). Cachexia was diagnosed as in Evans *et al.*, 2008. Inflammatory factors of different fat depots (subcutaneous adipose tissue SAT, visceral adipose tissue VAT and isolated adipocytes from the subcutaneous pad) were measured with Luminex xMAP technology.

Results: In SAT pro-inflammatory interleukins IL-1β, IL-2, IL-5, and IL-17A were significantly diminished in WSC compared to Control. IL-2 was decreased in isolated subcutaneous adipocytes of WSC, compared to Control ($p = 0.027$). A trend for reduction of IL-2 in CC was observed in VAT ($p = 0.05$). IL-17A was significantly decreased in adipocytes of CC but not in WSC compared to Control. In VAT IL-8 was significantly increased in CC compared to controls ($p = 0.022$) and IL-15, in CC, compared to WSC ($p=0.038$). Furthermore IP-10 was increased in VAT and SAT of CC compared to Control ($p = 0.02$). Interferon γ was significantly diminished in CC compared to Control and WSC ($p = 0.039$).

Conclusion: Changes of the inflammatory profile observed in SAT seem to be a result of cancer, while the increase of interleukins in VAT appear to be associated with cachexia. IP-10 is suggested as a potent inflammatory factor in cachexia, while IL-2 expression was consistently suppressed in all depots, we suggest these factors as possible markers of the syndrome.

3-35

Cancer chemotherapy mediated loss of lean body and fat mass in tumor-free female mice is IL-6 dependent

Lisa J. Wood[1], Collin R. Elsea[2]
[1]MGH Institute of Health Professions, School of Nursing, Boston MA USA, [2]Oregon Health & Science University, Portland, OR, USA

Background: Unfavorable changes in body composition specifically a loss of lean body mass (LBM) and bone mineral content (BMC) and gains in fat mass (FM) have been reported in breast cancer patients exposed to adriamycin-containing drug regimens. Elevated circulating levels of the inflammatory cytokine interleukin-6 (IL-6) have been observed in breast cancer patients undergoing chemotherapy. IL-6 plays an important role in the regulation of body composition. The purpose of the present study was to determine the specific role of IL-6 in cyclophosphamide-doxorubicin-5-fluorouracil (CAF)-induced changes in body composition using mice lacking IL-6.
Methods: Female wild type (WT) and IL-6-deficient mice were injected with 4 cycles of CAF or normal saline (NS) every 21-day. Treatment-related changes in LBM, FM, and BMC were assessed before and 3-weeks after the 4th CAF dose. Physical activity (voluntary wheel running) and food intake were measured continuously throughout the study.
Results: A genotype x drug interaction was observed for changes in LBM ($p = 0.047$) and FM ($p = 0.035$) but not BMC ($p = .569$), controlling for physical activity and food intake. Whereas WT mice lost LBM and FM during CAF treatment, IL-6-deficient mice did not. Treatment-related decreases in levels of the anabolic hormone insulin-like growth factor 1 (IGF-1) may contribute to LBM and FM loss since CAF decreased systemic IGF-1 levels in an IL-6-dependent manner.
Conclusions: These findings suggest that treatment induced IL-6 and possibly IGF-1 may play a role in the unfavorable changes in body composition observed in breast cancer patients exposed to adriamycin-containing drug regimens.

3-36

Tumour derived MIC-1/GDF15 leads to cancer cachexia dominantly by inducing prolonged anorexia

Samuel N Breit[1], Vicky WW Tsai[1], Shu Lin[2], Amanda Salis[3], David A Brown[1]
[1]St Vincent's Centre for Applied Medical Research, St Vincent's Hospital and University of New South Wales, [2]The Garvan Institute of Medical Research, Sydney. NSW, Australia, [3]The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, The University of Sydney, Sydney NSW, Australia

MIC-1/GDF15 is overexpressed by tumours from a majority of patients with many common cancers, including those of the colon, prostate, pancreas, and breast. In advanced cancer, blood levels of MIC-1/GDF15 can increase by up to 10-100 fold. We have previously reported that mice with tumor xenografts, engineered to overexpress MIC-1/GDF15, became cachectic. Further, the serum levels of the tumour derived human MIC-1/GDF15 were proportional to the degree of weight loss, with more marked effects in mice with serum levels greater than about 5-8ng/ml. Importantly, these serum levels were well within the range of those commonly seen in patients with diseases such as advanced cancer. Mice with tumours overexpressing MIC-1/GDF15 ate less and lost a substantial amount of fat and muscle, which could be reversed, without modifying tumour progression, by administering monoclonal antibodies to it and reproduced with recombinant MIC-1/GDF15 treatment. Additionally, our studies indicate that MIC-1/GDF15 overexpressing transgenic mice are lean and protected from the development of obesity. Further germline MIC-1/GDF15 gene deleted (MIC-$1^{-/-}$) mice eat more, weigh more and have greater adiposity than their syngeneic controls. These finding suggest that monoclonal antibodies to MIC-1/GDF15 may be used to treat cancer anorexia/cachexia and such humanised antibodies are currently in clinical development.
Several lines of evidence from our studies indicate that a major mechanism for MIC-1/GDF15 induced loss of lean and fat mass is its actions on the hypothalamus and brainstem demonstrated by: Pair feeding studies showing similar loss of lean mass in MIC-1/GDF15 treated compared to pair fed mice; systemically administered MIC-1/GDF15 rapidly activating neurons in feeding centres in the brain; direct injection or viral expression of MIC-1/GDF15 into the brain leads to anorexia and weight loss; and administering MIC-1/GDF15 inducing greater loss of lean mass in normal than obese mice. Further, surgical lesioning of the brainstem area postrema (AP) and the medial (m) nucleus of solitary tract (NTS), major sites of action of MIC-1/GDF15, abolished the anorexic actions of recombinant MIC-1/GDF15, making the mice resistant to MIC-1/GDF15 induced weight loss. The available evidence suggests that MIC-1/GDF15 may subvert a physiological pathway of appetite regulation to cause anorexia, which then leads to cachexia.

3-37

TLR4 deletion reduces browning and attenuates inflammation in adipose tissue in cancer cachexia syndrome

Felipe S. Henriques[1], Felipe O. Franco[1], Juliana C. Vieira[1], Magno A. Lopes[1], Kaltinaitis B. Santos[1], Pamela V. Knobi[1], Luana G. Leal[1], Claudio S. Shida[2], A. Guilherme[3], Miguel L. Batista Jr[1]
[1]Laboratory of Adipose Tissue Biology, Integrated Group of Biotechnology, University of Mogi das Cruzes, Mogi das Cruzes, São Paulo, Brazil, [2]Department of Biomedical Engineering, Federal University of Sao Paulo, Sao Jose dos Campos, São Paulo, Brazil, [3]Division of Endocrinology, Metabolism, and Diabetes, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Background and aims: Cancer cachexia (CC) is a wasting syndrome characterized by systemic inflammation, body weight loss, atrophy of white adipose tissue (WAT) and skeletal muscle. Recently, white-to-brown adipose tissue remodeling (browning) is response to CC was demonstrated to take place early during CC stages, before

skeletal muscle atrophy. WAT browning is associated with an increased expression of uncoupling protein 1 (UCP1). Chronic inflammation and inflammatory pathways seems to play important role in to modulate UCP1 expression in WAT. Toll Like Receptor 4 (TLR4) is the receptor for LPS and when stimulated, activates inflammatory pathways and induces cytokine expression. However, few studies have addressed a possible relationship between WAT browning, TLR4 pathway and adipose tissue inflammation in cancer cachexia syndrome.

Methods: Male C57BL/6 mice (6-8 week-old), knockouts and wild type (WT) for Toll like Receptor 4 (TLR4 -/-) were subcutaneously inoculated with 300μl (3,5 ×105) of Lewis Lung Carcinoma (Tumor) and vehicle-saline. Subcutaneous (SCAT) and mesenteric (MEAT) adipose tissue were collected on the 27th day after tumor cells injection. Morphological and immunohistochemistry analyses were obtained by light microscopy, while the gene expression analysis was performed by qPCR.

Results: Body weight loss was evident in both tumor groups, which showed a reduction of 12.27% in the Tumor-WT and 6.82% in the Tumor-TLR4-/-. TLR4 deflection reduced WAT browning cachexia-induced in, showing down-regulation of both gene and protein expression of UCP1 in SCAT ($p< 0,01$) when compared with the Tumor-WT groups. MEAT demonstrated a decrease in TNFa, CD68 and CD3 positive cells in the Tumor-TLR4-/- when compared to with Tumor-WT.

Conclusion: Taken together, these results strongly suggest that TLR4 deletion reduces browning and attenuates inflammation in WAT. Thus, TLR4 protein may play an important role in WAT browning which makes the TLR4 a possible interesting therapeutic target for cancer cachexia syndrome.

3-38

Patterns of skeletal muscle dysfunction in patients with lung cancer

Matthew Maddocks[1], Charles C. Reilly[2,3], Jason Nunn[1,3], Caroline J. Jolley[2], Irene J. Higginson[1], John Moxham[2], Gerrard F. Rafferty[2]

[1]Cicely Saunders Institute, Division of Palliative Care, Policy & Rehabilitation, King's College London, London, UK, [2]Department of Respiratory Medicine, Division of Asthma, Allergy & Lung Biology, King's College London, London, UK, [3]Therapies Department, King's College Hospital NHS Trust, London, UK

Background and aims: Skeletal muscle dysfunction is commonly reported in lung cancer but little is known about the distribution of muscle weakness. Systemic inflammation is likely to produce global weakness whereas physical inactivity would, via deconditioning, lead to weakness most marked in the lower limb. The aim was, therefore, to assess the pattern of respiratory and peripheral muscle weakness in patients with lung cancer as compared to age- and gender-matched healthy controls.

Methods: Muscle strength was assessed using maximal voluntary contraction (MVC) of the quadriceps (QMVC), ankle dorsiflexors (ADMVC) and adductor pollicis (APMVC), as well as hand grip strength. Respiratory muscle strength was assessed using maximum inspiratory (PImax) and expiratory (PEmax) mouth pressure, and sniff nasal inspiratory pressure (sniff Pnasal). Mean daily step count was assessed using accelerometry.

Results: Fourteen patients (12 non-small cell; 8 female; mean (SD) age 62(11) years) and 14 healthy controls (9 female; 59(10) years) were studied. Nine patients reported weight loss (>5% over 6 months) and six had abnormal biochemistry (C-Reactive protein >10 mg/l or albumin <35 g/l). Significant reductions (mean difference [95% CI]) in QMVC (−6.56 [0.26,12.9] kg, p = 0.042) and ADMVC (−4.18 [−0.07, −8.30] kg, p = 0.046) were observed in the patient group compared to control. Across both groups, QMVC (r = 0.55,p = 0.005) and ADMVC (r = 0.45, p = 0.02) correlated significantly with daily step count. In contrast, no between-group differences were seen in upper limb strength (APMVC −0.07 [−0.24, 0.10]; hand grip −1.1 [−8.6, 6.4] kg), or respiratory muscle strength (PImax 5.59 [21.3, −10.1], PEmax −4.88 [−26.7, 16.7], sniff Pnasal 2.93 [19.4, −13.5] cmH_2O).

Conclusions: Upper limb and respiratory muscle strength were preserved in people with lung cancer and abnormal metabolism. However, strength of proximal and distal muscles of the lower limb was reduced. This pattern suggests physical inactivity may be a key aetiological factor in the skeletal muscle weakness observed in this group.

3-39

Cancer anorexia: hypothalamic dysfunction and its association with inflammation and appetite-regulating peptides in lung cancer patients

Alessio Molfino[1], Alessandro Iannace[1], Maria Chiara Colaiacomo[2], Alessio Farcomeni[3], Patrizia Seminara[1], Maria Ida Amabile[1], Gianfranco Gualdi[2], Maurizio Muscaritoli[1], Alessandro Laviano[1], Filippo Rossi Fanelli

[1]Department of Clinical Medicine, Sapienza University of Rome, Italy, [2]Department of Emergency, Radiology Unit, Policlinico Umberto I, Sapienza University of Rome, Italy, [3]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy

Background and aims: Energy homeostasis is mediated by the hypothalamus, whose inflammation-induced functional derangements contribute to the onset of anorexia in cancer. By using functional magnetic resonance imaging (fMRI), we determined the patterns of hypothalamic activation after oral intake in anorexic (A), non-anorexic (NA) cancer patients, and in controls (C).

Methods: Lung cancer patients were considered for the study. Hypothalamic activation was recorded in A and NA patients and in C by fMRI, before (T0), immediately after (T1) the administration of an oral nutritional supplement, and after 15 minutes (T2). The grey of the hypothalamus and BOLD intensity were calculated and normalized for basal conditions. Interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, ghrelin and leptin plasma levels were measured. A statistical parametric mapping was used.

Results: Thirteen lung cancer patients (7M, 6F; 9A, 4NA) and 2 C (1M, 1F) were enrolled. Controls had the lowest BOLD intensity. At all-time points, anorexic patients showed lower hypothalamic activity compared to NA ($p<0.001$) (T0: 585.57 ± 55.69 vs 667.92 ± 33.18, respectively; T1: 536.50 ± 61.70 vs 624.49 ± 55.51, respectively; T2: 556.44 ± 58.51vs 615.43 ± 71.50, respectively). A patients showed greater BOLD signal reduction during T0-T1 than NA

(-8.5% vs −6.80%, $p<0.001$). Independently from the presence of anorexia, BOLD signals modification before and after oral challenge correlated with basal values of IL-1 and ghrelin ($p<0.001$).
Conclusions: Hypothalamic activity in A cancer patients is reduced respect to NA and responds differently to oral challenges. The gut-brain axis is impaired in A cancer patients possibly through the direct involvement of cytokines and ghrelin.

3-40

Development of cancer cachexia-associated cardiac atrophy over time in advanced non-small cell lung cancer: First report in human patients

Seyyed Mohammad Reza Kazemi-Bajestani[1], Harald Becher[2], Charles Butts[3], Naveen S. Basappa[3], Michael Smylie[3], Anil Abraham Joy[3], Randeep Sangha[3], Andrea Gallivan[1], Quincy Chu[3], Vickie Baracos[1]
[1]Department of Oncology, Division of Palliative Care Medicine, [2]Department of Medicine, Division of Cardiology, Alberta Cardiovascular and Stroke Research Centre, [3]Department of Oncology, Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Canada

Background and aims: Development of cardiac atrophy in parallel to skeletal muscle (SM) and fat wasting in cancer cachexia are proven in rodent studies; however, this phenomenon has not been investigated in humans and *cardiac atrophy* is not a well-recognized clinical entity. Our aim was to assess whether cardiac atrophy occurs in patients with advanced non-small cell lung cancer (NSCLC) and to assess its possible correlation with skeletal muscle and fat wasting.
Methods: Patients with advanced NSCLC were evaluated at 2 times, prior to 1st line palliative carboplatin doublet chemotherapy and after 4 treatment cycles (4 months later). Comprehensive echocardiographic examination was performed for measurement of left ventricular mass (LVM), LV ejection fraction (LVEF) and global longitudinal strain (GLS, an index of subtle deterioration of LV function). At the same time points, computed tomography images were analyzed to quantify SM and total adipose tissue (TAT) wasting and fatigue was measured utilizing a validated questionnaire (FACIT-F).
Results: Thirty patients [50% male; 64.7 ± 7.6 years] completed the study thus far. Fourteen patients (46.7%) developed > 10% LVM atrophy over the course of 4 months (range -11.9% to -24.5%). Considering all patients, changes of LVM (%) correlated with cachexia parameters: [all changes (%)] LVM *vs* TAT ($r = 0.56$; $p = 0.002$); LVM *vs* SM ($r = 0.36$, $p = 0.05$); LVM vs total SM+TAT($r = 0.61$; $p<0.001$). Percentage loss of LVM also correlated with worsening of fatigue (%) ($r = 0.69$, $p<0.001$). Although LVEF had not changed significantly over time ($p=0.25$), GLS deteriorated significantly ($p=0.003$). Worsening of GLS (%) also correlated with % loss of LVM ($r = 0.63$, $p<0.001$).
Conclusions: This is the first report demonstrating dynamic loss of LVM, concurrently with fat and skeletal muscle loss in patients who are treated with palliative chemotherapy using defined imaging measurements. Cardiac atrophy correlates strongly with worsening of fatigue and deterioration of GLS. This project is ongoing and number of follow up patients will be increased in upcoming months. Cardiac and inflammatory biomarkers and tumor response are also being evaluated.

3-41

Electrocardiographic finding change in advanced non-small cell lung cancer patients

Takuya Oyakawa[1], Nao Muraoka[1], Ayano Yamada[1], Kei Iida[1], Masatoshi Kusuhara[2], Tateaki Naito[3], Toshiaki Takahashi[3], Keita Mori[4]
[1]Division of Cardiology, Shizuoka Cancer Center, Shizuoka, Japan, [2] Division of Region Resources, Shizuoka Cancer Center, Shizuoka, Japan, [3] Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [4] Clinical Trial Coordination Office, Shizuoka Cancer Center, Shizuoka, Japan

Background: There are several reports that tumor can lead to cardiac atrophy. The aim of this study is to reveal the association between clinical course of advanced non-small cell lung cancer (NSCLC) and change of electrocardiographic findings.
Methods: We retrospectively reviewed 134 patients who had advanced NSCLC and was started chemotherapy between January 2010 and September 2011 at our hospital. Electrocardiogram was obtained at baseline, 6 months after diagnosis (T6), and 12 months after diagnosis (T12). Both Sokolow-Lyon voltage (SV1+RV5: SLV), and QRS duration (QRSD) correlates well with left ventricular mass (Circulation 1981.6:63). We measured lumbar skeletal muscle index (LSMI) by CT, and evaluated SLV (mV) and QRSD (msec) on an electrocardiogram. Bundle branch block, cardiomyopathy, cardiac infarction, and the patient with pericardial fluid were excluded. At baseline, echocardiography was performed on 26 patients, therefore we estimated their left ventricular mass (Devereux).
Results: The median age and PS were 66 years (range, 35-86) and 0 (0–3). 80 patients were male. Means (SD) of BMI was 22.5 (3.4) kg/m^2. A total of 110 patients at baseline, 21 patients at T6, and 28 patients at T12 were assessable for electrocardiogram findings. LSMI decreased significantly between baseline and T6 or T12 (T6: $p = 0.001$, T12: $p = 0.001$). Both QRSD (T6: $p = 0.027$, T12: $p = 0.020$) and SLV (T6: $p = 0.005$, T12: $p = 0.001$) simultaneously decreased significantly between baseline and T6 or T12 (Wilcoxon signed-rank test). At baseline, Both QRSD and SLV were correlated with estimated left ventricular mass (QRSD: correlation coefficient (CC): 0.60, $p = 0.001$, SLV: CC: 0.39, $p = 0.048$).
Conclusion: LSMI and QRSD or SLV had simultaneously decreased significantly over time in advanced NSCLC patients. These findings might be represent atrophy of the cardiac muscle in cancer cachexia patients. Electrocardiogram is simple and inexpensive examination, but it may be useful for follow up cardiac cancer cachexia.

3-42

Tumour-derived muscle atrophy signalling in a model of lung cancer cachexia

Ramon Langen[1], Jos van der Velden[2], Cheryl van de Wetering[2], Marco Kelders[1], Annemie Schols[1]
[1]Maastricht University Medical Center+, NUTRIM School of Nutrition and Translational Research in Metabolism, Department of Respiratory Medicine, [2]University of Vermont, Department of Pathology

Background and aims: The underlying triggers that induce muscle atrophy in lung cancer cachexia are still elusive, but are thought to involve tumour- or host derived factors. We hypothesized that atrophy inducing factors derived from lung tumours trigger muscle atrophy in a mouse model of lung cancer cachexia.
Methods: CCSP-rtTA/TetO-Cre/LSL-KRAS^{G12D} (KRAS^{G12D}) mice were used as an epithelial-specific inducible lung cancer cachexia model. *In vitro,* differentiated C2C12 skeletal muscle cells were treated with either Broncho alveolar lavage fluid (BALF), isolated from the KRAS^{G12D} mice, or conditioned medium (CM) from a primary lung epithelial cell line (MTEC) harbouring a KRAS^{G12D} mutation, or CM from a primary cell line derived from a human lung tumour, referred as HBCL1. C2C12 myofibrillar protein content was assessed by Western Blotting, and mRNA expression levels of ubiquitin 26S-proteasome (UPS) and the autophagy-lysosomal pathway (ALP) constituents were determined in C2C12 or skeletal muscle by qPCR.
Results: In KRAS^{G12D} mice, body weight and muscle mass was decreased following induction of lung cancer compared to control mice. mRNA expression levels of Atrogin-1, Lc3b, BNIP3, and Gabarapl1 were increased in gastrocnemius muscle. In C2C12 myotubes Myosin Heavy Chain protein levels were reduced after treatment with BALF or CM from KRAS^{G12D} mice or MTEC cells, respectively. Incubation of C2C12 myotubes with KRAS^{G12D} BALF or MTEC-CM, or HBCL1-CM recapitulated some, but not all of the increases in mRNA transcripts of genes involved in proteolysis observed in cachectic mouse muscle.
Conclusions: These data demonstrate that CCSP-rtTA/TetO-Cre/LSL-KRAS^{G12D} mice may be useful to study lung cancer cachexia, and suggest that atrophy inducing factors derive directly from the lung tumour.

3-43

Elderly patients with cancer cachexia tend to have longer length of hospital stay and higher cumulative medical costs during the first year of cancer treatment for the advanced non-small-cell lung cancer

Tateaki Naito[1], Taro Okayama[2], Takashi Aoyama[3], Haruyasu Murakami[1], Hirotsugu Kenmotsu[1], Akira Ono[1], Kazushige Wakuda[1], Keita Mori[4], Akira Tanuma[2], Toshiaki Takahashi[1]
[1]Division of thoracic oncology, Shizuoka cancer center, Shizuoka, Japan, [2]Division of rehabilitation medicine, Shizuoka cancer center, Shizuoka, Japan, [3]Division of nutrition, Shizuoka cancer center, Shizuoka, Japan, [4]Clinical trial coordination office, Shizuoka cancer center, Shizuoka, Japan

Background and aims: Cancer cachexia is often seen in the elderly people living with advanced non-small-cell lung cancer (NSCLC). However, little is known about its impact on use of medical resources and costs. The aim of this study was to explore the relationship among the presence of cachexia, length of hospital stay, and medical costs during the anticancer treatment of elderly NSCLC patients.
Methods: This is the prospective longitudinal observational study. Patients aged >=70 years with advanced NSCLC (stage III-IV) scheduled to commence first-line chemotherapy (n=30) or radiotherapy with or without chemotherapy (n=30) were enrolled. Cachexia was diagnosed by the international criteria (Fearon K, 2011). Mean cumulative function of length of hospital stay and medical costs (\, Japanese yen and $, US dollar) for the first year was calculated.
Results: Among 60 patients (17 women and 43 men) enrolled from Jan. 2013 to Nov. 2014, median age was 76 (range, 70-89) years. Cachexia was diagnosed in 35 (58%) patients. During the first year from the study enrollment, cachexia patients needed longer length of hospital stay (69 vs 39 days per year, Wilcoxon test p=0.0004) and consumed higher medical costs (\4,121,826 [$33,275] vs \2,533,587 [$20,453] per year, p=0.0002) than non-cachexia patients.
Conclusions: Cancer cachexia is commonly seen in elderly patients with advanced NSCLC. Patients with cachexia at baseline required multiple prolonged hospitalizations and consumed higher medical costs during the first year of their cancer journey. (Clinical Trials Registry No. UMIN000009768)

3-44

Body composition and treatment outcome in resectable gastric cancer

Eirik K. Aahlin[1], Tomoyuki Irino[2], Neil Johns[3], Torkel Brismar[2], Magnus Nilsson[2], Arthur Revhaug[1], Kristoffer Lassen[1]
[1]Department of GI and HPB Surgery, University Hospital of Northern Norway, Tromsø, Norway, [2]Division of Surgery, CLINTEC, Karolinska Institutet and Department of Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden, [3]Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Background and aims: Body composition analyses from computer tomography (CT) scans have been used to assess sarcopenia and cachexia in cancer patients. We aimed to investigate body composition analyses and their relation to disease severity and outcome in patients undergoing treatment for resectable gastric adenocarcinoma.
Methods: A cohort analysis of all patients treated for resectable gastric adenocarcinoma in two Scandinavian university hospitals from 2008-2011 was performed (n=137). Body composition analyses were performed on CT images taken for routine diagnostics and staging. Both preoperative single scans and series of repeat CT examinations were analyzed. Base-line patient characteristics, risk factors, stage of disease, postoperative complications and three-year mortality were retrieved from patient files.
Results: Of the 137 patients who underwent gastrectomy with lymphadenectomy in the period, 70 patients (51.1%) patients died within three years. Perioperative chemotherapy was given to 58 (42.3%) patients and forty (29.2%) patients suffered severe postoperative complications. There was a significant reduction in patients' lean tissue during neoadjuvant chemotherapy (p=0.001), but no association between such loss and any recorded outcome. Older age and female gender, but not advanced histopathological stage, was associated with lower preoperative skeletal muscle tissue index. Increased three-year mortality was observed in patients with preoperative skeletal muscle tissue index within the lowermost quartile (OR=3.25, 95% CI=1.25-8.45, p=0.016). Major losses of fat tissue were seen postoperatively and the median estimated total tissue loss during the first year after gastric resection was 16.2 kg (IQR: 8.3-30.0).

Conclusions: Patients lose lean tissue during neoadjuvant treatment for gastric cancer and a substantial amount of fat after gastric cancer resections. Low preoperative skeletal muscle index, although not affected by disease severity, was associated with worse prognosis.

3-45

Skeletal muscle mass is associated with severe dysphagia in cancer patients

Hidetaka Wakabayashi
Department of Rehabilitation Medicine, Yokohama City University Medical Center, 4-57 Urafune-chou, Minami ward, Yokohama city, Japan

Background and aims: The purpose of this study was to assess the association between skeletal muscle mass, activities of daily living (ADLs), and severe dysphagia in cancer patients.
Methods: A nested case-control study was performed in 111 consecutive cancer patients with dysphagia who were prescribed speech therapy. Skeletal muscle mass comprising the cross-sectional area of the left and right psoas muscles was assessed via abdominal computed tomography at the third lumbar vertebral level. ADLs were evaluated by the Barthel Index. The severity of dysphagia was assessed by the Food Intake Level Scale and was characterized by non-oral feeding or oral food intake at discharge. Univariate and logistic regression analyses were applied to examine the associations between dysphagia, skeletal muscle index (SMI), and ADLs.
Results: There were 86 males and 25 females (mean age, 70 years). The mean SMI was 5.68 ± 1.74 cm^2/m^2 in males and 4.43 ± 1.21 cm^2/m^2 in females. The median Barthel Index score was 20. Thirty-three patients were on non-oral feeding at discharge. The mean SMI did not differ significantly between non-oral feeding and oral food intake groups in t-test. The median Barthel Index score were lower in the non-oral feeding group in Mann-Whitney U test. Forced entry logistic regression analysis of the severity of dysphagia adjusted for age, sex, SMI, Barthel Index score, serum albumin, cancer type and stage, and vocal cord paralysis showed that SMI was associated independently with oral food intake at discharge. Barthel Index score showed a tendency to be associated with oral food intake. Stepwise logistic regression analysis showed that SMI and Barthel Index score were associated independently with oral food intake at discharge.
Conclusions:Skeletal muscle mass is associated with severe dysphagia in cancer patients. ADLs show a tendency to be associated with severe dysphagia in cancer patients.

3-46

Lipocalin-2 is up-regulated in experimental cancer cachexia

Junichi Ishida[1], Sandra Palus[1], Celine Latouche[2], Frederic Jaisser[2], Stefan D. Anker[1], Jochen Springer[1]
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]INSERM, U872, Centre de Recherche des Cordeliers, Paris, France

Lipocalin-2 is commonly associated with kidney injury and critically ill patients (heart failure, sepsis, multi-organ failure). Moreover, it is thought to play a role in cancer cell motility. Here we compared the mRNA expression of lipocalin-2 in the heart of cachectic rats bearing the Yoshida AH-130 hepatoma (n=16) to that of the aldosterone antagonist spironolactone-treaded (5 or 50 mg/kg/d, n=11 and 9, respectively) tumor-bearing rats as well as healthy controls (n=10). Plasma levels of lipocalin-2 and aldosterone were assessed by ELISA. Tumor bearing rats lost 45 ± 4g body weight, while controls gain 61 ± 3g ($p<0.001$) after 16 days. Five mg/kg/d spironolactone reduced wasting (-25 ± 10g) and 50mg/kg/d stopped weight loss (+0.5 ± 16g, both $p<0.05$). Cardiac lipocalin-2 mRNA expression was up-regulated by 93% compared to controls ($p<0.05$) and was reduced to control levels by 50 mg/kg/d spironolactone ($p>0.05$), while the 5mg/kg/d dose was not effective. Aldosterone was up-regulated from 337 ± 7 pg/mL in controls to 591 ± 31 pg/mL in the placebo group ($p<0.001$) and reduced to 396 ± 22 pg/mL in animals treated with 50mg/kg/d spironolactone ($p<0.01$). Plasma levels of lipocalin-2 were increased in tumor-bearing rats (1462 ± 360 g/L) compared to controls (93 ± 6 g/L, $p<0.001$). High dose spironolactone reduced lipocalin-2 levels to 530 ± 77 g/L ($p<0.05$ vs placebo). Cardiac function assessed by echocardiography was markedly improved by high dose spironolactone. Cardiac output on day 11 was decreased in the placebo group compared to control 49 ± 7 mL/min vs 80 ± 7 mL/min, respectively $p<0.01$). This functional impairment was reduced by high dose spironolactone (79 ± 7mL/min, $p<0.01$ vs placebo), which may functionally reflect the reduction of lipocalin-2 mRNA in the heart and protein in plasma. This may suggest that lipocalin-2 could potentially be used as a biomarker to assess cardiac impairment in cancer cachexia.

3-47

The xanthine oxidase inhibitor febuxostat improves survival in experimental cancer cachexia

Masaaki Konichi[1], Loes Pelgrim[2], Stephan von Haehling[1,2], Sandra Palus[1], Wolfram Doehner[4], Stefan D. Anker[1], Jochen Springer[1]
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]Radboud Universiteit Nijmegen, The Netherlands, [3]Center for Stroke Research Berlin, Charité Medical School, Berlin, Germany

We have previously shown that the activity of the xanthine oxidase is induced in cancer cachexia and that its inhibition by allopurinol or oxypurinol improves survival and reduces wasting in the Yoshida hepatoma cancer cachexia model (Springer et al. Int J Cancer 2012). Here we tested the effects of the second generation xanthine oxidase inhibitor febuxostat at 5 mg/kg/d (n = 16) compared to placebo (n = 41) in the same model.
Wistar rats (approx. 200g) were treated daily with febuxostat or placebo for 17 days. Weight change, quality of life and body composition were analysed. After sacrifice the proteasome activity in the gastrocnemius muscle was investigated. Muscle specific proteins involved in metabolism were analysed by Western blots.

Treatment of the tumor-bearing rats with febuxostat led to a significantly improved survival compared to placebo (HR: 0.44, 95%CI: 0.21-0.91, p=0.0272). Loss of body weight was reduced (-26.3 ± 12.4g) compared to placebo (-51.1 ± 1.9g, p=0.0041). Wasting of lean mass was attenuated (-12.7 ± 10.8g) vs placebo (-31.9 ± 2.1g, p=0.0119), while the effects on fat mass did not reach statistical significance (-10.1 ± 1.6 and -12.5 ± 0.5 for febuxostat and placebo, respectively, p=0.07). No effects on quality of life markers (locomotor activity and food intake) were observed. Febuxostat had no effect on the proteasome activity, however the, the pAkt/Akt ratio was improved by febuxostat (0.94 ± 0.08) vs placebo (0.41 ± 0.05, p=0.0004) at the end of the study suggesting an increase in protein synthesis. Febuxostat improved survival of tumor-bearing rats and attenuated cachexia progression.

3-48

Angiotensin-II receptor 1 antagonism in cancer cachexia

Masaaki Konishi[1], Cathleen Drescher[1], Junichi Ishida[1], Sandra Palus[1], Andrew JS. Coats[2], Stefan D Anker[1], Jochen Springer[1]
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]Monash University, Australia and University of Warwick, UK

Angiotensin-II has been shown to be up-regulated in catechetic states and the ACE-inhibitor imidapril has been used in a phase-III clinical cancer cachexia trial, which showed an increased body weight in patients with non-small-cell lung cancer and colorectal cancer. However, imidapril had no effect on survival in the Yoshida hepatoma cachexia model (Springer et al. Eur Heart J. 2013). Angiotensin-II predominantly elicits AT1 mediated responses, because of the predominant expression of the AT1 receptor. Activation of the renin-angiotensin system (RAS) is usually associated with hypertension, inflammation, fibrosis and end-organ damage, all of which are mediated by the AT1 receptor. Using the Yoshida hepatoma model, the effect of the selective AT-1 antagonists olmesartan and telmisartan (both at 1 or 5 mg/kg/d) on survival, body weight and body composition was tested in 200g male Wistar rats vs placebo. Both sartans had no significant beneficial effect on survival: 1mg/kg/d olmesartan (n = 12; HR: 1.98; 95%CI: 0.82-4.79; p = 0.13), 5 mg/kg/d olmesartan (n=16; HR: 2.34; 95%CI: 1.06-5.18; p = 0.0357), 1 mg/kg/d telmisartan (n = 114; HR: 0.62; 95%CI: 0.30-1.29; p = 0.20) and 5mg/kg/d telmisartan (n = 14; HR: 4.76; 95%CI: 1.85–12.3; p = 0.0012); all vs placebo (n = 44). Rats showed no difference in baseline body weight. While weight loss was attenuated by olmesartan (1mg/kg/d: −32 ± 5g; 5mg/kg/d: −30 ± 6g vs placebo: −51 ± 2g, both $p<0.05$), telmisartan had no effect on weight loss or body composition. Olmesartan (1mg/kg/d: −17.3 ± 4.4g; 5mg/kg/d: −9.2 ± 2.9g) and 5 mg/kg/d telmisartan (−26.4 ± 8.0g) reduced wasting of lean body mass compared to placebo (−33.1 ± 1.9g, all $p<0.05$). Placebo-treated rats lost 12.7 ± 0.5g fat mass, which was significantly reduced by 1mg/kg/d (−7.3 ± 1g, $p<0.001$) or 5 mg/kg/d olmesartan (−7.1 ± 0.8g, $p<0.001$), while telmisartan had no effect on fat mass wasting. Taken together, antagonism of the angiotensin-II receptor 1 had very limited effects in the Yoshida hepatoma model and the reduction of wasting may even be due to an earlier death of the animals.

3-49

Cachexia mediates alterations in the neuromuscular junction in a murine model of colorectal cancer

Adrian G. Todd[1], Sarah M. Judge[2], Andrew R. Judge[2], Darin J. Falk[1]
[1]Pediatrics, University of Florida, Gainesville, FL, USA, [2]Physical Therapy, University of Florida, Gainesville, FL, USA

Background and aim: Cachexia is a complex metabolic syndrome that is estimated to affect nearly one half of all patients with cancer. Cachexia is a major risk factor for decreased life expectancy which is presumed to be due, in part, to the development of respiratory complications. Indeed, patients with cancer have respiratory muscle dysfunction, documented by a diminished ability to generate sufficient inspiratory pressure which can impair airway clearance and facilitate the development of pneumonia, which is a major cause of respiratory failure and death in critically ill patients. In preclinical models, this respiratory muscle dysfunction has been associated with diaphragm muscle fiber atrophy but could also be due to deficits localized to the neuromuscular junction. Thus the aim of the present work was to identify whether alterations occur in the diaphragmatic neuromuscular junctions of tumor bearing mice during the progression of cachexia.
Methods: Mice were injected with either PBS (CON group) or Colon-26 (C26) cells and diaphragms harvested after either 20 or 26 days, reflective of moderate (C26-mod) and severe (C26-severe) cachexia, respectively. Pre- and post-synaptic morphometry and the mRNA level of critical NMJ regulators were measured.
Results: In C26-severe there was a significant reduction in endplate area and an alteration in the mRNA levels of critical pre- and post-synaptic regulators of composition and signaling in the NMJ when compared to CON. There were no changes in the post-synaptic endplate area of C26-moderate compared to CON.
Conclusion: These results demonstrate significant alterations in the regulation and integrity of the neuromuscular junction are present in the diaphragm of severely cachectic C26 tumor bearing mice. Future studies will determine if changes localized to the NMJ contribute to cachexia-related loss of proper respiratory and ambulatory function.

3-50

Computed tomography compared with standard clinical measurements to assess body composition, facilitating the identification of sarcopenia and cachexia in colorectal malignancy

Debra J. Gibson[1], Simon Lal[2], Boyd Strauss[3], Chris Todd[1], Mark Pilling[1], Sorrel Burden[1]
[1]School of Nursing, midwifery and social Work, University of Manchester, Manchester, UK, [2]Intestinal Failure Unit, Salford Royal

Foundation Trust, Salford, UK, [3]School of Clinical Sciences, Monash University, Victoria, Australia

Background: Malnutrition, sarcopenia and cachexia have been shown to adversely affect clinical outcome in patients with colorectal cancer (CRC). These conditions can be identified by assessing body composition, specifically skeletal muscle, in combination with measurements of physical function (PF), weight loss and inflammation. Computed tomography (CT) provides a novel method for assessing body composition. This study aimed to determine the role of CT scans in assessing reduced skeletal muscle and use of CT as a criterion measure in comparison to other clinical assessment techniques.
Methods: CT scans were obtained for people with CRC. Body composition was analysed from CT images (Slice-O-Matic software). This was compared to body composition measured by: bioelectrical impedance analysis (BIA), mid arm muscle circumference (MAMC); patient generated subjective global assessment (PG-SGA); and 4-site skinfolds. Handgrip strength and short form 36 (SF36) were used to measure PF. C-reactive protein (CRP) was measured to assess inflammation.
Results: CT scans were obtained for 100 people. CT scans identified low skeletal muscle in 29% of participants. BIA and MAMC showed good levels of agreement (Area under the curve [AUC] = 0.619, $p < 0.001$ and AUC = 0.625, $p<0.005$ respectively). Using handgrip as PF, CT scans identified 14.1% and 5.2% of participants as having sarcopenia and cachexia respectively. BIA showed good levels of agreement (AUC = 0.738, $p<0.001$ and AUC = 0.723, $p<0.001$ respectively).
Conclusions: These data highlight the importance of correct classification of low muscle mass. BIA and MAMC are valid to assess muscle mass, compared to CT as a criterion measure. Handgrip strength rather than SF-36 provides a good assessment of PF in relation to identifying reduced muscle strength in sarcopenia. Clinical data from this study will be useful in altering practise for correct identification of sarcopenia and cachexia, particularly in the absence of CT scans.

3-51

Circulating Activin A is predictive of survival in cancer patients

Audrey Loumaye[1,2], M. de Barsy [2], M. Nachit [1], P. Lause [1], L. Frateur [3,4], A. Van Maanen [4], P. Trefois[5], D. Gruson [1,6], J.P. Thissen[1,2]
In behalf of King Albert II Cancer Institute of the Cliniques Universitaires St-Luc
[1]Endocrinology, Diabetology and Nutrition Dept, IREC, Université Catholique de Louvain, Brussels, Belgium , [2]Endocrinology and Nutrition Dept, [3]Dietetic Dept, [4]King Albert II Cancer Institute, [5]Medical Imaging Dept, [6] Laboratory Medecine Dept, Cliniques Universitaires St-Luc, Brussels, Belgium

We demonstrated that human cancer cachexia is associated with increased circulating concentrations of Activin A (ActA). Given the cachectic and anorectic effect of ActA demonstrated in animal models, our observation suggests that ActA might play a role in the development of human cancer cachexia. Indeed, circulating ActA was correlated positively with weight loss and negatively with skeletal muscle density (SMD), two well-established prognosis factors in cancer patients.
Our goal was to investigate the value of circulating ActA as a marker of survival in cancer patients.
Patients with colorectal or lung cancer were recruited at the time of diagnosis or at relapse and had clinical, nutritional (SNAQ score) and functional (ECOG, QLQC30) assessment. Body composition and SMD were measured by CT-scan and plasma concentrations of ActA were determined. Overall survival (OS) was estimated during 12 months (-1/+2 months) after inclusion.
Among 152 patients included in the study, survival data was available for 149 patients. Patients with high levels of ActA (>665 pg/ml) had lower OS (68%) than those with levels in the normal range (84%; $p<0.01$). Furthermore, compared to alive patients, patients who deceased during the year of follow-up exhibited at baseline higher plasma ActA levels (589 pg/ml [363-17660] vs 415 [165-9402]; $p<0.001$), greater weight loss (6% [0-21] vs 3% [0-25]; $p<0.05$), lower SMD (24.6 UH [10.9-54.8] vs 33.3 UH [0.2-62.2]; $p<0.05$) and higher prevalence of low muscularity (56% vs 37%; $p<0.05$). These patients had also a more severe anorexia ($p<0.05$), more symptoms ($p<0.0001$) and poorer quality of life ($p<0.05$) and physical function ($p<0.0001$). As expected, lung cancer and invasive tumor, as assessed by N and M score, were more prevalent in this group.
In cancer patients, a high circulating concentration of ActA was associated with a shorter OS. Significant weight loss, low muscularity and low SMD, were also associated with a poor prognosis.

3-52

Is there an association between body composition and chemotherapy induced toxicities in colorectal cancer?

Rogier L.C. Plas[1,2], Klaske van Norren[1,2], Maarten de Bakker[1], Nadia Botros[1], Renger F. Witkamp[1], Annebeth Haringhuizen[3], Ellen Kampman[1], Renate M. Winkels[1]
[1]Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands, [2]Nutricia Research, Utrecht, The Netherlands, [3]Medical Oncology, Ziekenhuis Gelderse Vallei, Ede, The Netherlands

Chemotherapy treatment of patients is regularly accompanied by toxicities. Severe toxicities can lead to dose-limitation which might result in an incomplete treatment response. Administration of chemotherapeutic drugs is based on body surface area, which is calculated from body height and weight. Chemotherapeutic drugs commonly used in colorectal cancer treatment like capecitabine (oral pro-drug of 5-FU) and oxaliplatin supposedly distribute in lean body mass. Patients with a low muscle-to-fat ratio may be prone to receive excessive doses of cytostatic drugs locally. We hypothesise that this local overdosing might cause toxicities. The aim of the current study is to determine whether there is an association between body composition and chemotherapy-induced toxicities in (neo-)adjuvant treated patients diagnosed with colorectal cancer. Here we present the patient characteristics.

In this retrospective observational study, performed in hospital Gelderse Vallei, Ede, the Netherlands, skeletal muscle surface index and total adipose tissue surface index were determined at the third lumbar spine using CT-scans made within 100 days of diagnosis. Information on dose-limiting toxicity (dose reduction, cycle break, cycle stop, hospitalization) was retrieved via medical chart review.

129 colorectal cancer patients in cancer stage II-IV and treated with adjuvant chemotherapy were included. Mean age at diagnosis was 64 ± 11 and BMI was 25.9 ± 4.4 kg/m^2 (mean ± SD) with more than half of the patients being overweight (BMI>25 kg/m^2). Median muscle-to-fat ratio was 0.46 [0.31-0.66(25th to 75th percentile)]. Of all patients, 85% received CAPOX therapy (a combination of capecitabine with oxaliplatin) and 15% received only capecitabine. Dose-limiting toxicities were present in 82% of the patients. The median administered dose was 86% [70–97%] of the planned dose.

Patient characteristics indicate a relatively large number of overweight patients and high toxicity incidences. Statistical analysis is ongoing to investigate possible relations between body composition and toxicities. This will be presented during the conference.

3-53

Suppression of colorectal cancer-associated cachexia and inhibition of tumor growth by the selective androgen receptor modulator AUSRM-057

Marie Jourdain, Shinji Hatakeyama, Fiona Bello, Heidi Jeker, Hansjoerg Keller

Novartis Institutes for Biomedical Research (NIBR), Musculoskeletal Disease Area, Basel, Switzerland

We have recently identified AUSRM-057 as a new selective androgen receptor modulator (SARM) for transdermal administration. Here, we report its efficacy in preventing muscle wasting in the mouse CT26 colon cancer cachexia model. Male Balb/c mice were inoculated with CT26 tumor cells and treated three days later s.c. with 1 mg/kg or 10 mg/kg AUSRM-057 q.d. for 3 weeks in groups of 12 animals. As control groups, animals were sham treated, injected with vehicle or injected s.c. twice a week with 100 mg/kg testosterone propionate (TP). Growing tumors led to significant body weight (BW) decrease of 10% at 3 weeks. Both doses of AUSRM-057 fully prevented tumor-induced BW loss. TP significantly increased BW by about 10% over sham controls. AUSRM-057 also significantly inhibited tumor growth at 10 mg/kg by 48%. Furthermore, AUSRM-057 dose-dependently suppressed skeletal muscle (m. tibialis, gastrocnemius, quadriceps), kidney, prostate and adipose tissue atrophy and prevented tumor-induced splenomegaly. Moreover, AUSRM-057 dose-dependently decreased testis weight by about 15%, but, in contrast to TP, did not induce prostate hypertrophy. CT26 tumors massively induced serum activin A (ActA) levels (14-fold) compared to sham animals. ActA induction was significantly and dose-dependently reduced by AUSRM-057 (51% and 78% for 1 mg/kg and 10 mg/kg, respectively). TP also reduced activin A levels by 62%. Correlation analysis showed significant positive linear relationships between serum activin A levels and tumor weights in animals treated with AUSRM-057 and TP. Finally, qPCR expression analysis showed strong expression of ActA and androgen receptor (AR) in tumor samples. AR expression was significantly reduced by 37% in the high dose AUSRM-057 group, but not by the other treatments and ActA was not significantly influenced. These data suggest that the SARM AUSRM-057 exerts a two-pronged beneficial effect on AR-expressing colon cancer-cachexia by suppressing cachexia and inhibiting tumor growth.

3-54

A comparative study of software programs for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients

Jeroen L.A. van Vugt[1], Stef Levolger[1], Marcel Koek[2], Wiro J. Niessen[2,3], Sten P. Willemsen[4], Ron W.F. de Bruin[1], Jan N.M. IJzermans[1]

[1]Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Department of Radiology and Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Faculty of Applied Sciences, Delft University of Technology, Delft, The Netherlands, [4]Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands

Background and aims: The association between body composition (e.g. sarcopenia or visceral obesity) and treatment outcomes, such as survival, using single-slice computed tomography (CT) based measurements has recently been studied in various patient groups. These studies have been conducted with different software programs, each with their specific characteristics, of which the inter-observer, intra-observer and inter-software correlation are unknown. Therefore, a comparative study was performed.

Methods: Fifty abdominal CT scans were randomly selected from 50 different patients and independently assessed by two investigators. Cross-sectional muscle area (CSMA, i.e. rectus abdominis, oblique and transverse abdominal muscles, paraspinal muscles and the psoas muscle), visceral fat area (VFA) and subcutaneous fat area (SFA) were segmented by using standard Hounsfield unit ranges and computed for regions of interest. The inter-software, intra-observer, and inter-observer correlations for the CSMA, VFA, and SFA measurements using FatSeg, OsiriX, ImageJ, and sliceOmatic were calculated using intra-class correlation coefficients (ICC) and Bland-Altman analyses. Cohen's κ was calculated for the agreement of visceral obesity and sarcopenia assessment.

Results: Bland-Altman analyses and intra-class correlation coefficients indicated that the CSMA, VFA, and SFA measurements between the different software programs are highly comparable (ICC 0.999–1.000, $p<0.001$). No proportional systematic bias (all $p>0.05$) was observed, except between VFA measurements with ImageJ and sliceOmatic ($p = 0.036$). All programs adequately

distinguished between the presence or absence of sarcopenia ($\kappa = 1.00$) and visceral obesity ($\kappa \geq 0.96$). Furthermore, excellent intra-observer (ICC 0.999–1.000, $p < 0.0001$) and inter-observer agreement (ICC 0.994–0.999, $p < 0.0001$) for all software programs were found.

Conclusions: FatSeg, OsiriX, ImageJ, and sliceOmatic showed an excellent agreement for CSMA, VFA, and SFA measurements on abdominal CT scans. Furthermore, excellent inter- and intra-observer agreement were achieved. Therefore, results of studies using these different software programs can reliably be compared.

3-55

Defining the role of dietary intake in determining weight loss in patients attending a cancer cachexia clinic

Rima Nasrah, Mary Kanbalian, Christina Van der Borch, Sara L. Wing, Nelda Swinton, R. Thomas Jagoe
McGill Cancer Nutrition Rehabilitation Program, Segal Cancer Centre, Jewish General Hospital

Background and aims: A recent literature review was inconclusive regarding the role of dietary intervention in treating or preventing weight loss in cancer cachexia. To investigate this further we analysed the relationship between dietary intake and weight change in patients attending a multidisciplinary clinic specializing in cancer cachexia.

Methods: A retrospective analysis of patients with advanced (stage III/IV) cancer attending the McGill Cancer Nutrition Rehabilitation program clinic at the Jewish General Hospital (CNR-JGH). Reported body weight (BW) at 6-12 months and 6 weeks prior to referral were recorded. BW and energy and protein intake (24hr recall) at baseline (V1) and visits 2 and 3 were obtained (mean(SD) total intervention: 11.6(3.5) weeks). Correlation analysis between energy and protein intake and weight change (WtChg) prior to, and while attending, the CNR-JGH was performed.

Results: Data on 320/405 patients who completed dietary records were analysed. Mean(SD) WtChg over 6-12 months and 6 weeks before referral were −10.6(9.5) and −2.8(5.8)%, respectively. Only 17.5% of patients achieved current recommended cancer-specific energy (30 kcal/kg) and protein (1.3 g/kg) intake at V1. WtChg prior to referral correlated with energy and protein intake at V1 e.g. protein/kg vs. WtChg over prior 6 wks: $r = 0.28$, $p < 0.0001$.While attending CNR-JGH, weight stabilized (mean(SD) weight change: +0.6(4.1) kg) and mean intake increased: from 25 to 31 kcal/kg for energy ($p < 0.001$) and from 1.0 to 1.4 g/kg for protein ($p < 0.001$). WtChg while attending CNR-JGH also correlated with energy and protein intake e.g. energy/kg vs. WtChg: r=0.3 and $p < 0.001$.

Conclusions: A high proportion of weight-losing cancer patients are not consuming recommended levels of energy and protein. Dietary intake correlates with prior weight change both before and after attending the CNR-JGH program. Interventions at CNR-JGH lead to increased dietary intake and stabilization of weight. Increasing dietary intake is a vitally important factor in combating cancer-related weight loss.

3-56

Pilot study of subjective taste and smell changes in treatment-naive patients with solid tumours

Lorraine Spotten[1], Clare Corish[1], Cliona Lorton[2,4], Pauline Ui Dhuibhir[4], Brenda O'Connor[3,4], Moya Cunningham[5], Nazmy El Beltagi[5], Charles Gillham[5], Declan Walsh[2,3,4]
[1]School of Biological Sciences, Dublin Institute of Technology, Dublin, Ireland, [2]Faculty of Health Sciences, Trinity College Dublin, Ireland, [3]School of Medicine and Medical Sciences, University College Dublin, Ireland, [4]Dept. of Academic Palliative Medicine, Our Lady's Hospice, Dublin, Ireland, [5]St. Luke's Radiation Oncology Network, Dublin, Ireland

Background and aims: Taste and smell changes (TSCs) have been mostly studied in cancer post-chemotherapy (CT) or radiotherapy (RT), and in head and neck (H&N) tumours. They may present as part of a symptom cluster along with anorexia, early satiety and weight loss, which can negatively impact nutritional status. The aims of this study were to examine the prevalence, severity and characteristics of TSCs and their relationship with co-occurring symptoms in non-H&N solid tumours before CT or RT.

Methods: A prospective observational study was conducted. Forty consecutive pre-treatment cancer referrals who attended radiation oncology outpatients over a six week period were recruited. Data on TSCs, symptoms, dietary intake and nutritional status were obtained by the 'Taste and Smell Survey' and the 'abridged Patient-Generated Subjective Global Assessment' (abPG-SGA). Weight and height were measured, and BMI calculated. SPSS® was used for statistical analysis. Two-sided P values <0.05 were statistically significant.

Results: Most were newly diagnosed (70%; n=28). 19 (48%) reported TSCs. 9 noted stronger sweet taste and 7 stronger salt taste. Of those, 4 reported stronger and 4 weaker odour sensation. Those deemed at nutritional risk by the abPG-SGA had more TSCs (P=0.057). TSCs were significantly associated with dry mouth ($P<0.01$), early satiety ($P<0.05$) and fatigue ($P<0.05$).

Conclusions:

- TSCs preceded CT or RT in almost half of treatment-naive patients with solid tumours, notable stronger sweet and salt tastes.
- Most of those at nutritional risk reported TSCs.
- TSCs were significantly associated with other symptoms.
- Future research and clinical guidelines, with a common terminology for assessment, diagnosis and management of cancer TSCs are needed.

3-57

A high protein diet can prevent weight gain during breast cancer chemotherapy

Diana V. Artene[1], Alexandru Blidaru[2]
[1]Carol Davila Medicine University, Bucharest, Romania, [2]Oncology Department, Alexandru Trestioreanu Institute of Oncology, Bucharest, Romania

Many breast cancer patients gain weight during chemotherapy - increasing recurrence and mortality risks – gain still present 3 years after the end of the chemotherapy administration. The main weight gains causes are aggravated by chemotherapy through sarcopenia, and sustained by the eating behaviour and sedentariness of the breast cancer patients. High protein diets based on foods naturally high in proteins, omega-3 fatty acids, calcium, pro- and prebiotics can improve body composition by increasing insulin and leptin sensitivity, by ameliorating dysbiosis and by counteracting skeletal muscle protein catabolism, and can assist in recurrence prevention through a moderate intake of glucose.

Therefore, the current study is meant to answer two questions: is a high protein diet effective in preventing weight gain in breast cancer patients during chemotherapy; and is there any point in postponing to apply preventive weight gain interventions until the end of the treatment?

24 breast cancer patients during either neoadjuvant or adjuvant chemotherapy and 40 breast cancer patients after a minimum of 2 years after surgery were asked to follow a high protein diet. Patients were instructed to eat only when physically hungry, to respect the recommended portion size and to keep a food journal. We measured weight, body fat, skeletal muscle, and visceral fat with a bioelectrical impedance scale after checking for hydration status.

The average loss was 1.8 ± 3.2 kg ($p = 0{,}001$) and $2.4 \pm 3.2\%$ of body fat ($p = 0.001$) body fat without losing skeletal muscle. The only statistical difference obtained between groups was that breast cancer survivors also lost 0.4 ± 0.7 % ($p = 0.001$) visceral fat. So, a high protein diet is as effective during chemotherapy as it is 2 years after surgery, but physical exercise interventions may also be needed for visceral fat loss.

3-58

Pre-cachexia and cachexia at first medical oncology visit: nutritional and metabolic alterations significantly affect outcomes of cancer patients

Simone Lucia[1], Sara Emerenziani[2], Marco Imperatori[3], Maria Paola Rescio[2], Zaira Aversa[1], Giuseppe Tonini[3], Daniele Santini[3], Filippo Rossi Fanelli[1], Maurizio Muscaritoli[1]

[1]Department of Clinical Medicine, Sapienza University of Rome, Italy, [2]Gastroenterology Unit, Campus BioMedico University, Rome, Italy, [3]Oncology Unit, Campus BioMedico University, Rome, Italy

Background and aims: Nutritional and metabolic alterations are common in cancer patients and may occur at any time during the course of the disease. The present study aims at elucidating the impact of such alterations on clinical outcomes, including need for hospitalization, treatment toxicity and survival.

Methods: After informed consent was obtained, cancer patients undergoing first medical oncology visit were consecutively enrolled. Blood samples were collected for inflammatory markers (C Reactive Protein,CRP) and other biochemical analysis. A 6-,12- and 24-month follow-up was performed in order to evaluate need for hospitalization, treatment toxicity and survival rates. Statistical analysis was performed by IBM SPSS Statistics v.20 using appropriate tests in accordance with variables and parameters analyzed.

Results: 102 patients (50M:52F; 63 ± 12years) were enrolled. Respiratory, breast, pancreas and colorectal cancer accounted for $>80\%$ of main primitive sites, with a prevalence of patients in advanced disease stage (stage III 25%, stage IV 67%). At the first medical oncology visit, 63/102 cancer patients (62%) had already experienced weight loss (WL) and 27/102(43%) had WL $>5\%$. The prevalence of cachexia and pre-cachexia was 26.5% and 22.5%, respectively while anorexia was present in 47% of patients. Cachectic patients showed significant changes in WL, CRP, albumin and hemoglobin. Treatment toxicity was present in 14 patients (13,7%) and was significantly correlated with %WL ($p = 0.029$), CRP ($p = 0.034$), anorexia ($p = 0.017$), and hospitalization at 6, 12 and 24 months ($p < 0.05$). 6-month hospitalization was positively correlated with anorexia ($p = 0.011$), CRP ($p = 0.007$) and cancer site and stage ($p < 0.01$). Moreover, hospitalization was negatively correlated with survival ($p < 0.01$). Survival was significantly associated with inflammation ($p < 0.01$), anorexia ($p < .0001$), cancer site and stage ($p < 0.0001$) and WL ($p < 0.01$).

Conclusions: Pre-cachexia and cachexia are highly prevalent in cancer patients even upon first medical oncology visit. Prevention, early diagnosis and treatment of nutritional and metabolic changes appear mandatory in cancer patients in order to improve quality of life, toxicity and survival rates.

3-59

Patient specific CT-based lean body mass estimation correction for standardized uptake value in Positron Emission Tomography [PET] imaging

Vickie E. Baracos, W Makis, R Reif, M Wieler, AJB McEwan, and T Riauka

University of Alberta, Edmonton, Alberta, Canada

Background: F^{18} Fluorodeoxyglucose (FDG) PET cancer imaging allows for quantification of tissue and tumor tracer uptake by the calculated Standardized Uptake Value [SUV]. SUV is generally based on the patient's weight. More recently SUVs are being based on lean body mass (LBM), denoted SUL, on the assumption that F^{18}-FDG distributes in LBM. We hypothesized the current practice of estimating LBM from patient height, weight, age and sex in order to calculate SUV significantly biases SUV estimates, as LBM shows very wide variation independently of these factors. We propose that the computed tomography (CT) component of the PET-CT may be used to precisely quantify LBM which can then be used to calculate a patient specific SUL, denoted SUL_{PS}.

Methods: 197 (99 ♀ and 98 ♂) consecutive F^{18}-FDG PET-CT scans done over a 2 month period on a single camera were selected for inclusion. No other patient inclusion criteria were required. CT skeletal muscle was assessed using the CT slice containing the L3 vertebral body which is directly related ($R^2 = 0.94$) to LBM verified by dual energy x-ray. Four SUV measures were compared: body weight based (SUV_W), estimated LBM from the James equation (SUL_{James}) and from

the Janmahasatian equation (SUL_{Janma}), and the CT based LBM (SUL_{PS}).
Results: Women (age 59.7±15.5 years) and men (age 59.4±13.7) were analyzed separately. Body weight for women was 67.4±16.6 kg and for men was 82.3±17.38 kg. LBM (in kg) using James, Janmahasatian, and CT methods give 44.7±5.4, 40.8±6.2, and 38.4 ±5.8 kg for women and 61.0±7.4, 60.4±7.6, and 54.9±8.7 kg for men. A likely explanation for the consistent overestimation of LBM by these equations, when compared with CT, is the original calculations were derived from younger populations without disease and comorbidities and their associated muscle wasting. Normal liver uptake of F^{18}-FDG evaluated using the four methods give SUV_W, SUL_{James}, SUL_{Janma}, and SUL_{PS} of 2.15±0.44, 1.47±0.24, 1.33±0.21, and 1.25±0.23 for women and 2.22±0.41, 1.67±1.67, 1.65±0.30, and 1.51±0.34 for men. The differences between these quantities are all statistically significant ($p < 0.001$). Much of the disease reported on a daily basis in clinical tumor imaging is in the SUV 3-10 range, thus the average difference between SUV_W and SUL_{PS} (0.7 - 0.9 SUV units) is clinically important.
Conclusions: We propose a novel method for estimating LBM using the CT component of PET-CT which can be used to calculate patient specific SUL values for better patient management.

3-60

A novel *Drosophila melanogaster* larval model for cancer cachexia

Joseph Hodgson, Marcos Vidal
Drosophila Approaches to Cancer, Cancer Research UK Beatson Institute, Glasgow, UK

Aims: Cancer cachexia is a common secondary pathology that results in dramatic loss of skeletal muscle and adipose tissue. Cachexia reduces tolerance to chemotherapy, seriously affects quality of life, and is thought to cause around 20% of cancer-related deaths. Here we present a potential *Drosophila* model of cancer cachexia. We aim to utilise this model to investigate the mechanisms behind cachectic muscle wasting, and its role in tumour growth.
Methods: Imaginal disc tumours were generated by three different approaches:

(i) eye disc-specific generation of MARCM clones, with inactivated tumour suppressor scribble and expression of oncogenic Ras^{V12};
(ii) wing disc-specific expression of Ras^{V12} and RNAi knockdown of tumour suppressor dlg;
(iii) whole animal mutants for scribble

Muscle loss was determined by assessing the volume of the 4^{th} segment of the ventral 7^{th} muscle.
Results: As previously described, tumour-bearing larvae were developmentally delayed and bloated. Muscle wasting was observed only when tumours expressed Ras^{V12}. Between 6 and 14 days after egg deposition Ras^{V12};scribble tumours resulted in mean muscle volume decrease of 66%, while Ras^{V12};dlg-IR tumours resulted in a mean decrease of 54%.
Wasting muscles also accumulated intramyocellular lipid droplets, a phenotype reported in cachectic patients but not yet reported in any published cachectic model system. No lipid droplets were seen in non-wasted muscle, including muscle from scribble tumour-bearing larvae.
Starvation, developmental delay, or both, were shown to be incapable of inducing similar muscle phenotypes.
Conclusions: These experiments show this model provides a foundation for future investigation into cancer cachexia using *Drosophila*. However, novel genetic tools must be developed in order to interrogate the biological mechanisms behind these phenotypes, as current systems do not facilitate the examination of gene function in the muscle during pathology.

3-61

Low muscle attenuation correlates with protein levels in patients with GI cancer

Michael I. Ramage[1], Neil Johns[1], Christopher D. A. Deans[1], James A. Ross[2], Richard J. E. Skipworth[1], Carsten Jacobi[3], Kenneth C. H. Fearon[1]
[1]Department of Clinical Surgery, University of Edinburgh, Edinburgh, UK, [2]Tissue Injury and Repair Group, University of Edinburgh, Edinburgh, UK, [3]Novartis Institutes for Biomedical Research, Novartis Campus, Basel, Switzerland

Background: Cachexia has a significant impact on cancer patients' quality of life, clinical outcomes, and has recently been defined internationally. In assessing body composition in cancer cachexia, the validated quantification of skeletal muscle mass on staging CT scans is a well-recognised tool. These analyses use Hounsfield Units (HU) as a surrogate marker for muscle quality/composition. We aimed to correlate the protein content of muscle biopsies from cancer patient with CT-defined markers of muscle mass and quality.
Methods: Patients undergoing cancer resection had staging CTs analysed, and operative skeletal muscle biopsies were analysed for protein content (BCA protein assay kit). SPSS was used to find Spearman's rank correlation coefficient for the variables of interest.
Results: Thirty two cancer patients (12 pancreatic, 12 oesophageal, 4 gastric, 3 OGJ, and 1 duodenal) were included. 24 number of patients were sarcopenic on CT, with a median muscle area of 132.4cm2 (range 86.9-235), median L3 HU of 39.2 (range 25-56), and median percentage weight loss of -3.6 (range -10.9-25). Median protein content of rectus abdominis muscle was 89.3microg/mg wet weight (range 71-141). There was a weak positive correlation between muscle biopsy protein content and HU (r=0.406, p 0.021), and weak negative correlations between protein content and percentage weight loss (r= – 0.416, p 0.018) or actual weight loss (r= -0.423, p 0.016). Protein content did not correlate significantly with any other CT markers of body composition, including subcutaneous and visceral adipose tissue. HU correlated with age (r= -0.543, p 0.001), but not CRP (r=0.37, p 0.839).
Conclusion: Muscle quality, as defined by HU, is a potential surrogate marker for rectus abdominis muscle protein content in cancer patients. Further work is required to assess how specific protein fractions (e.g. myosin) are associated with overall body composition.

3-62

Omega-3 and omega-3/curcumin-enriched fruit juices decrease tumour growth and improve muscle wasting in tumour-bearing mice

Sílvia Busquets[1,2], Enrica Marmonti[1], Maria Öhlander[3], Janne Sand Mathisen[3], Francisco J. López-Soriano[1,2], Josep M. Argilés[1,2]
[1]Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain, [2]Institut de Biomedicina de la Universitat de Barcelona, Barcelona, Spain, [3]Smartfish AS, Norway

Background and aims: The aim of the present investigation is to evaluate the effects of a juice containing essential nutrients (marine omega-3 fatty acids (EPA and DHA), a polyphenol rich juice, vitamin D3, essential amino acids and dietary fibre) (CAX) and one juice enriched also with curcumin (CUR) alone or in combination with a chemotherapeutic agent (*sorafenib*) in a mouse cancer cachexia model.
Methods: Administration of CAX and CUR in the form of jellified pellets to mice bearing the Lewis lung carcinoma resulted in a 12 and 18% reduction in tumour weight, respectively.
Results: Interestingly, the CAX administration alone did not influence metastasis but in combination with chemotherapeutic treatment it decreased the weight of metastasis together with the percentage of damaged lung. In spite of the tumour reduction, the chemotherapy treatment alone did not result in changes in body weight. Conversely, in combination with sorafenib, both juices had and important effect on body weight loss. CUR also had an effect without chemotherapy. Concerning muscle weights, soleus mass was increased as a result of CUR treatment. Sorafenib-treated mice had tendency to show larger *soleus* muscles, this tendency being clearly significant when CAX was administered in combination with chemotherapy. A very clear statistically significant increase was observed in *tibialis* muscle when the animals were treated with either CAX or CUR. In combination with sorafenib, CAX treatment also resulted in larger *tibialis* muscles. In sorafenib-treated mice, juice treatment --either CAX or CUR-- resulted in a significant increase in grip force. In addition, administration of either CAX or CUR had a beneficial effect on the hematocrit in mice submitted to chemotherapeutic treatment.
Conclusions: It is concluded that administration of omega-3 and omega-3/curcumin-enriched fruit juices may have beneficial effects on muscle wasting and could be part of a multi-modal therapy for cancer cachexia.

3-63

Identification of intervention targets for a psychoeducational workshop for patients with cancer cachexia and their carers

Sally J. Wheelwright[1], Jane B. Hopkinson[2], Anne-Sophie Darlington[3], Deborah F. Fitzsimmons[4], Colin D. Johnson[1]
[1]Cancer Sciences, University of Southampton, Southampton, UK, [2]Cardiff School of Healthcare Sciences, Cardiff University, Cardiff, UK, [3]Health Sciences, University of Southampton, Southampton, UK, [4] Swansea Centre for Health Economics, Swansea University, Swansea, UK

Background: Cancer cachexia has a negative impact on the quality of life of both patients and their informal caregivers but there are few psychoeducational interventions to address this. This study is the first step in the development of a workshop to support patients with cancer cachexia and their carers.
Methods: Interviews were carried out with 5 patients, 5 carers and 5 health care professionals (HCPs) to create two logic models, one to identify the antecedents (root causes) of why unintentional weight loss is difficult for people with cancer and one for why it is difficult for their informal caregivers. The maps were supplemented with data from previously conducted semi-structured interviews with 39 patients and 12 HCPs and from systematic reviews of the patient and carer literature. Members of the project advisory panel rated the importance and changeability of each antecedent in the context of a workshop. The highest scoring antecedents were grouped to form intervention targets.
Results: A total of 54 antecedents were identified for patients and 65 for carers, with 15 patient antecedents and 14 for carers scoring above the mean for both importance and changeability. Not knowing what to do for the best, conflict with each other and negative emotions were high scoring patient and carer antecedents. Forcing self to eat rated highly for patients. Food provision and managing patient's dependency rated highly for carers. The high scoring antecedents were grouped together to form three intervention targets: providing information about eating well with cancer, resolving conflict and dealing with negative emotions.
Conclusion: Interviews and literature reviews have guided the intervention targets for a workshop on cancer cachexia aimed at both patients and their carers. Three areas, important and amenable to change, were identified. The workshop will educate, aid coping and provide relationship support.

4-01

Ghrelin deletion prevents aging associated sarcopenic obesity

Bobby Guillory[1], Jose M Garcia[1]
[1]Michael E. DeBakey VAMC and Baylor Coll. of Med., Houston, TX, USA

The epidemic of obesity affects the elderly disproportionally. Obese elderly individuals are known to have decreased muscle performance compare to normal weight elderly individuals, although their muscle mass is typically increased. This combination is often referred to as 'sarcopenic obesity' but the mechanisms underlying the development of muscle dysfunction in the setting of preserved muscle mass in obesity remains incompletely understood. Ghrelin is a potent orexigenic hormone and its administration increases body weight by enhancing appetite, muscle and fat accrual. However, its role during aging has not been well characterized. The goal of this study was to establish the role of ghrelin during aging on modulation of body mass and composition and muscle function.

Body weight, body composition, food intake, locomotor activity and energy expenditure (EE) were compared between young adult (6 month-old) and old (19 month old) ghrelin wild type (WT) and knock-out (KO) c57bl/6 male mice. Ghrelin deletion prevented fat accumulation and muscle strength and endurance loss associated with aging. Ghrelin deletion did not prevent the decrease in energy expenditure and spontaneous locomotor activity associated with aging but food intake was decreased in old ghrelin KO compared to old WT animals. The decrease in muscle AMPK, its downstream mediator *fas,* and fiber type switching seen with aging in WT was attenuated in KO animals. Hence, the prevention of the sarcopenic obesity phenotype in old animals is probably related to small decreases in food intake seen with aging in KO animals that albeit small, over time are likely to contribute to the development of obesity. The decrease in muscle strength and endurance, muscle fiber atrophy and fiber type switch seen with aging in WT mice appears to be mediated through ghrelin-modulated, AMPK-dependent pathways in muscle.

Work funded by the Dept. of Veterans Affairs (MERIT BX000507 to JMG) and the NIH (AG040583 to JMG and T32AG000183 to BG).

4-02

Dissecting the mechanisms of action of ghrelin in cancer cachexia: Evidence of GHSR1a-dependent and -independent mechanisms mediating muscle and fat atrophy.

Jlaohua Luo[1,2], Ji-an Chen[1,2], Avni Mody[3], Michael Ding[4], Jordan Kohler[1], Bobby Guillory[1], Jose M. Garcia[1]

[1]Michael E. DeBakey VAMC; Baylor Coll. of Med., Houston, TX, USA, [2]Third Military Medical University, Chongqing, China, [3]Texas A&M Univ, College Station, TX, USA, [4]Univ of California-Berkeley, CA, USA

Cachexia, involving muscle and fat loss, is an often lethal consequence of cancer. Ghrelin has been proposed as a treatment for cachexia by preventing cancer-induced muscle and fat loss and anorexia. However, its mechanisms of action are not well-understood. Particularly, whether these effects are mediated through the ghrelin receptor (GHSR1a) is not known.

Adult male c57/Bl6 mice with and without the GHSR1a gene were inoculated with the Lewis Lung Carcinoma (LLC) cell line. To separate the effects of ghrelin mediated through increases in food intake, groups of tumor-bearing WT and KO animals were administered ghrelin and pair fed (PF) to tumor-bearing animals. LLC tumor implantation induced anorexia that was reversed by ghrelin only in ghrelin WT animals. Tumor implantation also induced more profound weight loss in KO than in WT. Ghrelin prevented this weight loss; in WT animals this effect was more pronounced in ad-lib fed animals than in PF animals whereas in KO animal this effect was similar in ad-lib fed and PF animals and was of smaller magnitude. Muscle and fat mass were decreased by LLC inoculation and this was more marked in KO animals. These changes were prevented by ghrelin administration in both genotypes. The extent to which FM was preserved by ghrelin was similar between ad lid and pair fed animals. Markers of fat lipolysis increased with LLC implantation and this was more evident in KO animals. Ghrelin prevent this increase independently of food intake. Conversely, lipogenesis was decreased by LLC implantation and this was partially prevented by ghrelin.

In summary, we show here evidence of multiple mechanisms contributing to the effects of ghrelin in the setting of cachexia. Its orexigenic effects are GHSR1a-dependent but other effects on lipid metabolism and effects on muscle are at least in part GHSR1a-independent. Lack of endogenous GHSR1a exacerbates cachexia.

Work funded by the U.S. Dept of Veterans Affairs (I01-BX000507 and I01 CX000174 to JMG) and NIH Grant AG040583 to JMG. Dr Guillory is supported by NIA T32AG000183. Drs. Luo and Chen are supported by National Natural Science Foundation of China (81072262, 81372944).

4-03

Activation of Acylated Ghrelin Receptor, GHSR1, impairs Ghrelin anti-atrophic activity in skeletal muscle

Elia Angelino[1], Michele Ferrara[1], Sinome Reano[1], GianlucaGortan Cappellari[2], Hanna Sustova[1], Emanuela Agosti[1], Sara Clerici[1], Rocco Barazzoni[2], Nicoletta Filigheddu[1], Andrea Graziani[3]

[1]Dept. of Translational Medicine, Universita del Piemonte Orientale, Novara, Italy, [2]Department of Medical, Surgical and Health Sciences – University of Trieste, Trieste, Italy, [3]Division of Oncology, Ospedale San Raffaele, Universita vita e salute San Raffaele, Milano, Italy

Background and aims: Ghrelin is an acylated peptide hormone, acting through its acylation selective receptor, GHSR1, to stimulate appetite and GH release. However, most of circulating Ghrelin is unacylated, which does not bind to GHSR1 and does not stimulate food uptake and GH release. Both acylated and unacylated ghrelin (AG and UnAG), inhibit cardiomyocytes apoptosis, skeletal muscle atrophy, activate myogenic differentiation and share common binding sites in myocardial and skeletal muscle cells. In vivo UnAG protects from ischemic myocardial heart failure and skeletal muscle atrophy, acting through a novel yet unidentified receptor. Thus, AG is expected to regulate skeletal muscle mass both indirectly through activation of the GH/IGF1 axis and directly through the novel receptor. Here we investigated the putative anti-atrophic activity of AG.

Methods: Skeletal muscle atrophy has been induced in either wt or GHSR1-/- mice by sciatic nerve denervation or 48h fasting and the mice treated with either AG, UnAG or vehicle. Atrophy has been assayed by measuring muscle mass and muscle fiber diameter.

Results: AG treatment did not protect wt mice from muscle atrophy induced by either fasting or denervation, while UnAG, under the same conditions, did protect as previously reported. However in GHSR1-/- mice, both AG and UnAG treatment protected skeletal muscle from atrophy induced both by fasting and by sciatic denervation. These results are consistent with in vitro observations that long treatment of c2c12 myotubes with UnAG, but not with AG, results in up-regulation of serine phosphorylation of both Akt and S6K.

Conclusions: These observation strongly suggest that activation of the acylation-selective AG receptor, GHSR1, impairs AG anti-atrophic activity mediated by the novel acylation-unselective ghrelin receptor. These observations may provide a molecular explanation for previous finding reporting that UnAG but not AG, protect skeletal muscle from ischemic damage.

4-04

Anti-inflammatory potential of two selective ghrelin agonists

Aoife Cooke[1], Karl Cogan[2], Aoife Lott[1], Brendan Egan[2], Fiona McGillicuddy[1], Claudio Pietra[3], Helen Roche[1]

[1]Nutrigenomics Research Group, Conway Institute for Biomolecular and Biomedical Science and Institute for Food and Health, University College Dublin, Belfield, Dublin, Ireland, [2]Exercise Metabolism and Nutrigenomics Research Group, Institute for Sport and Health, School of Public Health, Physiotherapy, and Population Sciences, University College Dublin, Dublin, Ireland, [3]Helsinn SA, Research and Preclinical Development Department, Lugano, Switzerland

Background and aims: Ghrelin, a hormone produced in the gastrointestinal tract, is widely known as a regulator of hunger. Previous studies have demonstrated effectiveness for ghrelin in the treatment of cancer cachexia. Alongside the known appetite stimulatory effect, it is thought that these positive effects may be mediated through anti-inflammatory means. This work examines the anti-inflammatory effect *in vitro* and *in vivo* of two potent and selective ghrelin agonists; Anamorelin, a compound in phase 3 of development for lung cancer cachexia and HM01, a new small molecule acting as peripheral and CNS ghrelin agonist.
Methods: Testing of the anti-inflammatory effects of Anamorelin and HM01 was carried out in fibroblast, adipocyte and macrophage cell lines stimulated with the pro-inflammatory gram negative cell wall component lipopolysaccharide (LPS). For *in vivo* anti-inflammatory evaluation, mice were treated with anamorelin and HM01 for seven days prior to sub-cutaneous injection with LPS. Blood plasma, adipose, liver and skeletal muscle tissue were harvested for western blot and RT-PCR analysis, and adipose tissue was cultured *ex vivo*.
Results: Both Anamorelin and HM01 reduced secretion of the pro-inflammatory cytokine Interleukin-6 (IL6) in response to LPS challenge in macrophages, as well as reducing LPS induced activation of NF-κB in fibroblasts. Just seven days pre-treatment with Anamorelin and HM01 was sufficient to increase weight gain prior to LPS challenge, and also to reduce subsequent weight loss in LPS challenged mice. In addition, mice treated with ghrelin agonists displayed decreased secretion of IL6 from adipose *ex vivo* as well as decreased levels of circulating IL6 in blood plasma.
Conclusion: In summary, the results demonstrated a promising first-look into the anti-inflammatory effect of ghrelin agonists both *in vitro and in vivo*. Further work on these novel compounds is required in order to fully determine their mechanism of action, as well as to define their potential therapeutic uses.

4-05

RQ-00433412, a novel orally active small molecule ghrelin receptor agonist for potential use in cancer-related anorexia/cachexia syndrome

Nobuyuki Takahashi, Keiko Obata, Akiko Yamada, Akemi Sugiura, Aya Matsushita, Yasuhiro Iwata

Discovery Research, RaQualia Pharma Inc. (Research Institute of Environment Medicine, Nagoya University), Furo-cho, Chikusa-ku, Nagoya, Aichi, 464-8601, Japan

Background and aims: Ghrelin and ghrelin mimetic stimulate appetite and are one of the promising medications for cancer-related anorexia/cachexia syndrome (CACS). RQ-00433412 (RQ-412) is a novel, potent and selective ghrelin receptor agonist that stimulates growth hormone secretion in mice and rats and increase of body weight in normal mice following repeated oral administration. In this study, we investigated the effects of RQ-412 on the cisplatin-induced anorexia and AH-130 induced cachexia models in rats.
Methods: Cisplatin model; Cisplatin and RQ-412 were administered once a day for 3 days to the male Wistar rats, via i.p. or p.o., respectively. Body weight and food consumption were assessed daily during the experiments. AH-130 model; AH-130 Yoshida ascited hepatoma cells were inoculated intraperitoneally to the male Wistar rats. RQ-412 was administered via p.o. once a day for 6 days.
Results: Cisplatin-treated animals lost body weight significantly (-9.3% at day4). RQ-412 (3-30mg/kg) reduced weight loss dose-dependently and showed statistical significance at 10mg/kg dose. The percentage weight changes at day4 with RQ-412 treatment were -6.6, -2.4, -2.1%, respectively. Animals in the cisplatin-treated group showed a significant decrease in food intake during the experiment period (control; 52.1g, Cisplatin-treated group; 21.4g). RQ-412 increased food intake dose-dependently. Anamorelin (30mg/kg) also increased body weight and food intake in this model. Weight loss, AH-130 tumor injected animals exhibited decreased food intake, and wasting of muscle mass. Oral daily administration of RQ-412 (20mg/kg) in tumor-bearing rats significantly reduced the loss of body weight and muscle mass. Anamorelin showed moderate, but not significant efficacy in this cachexia model at 30mg/kg.
Conclusion: RQ-412 displayed superior efficacy than anamorelin in both of anorexia and cachexia model in rats at the tested doses. These results suggest that RQ-412 will be a useful and effective therapeutic agent for CACS. RQ-412 is currently in the pre-clinical test phase.

4-06

The novel ghrelin agonist HM01 increases muscle mass, fat mass and bone mineral density in cachectic colon-26 tumor-bearing mice

Fabienne O.Villars[1,2], Claudio Pietra [3], Claudio Giuliano[3], Thomas A. Lutz [1,2], Thomas Riediger[1,2]

[1]Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland, [2]Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland, [3]Helsinn SA, Research and Preclinical Development Department, Lugano, Switzerland

Background: The cancer anorexia-cachexia syndrome (CACS) is present in 80% of cancer patients and characterized by reduced dietary intake, increased catabolism and body weight (BW) loss. The hormone ghrelin exerts anti-inflammatory actions and positively affects energy balance and GH/IGF-1 levels. IGF-1 indirectly controls the expression of the ubiquitin ligases MuRF1 and

MAFbx, which are thought to mediate cancer-related muscle wasting. Hence, ghrelin agonists are considered as a possible anti-CACS treatment.

Methods and Results: Using a colon-26 mouse tumor model, we investigated if the novel CNS penetrating ghrelin agonist HM01 attenuates CACS. Compared to non tumor-bearing controls, tumor-bearing (TB) mice significantly reduced BW (21.1 ± 0.7 vs 24.8 ± 0.5 g), fat mass (0.33 ± 0.1 vs 1.35 ± 0.14 g), lean mass (13.6 ± 0.4 vs 15.6 ± 0.9 g), and spine bone mineral density (BMD) (300 ± 12 vs 353 ± 6 mg/cm^3), while blood inflammatory cytokine IL-6 were significantly elevated (471 ± 85 vs 2 ± 1 pg/ml). Furthermore, muscle MuRF/MAFbx mRNA levels were 9-fold increased. Starting at day 10 after tumor-induction (onset of cachexia), TB mice were treated orally with HM01 (10 mg/kg, p.o.) for 9 days until the end of the experiment. HM01 significantly increased hind limb muscle mass (357 ± 18 vs 307 ± 9 mg), fat mass (0.65 ± 0.2 vs 0.33 ± 0.1 g) and BMD (318 ± 5 vs 300 ± 4 mg/cm^3) relative to TB controls. At euthanasia 18 days after tumor induction, these effects were not related to changes in IL-6 (787 ± 180 vs 471 ± 85 pg/ml) or MuRF/MAFbx mRNA levels.

Conclusions: Although the role of the ubiquitin ligase pathway as a target for ghrelin-based pharmacological approaches needs further investigation, our results support the usefulness of ghrelin agonists as a possible anti-CACS treatment.

Supported by the Swiss National Science Foundation and the Krebsliga Zurich.

4-07

The novel ghrelin agonist HM01 ameliorates the anorexia-cachexia syndrome in tumor-bearing rodents

Tito Borner[1,2], Fabienne Villars[1,2], Laura Loi[1], Claudio Pietra[3], Claudio Giuliano[3], Thomas A. Lutz[1,2], Thomas Riediger[1,2]

[1]Institute of Veterinary Physiology, University of Zurich, Switzerland, [2]Center for Integrative Human Physiology (ZIHP), University of Zurich, Switzerland, [3]Helsinn SA, Research and Preclinical Development Department, Lugano, Switzerland

Background: Ghrelin is a peptide hormone secreted by the stomach during fasting. It positively affects energy balance by increasing food intake and reducing energy expenditure by acting on the hypothalamic arcuate nucleus (Arc). In the periphery ghrelin exerts anti-inflammatory actions and may counteract muscle wasting via GH/IGF-1 signaling. Ghrelin mimetics are considered a possible approach for the treatment of the cancer anorexia-cachexia syndrome (CACS). In this study we confirmed the ghrelin-like action of the novel CNS penetrating ghrelin agonist HM01 and we evaluated the therapeutic effect of chronic HM01 treatment in rodent models of CACS.

Methods and Results: In electrophysiological recordings, HM01 (10^{-7}–10^{-6}M) mimicked the effects of ghrelin (10^{-8}M) on neuronal activity of Arc neurons. During a 12-day chronic treatment period HM01 (50 μg/h sc, via osmotic minipump) increased food intake (FI) in healthy rats by 24%. In Morris-7777 hepatoma tumor-bearing (TB) rats the same HM01 treatment attenuated cancer anorexia leading to 30% higher FI compared to saline-treated TB animals. HM01-treated rats did not lose body weight during the treatment (-10.4 ± 1.7 g vs. 1.1 ± 2 g) and had significantly higher gastrocnemius and soleus muscle mass than TB controls. Furthermore, metabolic rate was also significantly reduced in HM01-treated TB rats. HM01 was also effective after chronic oral treatment in a mouse C26 colon carcinoma model of cachexia. Chronic HM01 administration (10 mg/kg, p.o.) for 9 days significantly reduced hind limb muscle wasting by 14% relative to TB controls.

Conclusion: In summary, HM01 mimics the neuronal effect of ghrelin in the Arc and positively affects energy balance in both healthy and tumor-bearing rats. HM01 counteracts cancer-related muscle wasting after chronic parental and oral adminstration. Therfore, ghrelin agonists like HM01 might be a promising approach for the treatment of CACS and possibly other forms of disease-related anorexia and muscle wasting.

Supported by the Swiss National Science Foundation and the Krebsliga Zurich.

4-08

Evaluation of safety and physiologic changes following 13 weeks of exposure to the selective androgen receptor modulator VK5211 (LGD-4033) in primates

Michael R. Bleavins[1], Jeffrey Tepper[2], Brian W. Lian[1]

[1]Viking Therapeutics, Inc., 12340 El Camino Real, Suite 250, San Diego CA, [2]Tepper Nonclinical Consulting, 197 Glasgow Lane, San Carlos, California 94070-3670

SARMs are tissue-selective androgen receptor ligands being developed to treat muscle loss associated with injuries such as hip fracture, as well as cancer, chronic illness, and age-related muscle loss. VK5211 is a novel non-steroidal, orally-active SARM that in animal models has demonstrated anabolic activity in muscles, anti-resorptive and anabolic activity in bones, and high selectivity for muscle versus prostate tissue. In humans, VK5211 has demonstrated encouraging safety and improvement in lean body mass when dosed for 21 days.

Cynomolgus monkeys received daily oral doses of VK5211 at 0, 0.6, 3, 15, or 75 mg/kg/day for up to 13 weeks. Consistent with a robust anabolic response, treated animals experienced body weight gains of 20% to 47% from baseline. These increases were 29% to 157% greater than those observed for male control animals and 100% to 267% greater than observed for female controls. When dosing was discontinued the animals retained approximately 70% of the increased weight over a 4-week recovery period.

No ophthalmic, electrocardiographic, or heart rate changes were observed. Serum glucagon levels were increased in males and in females but insulin levels were not significantly altered. Clinical signs were noted in males and females receiving ≥15 mg/kg/day VK5211. Minimal to moderate alterations in clinical pathology parameters were seen in VK5211-treated animals; these were not adverse. Some males at ≥15 mg/kg/day had mature-like prostate and seminal vesicles with immature testes. In females, uteri were in the secretory phase despite the absence of a corpus luteum in the ovaries, and decreased cornification of vaginal epithelium. These changes occurred at exposures ~ 30x the free concentration of VK5211 in previous clinical

studies and are unlikely to be safety concerns in an older human population.
A Phase 2 study with 12 weeks of treatment is planned to evaluate VK5211 in elderly patients recovering from hip fracture surgery.

4-09

Whey proteins promote post prandial positive nitrogen balance in a muscle wasting situation but probably for a too short period of time to translate into muscle sparing

Aurelia Revel, Marianne Jarzaguet, Carole Migné, Isabelle Savary-Auzeloux, Didier Rémond, Dominique Dardevet
INRA, Centre Clermont-Ferrand – Theix, UMR 1019 Unité de Nutrition Humaine, Saint-Genès-Champanelle, France; Univ Clermont 1, UFR Médecine, UMR1019, Unité Nutrition Humaine, Clermont-Ferrand, France

Background and aims: Muscle wasting occurred by an imbalance of muscle protein metabolism. Most of catabolic states are characterized by both an insulin and amino acid resistance which result into a food intake inefficiency to promote positive nitrogen balance during the post prandial period. So far, fast digested proteins (i.e whey) have been shown to be more efficient than casein to promote a stimulation of muscle protein synthesis (PS) in such situations; however, muscle mass is rarely improved. Our hypothesis is that this stimulation occurs only for a short period of time in the fed state, which remains insufficient to induce a significant increase in muscle mass. To address this point, a PS and proteolysis (PRO) kinetic study at the muscle level is required.
Methods: Adult mini pigs were catheterized into both the femoral artery and vein and infused with 13C Phe to assess continuously) muscle PS and PRO in the hindlimb by the substrate and tracer arterio-venous difference method (every 30min before (PA) and after food intake). The catabolic state was induced by glucocorticoid treatment (8d); both casein and whey effects on PS and PRO were tested over time for 6.5 h.
Results: After glucocorticoids, animals were in negative nitrogen balance at PA and casein intake had no effect on both PS and PRO and animals remained in negative nitrogen balance during the whole postprandial period. With whey, treated animals are able to generate a positive nitrogen balance for 120min after food intake (PS:+40% and PRO:-20%) which decreased thereafter along the postprandial period. Glucocorticoids were associated with insulin resistance (postprandial period: increased insulin/glycaemia). When fed whey, animals still presented hyperinsulinemia but normalized postprandial glycaemia.
Conclusions. Whey are more efficient to generate positive muscle nitrogen balance in catabolic states but it remained only for a short period of time which may limit their efficiency on muscle wasting. Nutritional strategies have to be studied to optimize the duration of whey efficiency in the catabolic states. By contrast, whey are interesting to control post prandial hyperglycaemia in muscle protein wasting situations.

4-10

Roles of exercise-induced gene, SPARC, against sarcopenia: link between extracellular matrix and mitochondria

Aicha Melouane[1], Antoine Carbonell[2], Mayumi Yoshioka[1], Makoto Kanzaki[3], Jack Pymirat[2], Jonny St-Amand[1]
[1]Functional Genomics Laboratory, CREMOGH, CHU de Québec Research Center, Molecular Medicine Department, Laval University Québec city, Canada, [2]Unit of Human Genetics, CHU de Québec Research Center, Medicine Department, Laval University, Quebec, Canada, [3]Department of Biomedical Engineering Graduate School of Biomedical Engineering Tohoku University, Japan

Background and aims: Aging leads to a reduction of skeletal muscle mass. We have identified the genes modulated in skeletal muscle (SM) by mild endurance training (ET) and highlighted the importance of mitochondrial oxidative phosphorylation (OXPHOS) and extracellular matrix (ECM) remodeling in the SM adaptation. One of the mild ET induced genes, secreted protein acidic and rich in cysteine (*SPARC*), a matricellular protein, has been shown to function as a modulator of cell proliferation and migration, a regulator of the ECM and a cell cycle inhibitor. In this study, we investigated the effect of SPARC on the modulation of ECM and mitochondrial function as well as its involvement in the link between these two compartments in C2C12 murine myoblasts. Furthermore, we explored the induction of SPARC expression after electronic pulse stimulation (EPS).
Methods: C2C12 myoblasts, were grown to 80-90% confluence. Their growth medium was replaced with fresh medium supplemented with different experimental conditions. The cells were maintained in this medium for 48h. Other confluent myoblasts were differentiated for 5 days to study the effect of SPARC on C2C12 differentiation or to apply EPS for 2 days. Expression levels of ECM, mitochondrial and SPARC genes/proteins were measured by western blot or QRT-PCR after exogenous inhibition/induction of SPARC. Myotubes formation was examined by light microscope after staining with hematoxylin.
Results: Exogenous inhibition/induction of SPARC was significantly modulated the expression of ECM markers, mitochondrial proteins and the differentiation of C2C12 cells. In addition to, EPS stimulates SPARC expression by 10-fold.
Conclusion: We demonstrated that SPARC plays critical role in C2C12 myoblasts differentiation and can act as a modulator of ECM and may have a direct effect on mitochondrial function. Moreover, SPARC, EPS-induced gene, may have an effect on exercise-induced changes in SM.

4-11

A potential role of actin-associated protein palladin in preventing cachexia

Ngoc Uyen Nhi Nguyen, Hao Ven Wang
Department of Life science, National Cheng Kung University, Tainan, Taiwan

Palladin is a microfilament-associated protein whose function in skeletal muscle differentiation has recently been emphasized. It was shown that a down-regulation of palladin gene expression in C2C12 myoblasts resulted in the formation of atrophying myotubes compared to those of the control. Therefore, palladin might have roles in preventing skeletal muscle loss. On the other hand, about 20% cancer-related deaths are due to cachexia - a type of metabolic cancer syndrome characterized by loss of skeletal muscle. To test whether palladin halts cancer-induced skeletal muscle wasting, we co-cultured palladin-knockdown myoblasts with pancreatic cancer cell lines and examined the formation of mature myotubes. Surprisingly, very less mature myotubes had been observed in palladin-deficient myoblasts-panc1 co-culture, compared to those of the myoblasts-panc1 co-culture. Moreover, a decrease in palladin expression in skeletal muscle myoblasts led to an increase of secreted myostatin in myoblast-pancreatic cancer co-culture medium. Thus, the loss of palladin in myoblasts and tumoral factors collectively promote cancer-induced skeletal muscle wasting. Palladin might be a novel humoral fact or that prevents cancer cachexia and represents a promising therapeutic approach to cachexia in pancreatic cancer.

4-12

β2-AR agonist formoterol triggers the distinct metabolic pathway of leucine in wasting C2C12 myotubes: Application of 13C based stable isotope-resolved metabolomics

Quan-Jun Yang[1], Cheng Guo[1]*, Lili Wan[1], Bin Li[1], Jinlu Huang[1], Jie Li[1], Gen-Jin Yang[2]

[1]Department of Pharmacy, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, P. R. China, [2]School of Pharmacy, Second Military Medical University, Shanghai, P. R. China

Background: Cancer cachexia is a multifactorial metabolic syndrome characterized by ongoing loss of body weight and lean body mass. Preserve of skeletal muscle mass is helpful for the prognosis and outcome. Our previous study had showed that β_2 - adrenergic receptor (β_2-AR) agonist formoterol could prevent the wasting of skeletal muscle, as well as alter the serum concentration of leucine. The present study was aim to investigate how β_2-AR agonist formoterol regulate the metabolism of leucine in cachexia related muscular atrophy.

Methods: Formoterol was added to reverse the atrophy of C2C12 myotubes induced by the glucocorticoid dexamethasone. Stable isotope labeled $^{13}C_6$-leucine was used to trace the metabolism process. The intracellular and extracellular metabolites was analyzed by NMR. Moreover, stable isotope-resolved metabolomics (SIRM) was employed to identify the limiting enzyme affecting leucine metabolism. In vivo cancer cachexia model was established by subcutaneously transplantation of CT26 tumor into mice.

Results: The dexamethasone-induced muscle atrophy was reversed by 0.1 μM fromterol from the cell size, as well as the expression of myosin heavy chain. The NMR spectrum profile gave the metabolites of leucine, such as α-ketoisocaproate, isovaleryl, 3-hydroxy-3-methylglutaryl, β-hydroxybutyrate, acetoacetate, demonstrating SIRM method was reliable for the research. Formoterol treatment resulted in the distinct accumulation of α-ketoisocaproate, which was the substrate of enzyme BCKDC. Furthermore, in vivo study showed 2mg/kg/d formoterol can inhibited the activity of muscle BCKDC.

Discussion: Leucine, as a branched chain amino acid, is essential for the synthesis of protein and it can promote the synthesis of skeletal muscle protein. BCKDC is the key limiting enzyme for the metabolism of leucine. Formoterol can alleviated the decrease of serum leucine and altered the metabolism of leucine. These results indicate β2-AR agonist formoterol can regulate BCKDC and its anabolism effect was partly due to the reprogramming of leucine metabolism.

4-13

Collagen-induced arthritis as a model of rheumatoid cachexia

Paulo Vinicius Gil de Alabarse[1,2], Rafaela Cavalheiro do Espírito Santo[1,2], Jordana Miranda da Souza Silva[1,2], Eduarda Correa Freitas[1,2], Andrelise Simões Almeida[1,4], Vivian de Oliveira Nunes Teixeira[1,2], Lidiane Isabel Filippin[1,3], Priscila Schmit Lora[1,4], Ricardo Machado Xavier[1,2]

[1]Laboratório de Doenças Autoimunes, Hospital de Clínicas de Porto Alegre, Brazil, [2]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre Brazil, [3]Mestrado em Saúde e Desenvolvimento Humano, Centro Uiversitário La Salle, Canoas, Brazil, [4]Faculdade de Biomedicina, Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil

Background: Rheumatoid arthritis (RA) extra-articular features frequently involve muscle wasting and metabolic alterations which in a context are known as rheumatoid cachexia. However, the syndrome characteristics is not yet established in RA so elucidation of rheumatoid cachexia is needed. Therefore, an animal model that mimics human condition may be useful.

Objectives: To study the cachexia parameters in collagen-induced arthritis (CIA) in mice.

Methods: CIA was induced in male DBA/1J mice. Clinical evaluations were performed in day zero and at 18, 25, 35, 45, 55 and 65 days after immunization, which were: clinical signs (arthritis score and paw edema), body weight (g), food intake, fatigue (by endurance exercise performance in min), grip strength (g), spontaneous locomotion (m). Also it was done the relative muscle weight (muscle weight in mg divided by total animal weight in g). Statistical analysis includes ANOVA and t-test. Difference was assumed if $p<0.05$.

Results: Arthritis score and paw edema confirm disease in CIA. Fatigue was higher in CIA group (36 ± 5min) than CO (45 ± 4min), as well as grip strength (CIA: 18 ± 10; CO: 54 ± 13g) and locomotion (CIA: 7 ± 4; CO: 21 ± 4m) was lower in CIA (at 35 days after immunization). Relative gastrocnemius muscle weight was also lower in CIA (CIA: 3.9 ± 0.6mg/g; CO:5.0 ± 0.6mg/g). Body weight change and food intake were not statistical different between groups.

Conclusions: CIA mice presented more fatigue, decreased strength and lower muscle mass, but unaltered food intake and body weight. These data demonstrate that CIA animals, besides characteristic articular findings, also show extra-articular events mimicking the

syndrome known as rheumatoid cachexia. Therefore, this model can be useful in the study of this syndrome.
FINANCIAL SUPPORT: CAPES, CNPq, FAPERGS, FIPE-HCPA.

4-14

The ubiquitin-proteasome system in muscle wasting of collagen-induced arthritis (CIA) treated with Etanercept or Methotrexate

Vivian de Oliveira Nunes Teixeira[1,2], Paulo Vinicius Gil de Alabarse[1,2], Khetam Ghannan[4], Jordana Miranda da Souza Silva[1,2], Gabriela Brendel Blum[1,2], Lidiane Isabel Filippin[1,3], Eugen Feist[4], Ricardo Machado Xavier[1,2]
[1]Laboratório de Doenças Autoimunes, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil, [2]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil, [3]Mestrado em Saúde e Desenvolvimento Humano, Centro Uiversitário La Salle, Canoas, Brazil, [4]Department of Rheumatology and Clinical Immunology, Charité- Universitätsmedizin Berlin, Germany

Background: Rheumatoid arthritis is an autoimmune inflammatory disease associated with systemic complications like fatigue and muscle wasting. Muscle wasting could be related to the ubiquitin-proteasome system. There are many established drugs used to treat RA, like etanercept and methotrexate, but their effects upon muscle wasting are still unknown.
Objectives: To evaluate if treatment with etanercept or methotrexate affects CIA muscle loss and ubiquitin-proteasome system.
Methods: Male DBA1/J mice were divided into 4 groups (n=8): CIA (saline); ETN (etanercept, 5.5mg.kg^{-1}) and MTX (methotrexate, 35mg.kg^{-1}), treated twice a week for 6 weeks, and a health group (CO). Treatments started one week after booster injection. Clinical score, hind paw edema, and body weight were analyzed during the experimental period. Tibialis anterior (TA) and gastrocnemius (GA) muscles were weighted after death. TA was used to measure myofiber area. GA was used to quantify proteasome activity and its mRNA expression by rtPCR. Statistical significance was considered if $p<0.05$.
Results: Treatments slowed disease development, observed through smaller clinical score and hindpaw edema in ETN and MTX vs CIA. ETN body weight (21 ± 1.0g) was significant different when compared to MTX (19 ± 1.3) at weeks 5 and 7. GA and TA muscles weight were heavier in ETN (80 ± 10 and 25 ± 2.1g) than MTX (80 ± 10 and 25 ± 2.1g, respectively). There was no significant difference in myofiber diameter among CIA groups. Caspase-like activity in 26S proteasome was higher in CIA (150%) and MTX (200%) vs CO. Expression of Psmb5 was enhanced in MTX vs CO. Expression of Psmb9 was enhanced in CIA and MTX vs CO.
Conculsions: Although both drugs improved the disease score, only etanercept was able to prevent muscle wasting. Moreover, CIA and MTX apparently are able to increase proteasome activity and expression. Further studies are necessary to explain the effects of TNF inhibition on muscle wasting and proteasome in arthritis.

FINANCIAL SUPPORT: CAPES, CNPq, FAPERGS, FIPE-HCPA.

4-15

Low level laser therapy activates satellite cells during muscle regeneration

Lidiane Isabel Filippin[1,2], Andrea J Moreira[2], Norma A P Marroni[3], Vivian Nunes de Oliveira Teixeira[2,3], Ricardo Machado Xaiver[2,3]
[1]Mestrado em Saúde e Desenvolvimento Humano, Centro Universitário La Salle, Canoas, Brazil, [2]Laboratório de Doenças Autoimunes, Hospital de Clínicas de Porto Alegre, Brazil, [3]Faculdade de Medicina, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil

Introduction: Skeletal muscles satellite cells (SC) seem to play a vital role in muscle regeneration after injury. The low level laser therapy (LLLT) have been used to accelerate the healing of injured soft-tissue, maybe through activation of SC, but its effects remain controversial.
Objective: Evaluate muscle regeneration after trauma when exposed to LLLT.
Methods: Male Wistar rats were separated in: Control (C); Trauma (T); and Trauma + Laser (L) groups. An injury on the gastrocnemius muscle was induced by a single impact blunt trauma on the gastrocnemius muscle belly. C and L groups received laser GaAs 5J/cm^2 2h post-trauma and once a day. Rats were killed at 3 or 14 days after injury. Spontaneous exploratory locomotion were assayed, histological analysis was performed and immunoassayed for IL-1beta, TNF-alfa and TGF-beta, and Western blot were performed for PAX-7, MyoD and myogenin. Statistical significance set for $p<0.05$.
Results: Locomotion were lower 6h post-trauma in T (35%) and L (28%) than C animals, and T had it sustained 3 days after. Inflammatory reaction, edema and myonecrosis were seen in T and were markedly attenuated in L group at 3 days post-trauma. TGF-beta was increased (130%) in T group 3 days after injury, L exposition attenuated 20%. Proinflammatory cytokines were higher in T and L groups compared to C at 3 days. PAX7 increased 66% at 3 days post-trauma in L group, whereas T had only 28%. Myogenin was increased to 90% in L group at 3 days compared to C. T had a delay in its activation, seen only at 14th day.
Conclusion: This study provides evidence of the activation of SC and ameliorate skeletal muscle regeneration in animals treated with LLLT. LLLT showed an effective alternative for treatment against muscle trauma and better muscle regeneration inducing less inflammation in tissue as well as increased regeneration.

4-16

Effects of chronic administration of arachidonic acid and docosahexaenoic acid on muscle cell type in the skeletal muscles of young rats

Michio Hashimoto, Takayuki Inoue, Masanori Katakura, Abdullah Al Mamun, Osamu Shido

Department of Environmental Physiology, Faculty of Medicine, Shimane University, Shimane, Japan

Introduction: We previously reported that arachidonic acid (20:4n-6, AA) deposition in the fast-twitch muscle of aged rats reduced cell volume with an increase in oxidative stress. Docosahexaenoic acid (22:6n-3, DHA) is also one of constituent of the cell membrane and DHA-derived docosanoids regulate the synthesis of eicosanoids derived from AA. In this study, we examined the effects of chronic AA and DHA administration on fatty acid composition, antioxidative status and morphology of rat skeletal muscles.
Methods: Young male Wistar rats (5 weeks old) maintained for two generations on a standard pellet containing no fish products were randomly divided into three groups: control group, DHA group (240 mg/kg BW/day) and AA group (240 mg/kg BW/day). Each oil was orally administered to rats (n = 8 in each group) for 13 weeks.
Results: Chronic DHA administration decreased the n-6/n-3 ratio and increased the DHA/AA ratio and ROS levels in the slow-twitch muscles (SO) of young rats. Chronic ARA administration decreased the linoleic acid levels and the DHA/AA ratio and increased the AA and ROS levels in the fast-twitch muscles (extensor digitorum longus muscles; EDL) of young rats. The muscle cell areas in the SO were not affected in each group, whereas those in the EDL were decreased in the AA group. Ratio of red muscle cell number per muscle cell number in the SO was lower in the DHA group, whereas red and inter mediate muscle cell mean areas was lower in the ARA group. Furthermore, MHC1, MHC2A and MHC2B expressions in the SO were decreased in the DHA group. MHC1 and MHC2A expressions in the EDL were higher in the DHA group, whereas these were lower in the ARA group.
Conclusion: Our study indicates a dietary fatty acid-dependent, differential regulation of contractile and metabolic properties between slow-type and fast-type muscles.

4-17

Electrophysiological, behavioral, and imaging analysis of neuromuscular Function in Aging C57BL/6J Mice

W. David Arnold[1,2,3], Kajri A. Sheth[1], Vicki L. McGovern[4] Arthur H Burghes[1,4]
[1]Division of Neuromuscular Disorders, Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [2]Department of Physical Medicine and Rehabilitation, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [3]Department of Neuroscience, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [4]Department of Molecular and Cellular Biochemistry, The Ohio State University Wexner Medical Center, Columbus, OH, USA.

Background: This study was designed to assess neuromuscular function in aging C57BL/6J mice to understand the timing of motor unit loss and the interaction between motor unit function, grip strength and muscle mass. We are also investigating whether overexpression of a specific protein can prevent this motor unit loss.
Methods: We performed electrophysiological measures of motor unit function including compound muscle action potential amplitude (CMAP) and motor unit number estimation (MUNE) in a cohort of 9 mice at 10, 13, 15,17, and 20 months (m). The longitudinal cohort and a younger cohort were also assayed with grip strength and hindlimb MRI and electrical impedance myography (EIM) for muscle size/quality. Mice with over expression of a specific protein were assessed for protection against motor unit loss.
Results: CMAPs at 10m (50.7 ± 12.4mV), 13m(43.6 ± 11.2mV), 15m (47.5 ± 6.7mV), and 17m (45.3 ± 5.7mV) were unchanged, but at 20m CMAPs are reduced (36.1 ± 6.1mV) ($p<0.05$). Similarly, MUNE is stable at 10m (341 ± 93), 13m (302 ± 98), and 15m (314 ± 51), but at 17m MUNE shows slight but not significant reduction (271 ± 51). At 20m, MUNE is reduced (225 ± 77) ($p<0.05$). Forelimb and all-limb grip normalized to body weight at 20m (3.11 ± 1.10g and 5.7 ± 0.86g, respectively) were unchanged compared to 11 month old mice (3.06 ± 0.69g and 5.62 ± 0.92g). Overexpression of a specific protein shows protection against motor unit loss opening avenues to treatment for sarcopenia.
Conclusion: Our preliminary data demonstrate motor unit loss prior to deficits in grip strength suggesting that motor unit loss may be an important and early determinant of aging-related sarcopenia. Further longitudinal assessment and data analyses of muscle size/quality are ongoing. In addition, we have identified an effect of improved nerve regeneration following overexpression of a specific protein. Because of the putative role of motor unit loss in aging-related muscle loss we are testing overexpression of this protein as a potential treatment.

4-18

Effects of a chaperone co-inducer (BGP-15) on contractile properties of single fibres from soleus muscle of rats exposed to deep sedation and mechanical ventilation

Nicola Cacciani, Heba Salah, Hannah Ogilvie, Lars Larsson
Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

Background and aims: We have studied the effects of a chaperone co-inducer (BGP-15) on muscle structural and functional impairment associated with deep sedation, neuromuscular blockade and mechanical ventilation. We hypothesized a positive effect of BGP-15 on fibre structure and function.
Methods: Female Sprague-Dawley rats were used in this study. Intravenous administration of BGP-15 was given to the rats for the whole duration of the experiments (5 or 10 days). The experimental groups were extensively monitored 24 hours per day. The soleus muscles were dissected from euthanized experimental and controls animals. Muscle bundles were then chemically skinned and prepared for contractile measurements. CSA, absolute force (P_0) and specific force (SF) i.e. absolute force/CSA, were measured at the single muscle fibre level. Transmission electron microscopy was used to study intermyofibrillar mitochondrial structure.
Results: After 5 days of treatment (deep sedation + neuromuscular blockade + mechanical ventilation) the SF decreased significantly compared to the controls. The administration of BGP-15 maintained

the SF at the control level after 5 days, however after 10 days it showed no effect on SF. On the contrary CSA values were not significantly affected by BGP-15 administration, therefore the improvement in SF at 5 days is essentially caused by the improvement of P_0, which is significant. Furthermore we observed that the proportion of abnormal IMF mitochondria was dramatically increased after both 5 and 10 days, of which BGP-15 treatment was seen to alleviate, significantly reducing the abnormal mitochondrial structure.

Conclusions: The restoration of SF is associated with BGP-15 administration, which might be transient and partially dependent on the structural integrity of the IMF mitochondria. This is compatible with the pharmacodynamics of BGP-15 which involves also the mitochondrial lipid structures.

4-19

Activin A induces muscle atrophy through p38β MAPK-activated catabolic pathway

Hui Ding, Guohua Zhang, Zhelong Liu, Ren-Kuo Lin, Yi-Ping Li
Department of Integrative Biology and Pharmacology, University of Texas Health, Science Center, Houston, TX, USA

Activation of type IIB activin receptor (ActRIIB) by its ligands in skeletal muscle induces muscle catabolism. However, the intracellular signaling mechanism that mediates ActRIIB-activated muscle catabolism is not defined. Despite the initial suggestions, emerging data indicate that Smad2/3 are likely nonessential to the catabolic effect mediated by ActRIIB. Here, by utilizing recombinant activin A we show that ActRIIB-activated muscle catabolism is mediated by p38**β** MAPK. Activin A treatment of C2C12 myotubes rapidly activated p38 MAPK and its effector C/EBP**β**, leading to upregulation of ubiquitin ligases MAFbx and UBR2, as well as activation of autophagy, resulting in MHC loss and myotube atrophy. These effects of activin A were blocked by p38 MAPK inhibitor SB202190. Using siRNA-mediated gene knockdown of p38 MAPK subtypes, we demonstrate that the catabolic activity of activin A is specifically mediated by p38**β** MAPK. Administration of activin A to mice (ip) recapitulated the activation of the catabolic pathway in muscle, which is blocked by administration of SB202190 or in mice with muscle-specific knockout of p38**β** MAPK. Therefore, ActRIIB activation of muscle catabolism is primarily mediated by p38**β** MAPK-activated signaling pathway.

Acknowledgement: This work is supported by Grant AR063786 from the National Institute of Health.

4-20

Can whole-body-vibration training attenuate weight loss and a reduction in muscle mass and function in tumour bearing cachectic mice?

Rogier L.C. Plas[1,2], Jvalini T. Dwarkasing[1], Miriam van Dijk[2], Hans J. M. Swarts[3], Evert M. van Schothorst[3], Renger F. Witkamp[1], Klaske van Norren[1,2]
[1]Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands, [2]Nutricia Research, Utrecht, The Netherlands, [3]Human and Animal Physiology, Wageningen University, Wageningen, The Netherlands

Treatment of cancer cachexia might become more effective using multiple target strategies, combining nutrition, exercise and pharmacological intervention. However, since frailty and fatigue are common in cancer patients, an exercise component might be problematic. Therefore, the present study aimed to test whether whole-body-vibration-training (WBV) could provide an alternative to attenuate loss of weight, muscle mass and function in tumour bearing mice.

24 CD2F1-mice (21.5 ± 0.2g) were stratified into four groups (control=[C], control+WBV=[C+V], tumour-bearing=[T] and tumour-bearing +WBV=[T+V]) and inoculated with $1x10^6$ C26 cells or sham injection. Animals of WBV groups underwent a daily exercise protocol (15min, 45Hz, 1.0g acceleration, starting day 1). During the intervention, body mass and daily-activity were assessed. On day 19 animals were killed, organ and muscle mass from the hind limbs, and *ex-vivo* muscle function of *m. soleus* (SOL) and *m. extensor digitorum longus* (EDL) were measured. For statistical analysis a one-way ANOVA, followed by Bonferroni adjustment was performed using SPSS 22.

A reduction in body mass was seen from day 15 in the T-group, which became significant from day 18 in the T+V-group (C and C+V compared to either T or T+V, respectively). Daily-activity decreased in all groups compared to C group. *M. gastrocnemius* (GAS), *m. tibialis* (TIB) and EDL mass was significantly lower in both tumour-bearing groups compared to control groups. SOL mass did not differ significantly between groups. Force-frequency measurements of SOL indicate a lower maximal force (F_{max}), contraction time (CT), relaxation time (RT) and rate of force onset (dF/dt) in T compared to C +V. This difference was not significant in the C and T+V group compared to all other groups.

In conclusion, these data suggest that WBV delays loss of body mass in tumour bearing mice. In addition, WBV seems to affect type I dominated SOL by increasing F_{max}, CT, RT and dF/dt.

4-21

New stable long-acting peptide GHS-R1a agonists as potential anti-cachectic therapeutics

Martina Holubová[1], Barbora Mikulášková[1,2], Jaroslav Kuneš[1,2], Blanka Železná[1], Lenka Maletínská[1]
[1]Institute of Organic Chemistry and Biochemistry AS CR, v.v.i., Prague, Czech Republic, [2]Institute of Physiology CAS, Prague, Czech Republic

Background and aims: Ghrelin, the only known orexigenic gut hormone, affects positively energy balance and possesses anti-inflammatory effects. Ghrelin and other ghrelin receptor (GHS-R1a) agonists are currently being investigated as anti-cachectic therapeutics. Octanoylation of ghrelin on Ser^3 is necessary for biological activity but also makes ghrelin highly unstable. We designed a series of peptide ghrelin analogs which are stabilized by replacing

octanoylated Ser^3 with a fatty acid coupled to diaminopropionic acid by stable amide bond, and further modified by incorporation of other non-coded amino acids, prolonging the fatty acid, incorporation of the second fatty acid or shortening the peptide chain. These new analogs were tested to elicit their potential anti-cachectic properties.

Methods: HEK293T cells with transfected hGHS-R1a receptor were used for competitive binding experiments and cell signaling studies (inositolphosphate accumulation, Ca^{2+} release). Acute effect on food intake was examined after SC administration to mice (0.1-10 mg/kg). Pharmacokinetics of analogs was tested in mice after SC administration (5 mg/kg); blood concentration of analogs was determined by ELISA. Anti-cachectic effects of selected analogs were tested in rats with subtotal nephrectomy (15 day SC administration) and in mice with lipopolysaccharide-induced cachexia.

Results: Ghrelin analogs showed similar affinities as ghrelin for cell membranes with transfected hGHS-R1a and activated ghrelin signaling comparably to ghrelin. SC administration of analogs to mice increased food intake dose-dependently and stronger than ghrelin. Analogs were significantly more stable *in vivo* than ghrelin. Repeated administration of the selected analog to cachectic rats increased body weight and reduced pro-inflammatory cytokines levels. A single SC administration of another analog to mice with lipopolysaccharide-induced cachexia increased food intake and expression of orexigenic neuropeptides in the hypothalamus and reduced pro-inflammatory cytokines in blood.

Conclusions: Tested ghrelin analogs are potent, stable, long-acting GHS-R1a agonists with pronounced anti-cachectic properties.

This project was supported by RVO:61388963 of ASCR.

4-22

Nitric oxide (NO) regulator drugs could be used as treatment for muscle loss in collagen-induced arthritis (CIA)

Paulo Vinicius Gil de Alabarse[1,2], Vivian de Oliveira Nunes Teixeira[1,2], Jordana Miranda da Souza Silva[1,2], Adrelise S Almeida[1,3], Lidiane Isabel Filippin[1,4], Ricardo Machado Xavier[1,2]

[1]Laboratório de Doenças Autoimunes, Hospital de Clínicas de Porto Alegre, Brazil, [2]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre Brazil, [3]Mestrado em Saúde e Desenvolvimento Humano, Centro Uiversitário La Salle, Canoas, Brazil, [4]Faculdade de Biomedicina, Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil

Background: Rheumatoid arthritis is an autoimmune inflammatory disease associated with systemic complications like fatigue and muscle weakness. Nitric oxide (NO) regulation can lead to anti-inflammatory and anti-arthritic effects as well as induce muscle repair in muscle injury, but its role in CIA has not yet been studied.

Objectives: To evaluate if treatment with NO synthase inhibitor (L-NAME) and the NO donor (SIN-1) affects CIA muscle loss

Methods: Female Wistar rats with CIA were separated in four groups (n = 8–10):CIA (saline); L-NAME (30mg.kg^{-1}); and SIN-1 (0.3 mg.kg^{-1}), treated twice a day for 10 days after the onset of the disease, and a health group (CO). Clinical score, hind paw edema, spontaneous locomotion, and body weight were analyzed. Ankle was collected and used for histological analysis. Tibialis anterior (TA), gastrocnemius and soleus muscles were weighted (g). TA was used for histological analysis and immune stained for TNF-alfa, TGF-beta and IL-1beta. Statistical significance was at $p<0.05$.

Results: Ankle histology confirmed that all CIA groups developed arthritis. In vivo analysis of hindpaw edema, clinical score, body and muscle weight, and spontaneous locomotion showed no difference among all groups. On the other hand, both L-NAME (48 ± 6.5) and SIN-1 (48 ± 6.5) groups have shown decreased disease severity than saline (77 ± 9.2) when analyzed by the area under curve. Muscle cross sectional area was higher in L-NAME (1074 ± 315μm) and SIN-1 (1115 ± 303μm) than saline (786 ± 243μm), however it did not reach CO diameter (1755 ± 278μm). All CIA groups had shown increased immune cells infiltration shown by TNF-alfa, TGF-beta and IL-1beta immune staining.

Conclusions: Nitric oxide regulator drugs data suggests good prospects as intervention for muscle loss. As was observed, even a simple drug that have main influence in vessel pressure shows preventive clinical score development and ameliorates muscle cross sectional area. The mechanism will be depicted by molecular analysis.

FINANCIAL SUPPORT: CAPES, CNPq, FAPERGS, FIPE-HCPA.

4-23

Megestrol acetate improves cardiac function in a model of cancer-cachexia induced cardiomyopathy by autophagic modulation

Vincenzo Musolino[1#*], Sandra Palus[2#], Anika Tschirner[3], Cathleen Drescher[2], Micaela Gliozzi[1], Cristina Carresi[1], Carolina Muscoli[1,4], Wolfram Doehner[5], Stephan von Haehling[2], Stefan D. Anker[2], Vincenzo Mollace[1,4], Jochen Springer[2]

[1]Institute of Research for Food Safety & Health (IRC-FSH), University of Catanzaro "Magna Graecia", Catanzaro, Italy, [2]Division of Innovative Clinical Trials, Department of Cardiology, University Medical Center Göttingen (UMG), Göttingen, Germany, [3]Applied Cachexia Research, Department of Cardiology, Charité Medical School, Berlin, Germany, [4]Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, Rome, Italy, [5]Center for Stroke Research, Charité Medical School, Campus Virchow- Klinikum, Berlin, Germany.

# Both authors contributed equally to this work.

Background: Cachexia is a complex metabolic syndrome associated with cancer. One of the features of cachexia is the loss of muscle mass, characterized by disbalance of protein synthesis and protein degradation. Muscle atrophy is due to hyperactivation of the main cellular catabolic pathways, including autophagy. Cachexia also affects cardiac muscle and the atrophy of the heart impairs cardiac function and is likely to contribute to mortality. Anti-cachectic therapy in patients with cancer cachexia is so far limited to nutritional support and anabolic steroids. The use of the appetite stimulant megestrol acetate (MA) has been discussed as a treatment for cachexia.

Methods: In this study the effects of MA were tested in cachectic tumour-bearing rats (Yoshida AH-130 ascites hepatoma). Rats were treated with 100mg/kg/d MA or placebo starting one day after

tumor-inoculation for 16 days. Body weight and body composition were assessed at baseline and at the end of the study. Cardiac function was analyzed by echocardiography at baseline and day 11. Locomotor activity and food intake were assessed before tumor inoculation and at day 11. Autophagic markers were assessed in gastrocnemius muscle and heart by western blot analysis.

Results: Treatment with 100mg/kg/d MA significantly attenuated the loss of body weight ($-9 \pm 12\%$, $p<0.05$;) and the wasting of lean and fat mass ($-7.0 \pm 6\%$ and $-22.4 \pm 3\ \%$, $p < 0.001$ and $p<0.05$ respectively). Administration of 100mg/kg/d MA significantly protected heart from general atrophy (633.8 ± 30 mg vs placebo 776 ± 10 mg, $p < 0.001$). Tumor-bearing rats displayed cardiac dysfunction, e.g. left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), the stroke volume (LVSV), the end dyastolic volume (LVEDV) and the end systolic volume (LVESV) were significantly impaired in tumou−r-bearing rats. MA significantly improved LVEF, LVFS and LVESV. Western blotting analysis showed an upregulation of the autophagic pathway in gastrocnemius and hearts of tumor-bearing rats. MA was able to modulate the autophagic markers (e.g. Beclin-1, p62, TRAF-6 and LC3) in the gastrocnemius and in the hearts of tumor-bearing rats. Most importantly, 100mg/kg/d MA reduced mortality (HR: 0.44; 95%CI: 0.20-1.00; $p = 0.0486$).

Conclusions*:* MA improved survival and reduced wasting through a marked downregulation of autophagy, occurring in both skeletal and heart muscle, the latter effect leading to a significant improvement of cardiac function. Our data suggest that MA might represent a valuable strategy to counteract the development of cancer cachexia-induced cardiomyopathy.

4-24

Inhibition of activin-like kinase 4/5 inhibits cancer cachexia associated muscle wasting

Stef Levolger, Jeroen L.A. van Vugt, Sander A. Huisman, Sandra van den Engel, Gisela Ambagtsheer, Wendy Bijman-Lagcher, Jan N.M. IJzermans, Ron W.F. de Bruin

Department of Surgery, Erasmus MC – University Medical Center, Rotterdam, The Netherlands

Background: Cancer mediated ACTRIIB-ALK4/5 heterodimer activation by myostatin is strongly associated with muscle wasting in cancer cachexia. We investigated the efficacy of ALK4/5 receptor blockers SB431542 (SB) and GW788388 (GW) in restoring the cabatolic/anabolic imbalance observed in cachexia.

Materials and methods: Forty CD2F1 mice were randomly allocated into five groups: C26 tumor-bearing (TB) SB treated animals (10 mg/kg, intraperitoneal [IP]), TB GW treated animals (10 mg/kg, IP), TB GW treated animals (10 mg/kg, oral gavage [PO]), vehicle (DMSO) control, and a group of healthy mice. Mice allocated in TB groups were inoculated subcutaneously with 0.5×10^6 C26 cells to induce cachexia. Starting one day following tumor inoculation mice received allocated treatment daily until sacrifice, on day 21, or upon bodyweight loss exceeding 20%. Bodyweight and grip-strength were recorded periodically. Tumor tissue and gastrocnemius (GCM) muscles were resected and weighed.

Results: Bodyweight loss was observed in the vehicle group (6%) and SB treated animals (3%), but not in GW treated animals. An increase in bodyweight of median 3% was observed following intraperitoneal treatment, and 4% following treatment via oral gavage. Mean weight of GCM muscles were 140 mg (SB), 155 mg (GW IP), 162 mg (GW PO), 167 mg (healthy) and 107 mg (vehicle). No muscle wasting was observed in GW treated animals ($p > 0.999$). Moreover, grip-strength remained comparable to healthy animals (+16%) following treatment using GW IP (+14%, $p = 0.834$) and GW PO (+4%, $p = 0.234$). The mean weight of resected tumor was 573 mg (SB), 410 mg (GW IP), 392 mg (GW PO), and 554 mg (vehicle). No difference in tumor mass was observed between all groups ($p = 0.503$).

Conclusion: Treatment with GW788388 prevented loss of body weight, GCM mass, and grip-strength in cancer cachexia.

4-25

Febuxostat reduces cancer cachexia-induced cardiomyopathy

Masaaki Konishi[1], Cathleen Drescher[1], Sandra Palus[1], Anika Tschirner[1], Stephan von Haehling[1], Wolfram Doehner[2], Stefan D. Anker[1], Jochen Springer[1]

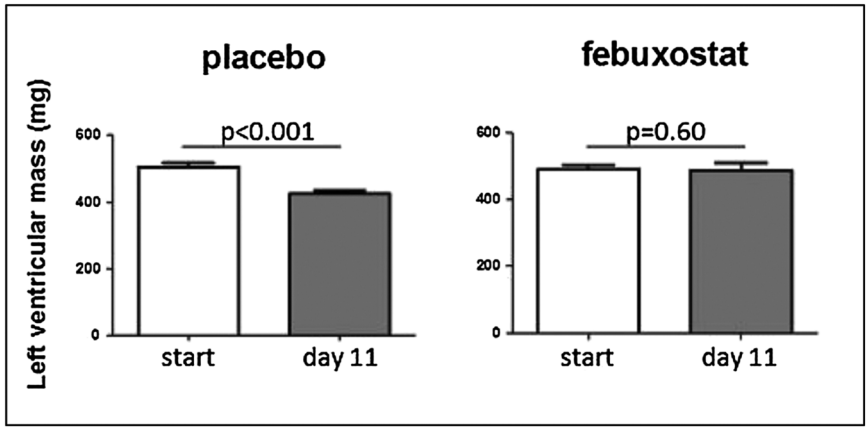
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]Charité Medical School, Berlin, Germany

Background: We have previously shown that the activity of the xanthine oxidase is induced in cancer cachexia and that its inhibition by the second generation xanthine oxidase inhibitor febuxostat improves survival and reduces wasting in the Yoshida hepatoma cancer cachexia model. Here we characterize the effects of febuxostat on cardiac function in the same model.

Methods: The Yoshida AH-130 hepatoma cancer cachexia rats were treated with febuxostat at 5 mg/kg or placebo per gavage daily. Cardiac function was analysed by M- and B-mode echocardiography on day 11.

Results: Left ventricular mass was similar at the beginning of the study among 2 groups (506 ± 10 mg in placebo vs 490 ± 13 mg in febuxostat, $p = 0.57$) and decreased significantly on day 11 in placebo group (425 ± 11 mg, $p<0.001$) but not febuxostat group (487 ± 23 mg, $p = 0.60$). The difference between before and after treatment was -81 ± 10 mg in placebo and -3 ± 28 mg in febuxostat group ($p<0.01$). Whereas changes in left ventricular fraction shortening (-10.3 ± 1.3 % vs -9.7 ± 1.7 %, $p = 0.79$) and dimension in diastole (-1.1 ± 0.1 mm vs -0.8 ± 0.3 mm, $p = 0.20$) were comparable among 2 groups, changes in stroke volume (-76 ± 6 µl in placebo vs -53 ± 15 µl in febuxostat, p=0.09) and cardiac output (-401 ± 25 ml/min in placebo vs -287 ± 69 ml/min in febuxostat, $p = 0.06$) tended to be mitigated in febuxostat group, suggesting the attenuated cardiac involvement of cancer cachexia.

Conclusion: Inhibition of xanthine oxidase by febuxostat had beneficial effects on cardiac mass and function in a rat model of



severe cancer cachexia. This effect may contribute to better outcome of animals treated by febuxostat.

4-26

Doxorubicin-induced responses in skeletal muscle oxidative capacity and the effects of blocking activin receptor ligands

Tuuli A. Nissinen[1], Riikka Kivelä[2], Joni Degerman[2], Aino Poikonen[1], Markus Räsänen[2], Eero Mervaala[3], Arja Pasternack[4], Olli Ritvos[4], Juha J. Hulmi[1,5]

[1]Department of Biology of Physical Activity, Neuromuscular Research Center, University of Jyväskylä, Jyväskylä, Finland, [2]Wihuri Research Institute and Translational Cancer Biology Research Program, University of Helsinki, Helsinki, Finland, [3]Department of Pharmacology, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [4]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland, [5]Department of Physiology, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Background and aims. Doxorubicin is a widely used and effective anthracycline chemotherapy drug. However, doxorubicin has several harmful effects, the most well-known being cardiotoxicity. In addition, doxorubicin has been shown to have detrimental effects on skeletal muscle tissue as well, including muscle atrophy and in some cases also possibly impaired mitochondrial function. Inhibiting myostatin/activin signaling by soluble activin receptor IIb (sActRIIB-Fc) could be an effective strategy to fight muscle loss induced by cancer and its treatment. However, it may have negative effects on skeletal muscle oxidative capacity and metabolism in some animal models. The aim was to examine the effects of doxorubicin and sActRIIB-Fc administration on skeletal muscle oxidative capacity and mitochondrial function.

Methods and results: The present study investigated a four-week period with first two weeks of intraperitoneal doxorubicin administration (4 x 6 mg/kg) in C57BL/6 mice. It resulted in impaired running performance assessed with an incremental treadmill running protocol ($P > 0.05$). However, no doxorubicin-induced changes were seen in skeletal muscle mitochondrial function analyzed with OROBOROS Oxygraph-2k, citrate synthase activity or expression of PGC-1α or mitochondrial proteins (respiratory chain subunits, porin/VDAC1 and cytochrome *c*). This suggests that the effects, if existed, were only transient. Contrary to previous results in dystrophic mice, intraperitoneal sActRIIB-Fc administration (5 mg/kg, 1–2x/wk) did not cause further impairment to running performance or mitochondrial function. In addition, sActRIIB-Fc administration resulted in increased mitochondrial porin/VDAC1 and respiratory chain CIII-UQCRC2 protein contents and did not cause any decline in PGC-1α or cytochrome *c* protein expression. However, sActRIIB-Fc administration decreased mitochondrial respiratory chain CI-NDUFB8 and CV-ATP5A protein contents.

Conclusions. These results suggest that blocking ActRIIB signaling may be a promising strategy to counteract chemotherapy-induced muscle loss without further damage to skeletal muscle oxidative capacity or mitochondria.

This work was supported by Academy of Finland grant No. 275922.

4-27

Possible reappraisal of the *angina pectoris* drug trimetazidine in the treatment of cachexia

Lucia Gatta[1]*, Fabrizio Pin[2]*, Laura Vitiello[1], Paola Costelli[2], Giuseppe Rosano[1], Elisabetta Ferraro[1]

[1]Laboratory of Pathophysiology of Cachexia and Metabolism of Skeletal Muscle, IRCCS San Raffaele Pisana, Rome, Italy, [2]Department of Experimental Medicine and Oncology, University of Torino, Italy

Background: The metabolic modulator trimetazidine (TMZ) blocks fatty acid β-oxidation and shifts ATP production towards glucose oxidation resulting in cell energy metabolism optimization. TMZ enhances the efficiency of myocardium metabolism and is used to treat *angina pectoris.* This led us to investigate the effect of TMZ also on skeletal muscle, in particular in cancer cachexia.

Methods: We had recently found that TMZ has a protective effect against atrophy *in vitro* (Ferraro-2013). In order to study the effectiveness of TMZ *in vivo*, the drug was administered to mice bearing the C26 colon-carcinoma, a well-characterized model of cancer cachexia.

Results: We have found that treatment of tumor hosts with TMZ does not modify body weight and muscle mass. Conversely, muscle fiber cross-sectional area and voluntary muscle grip strength are improved by TMZ. The latter also correlates with TMZ-induced hypoglicemia, suggesting that treated animals are effectively using more glucose than the untreated ones. Moreover, in *tibialis anterior* muscle, the levels of Myosin Heavy Chain (MyHC) and Carnitine-palmitoyl-transferase 1 (CPT1) mRNAs as long as the levels of Desmin transcript and protein increase upon TMZ treatment, whereas Atrogin-1 mRNA and protein levels decrease. Finally, our data revealed that TMZ enhances *in vivo* the expression of proteins typically induced by endurance exercise; MyHC-slow isoform, PPAR-gamma coactivator1-alpha (PGC1alpha) and the mitochondrial protein Tom20. In line with this, TMZ also decreases the expression of the 3 genes coding for the fast-twitching isoforms of MyHC and induces a more oxidative metabolism, as indicated by Succinate-dehydrogenase (SDH) activity increase and, in C2C12 cells, by higher mitochondrial membrane potential.
Conclusions: On the whole, these results suggest that TMZ acts like an "exercise mimetics" and positively interferes with skeletal muscle cell response to stress *in vivo*, supporting a possible reappraisal of this drug in the treatment of diseases characterized by muscle atrophy.

4-28

A selective angiotensin-II type 2 receptor agonist reduced cancer cachexia-induced cardiomyopathy

Masaaki Konishi[1], Cathleen Drescher[1], Sandra Palus[1], Anika Tschirner[1], Andrew J. Coats[2], Stefan D. Anker[1], Jochen Springer[1]
[1]Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany, [2]Monash University, Melbourne, Australia; Warwick University, Warwick, UK

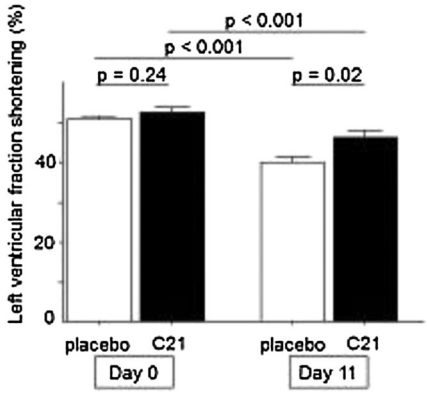
Background: Angiotensin-II has been shown to be up-regulated in cachexia. Angiotensin-II mediates its actions via AT1 and AT2 receptors, and AT2 receptor acts in anti-proliferative, anti-inflammatory, and anti-apoptotic ways. We sought to test the effects of compound21 (C21), a selective AT2 receptor agonist, on survival, body weight, and cardiac function in cancer cachexia model.
Methods: The Yoshida hepatoma AH-130 rats were treated with C21 at 0.2mg/kg (n = 15) or placebo (n = 44) per gavage daily for a maximum of 17 days. Cardiac function was analysed by M- and B-mode echocardiography on day 11. The proteasome/caspase activity as well as Western blotting for muscle-specific metabolic proteins in heart and gastrocnemius were analysed.
Results: C21 improved survival (hazard ratio: 0.45, p = 0.03) and reduced weight loss by 44% ($p<0.01$) at the end of study. Left ventricular fraction shortening (FS), a measure of systolic function, was similar at the beginning among groups (52.7 ± 1.1 in C21 vs. 50.9 ± 0.7% in placebo, p = 0.24) and decreased on day 11 in both groups ($p<0.001$). On day 11, however, FS was significantly greater in C21 group than placebo (46.3 ± 1.8 vs. 39.9 ± 1.3%, p = 0.02). Heart rate (380 ± 14 vs. 342 ± 9bpm, p = 0.04), left ventricular mass (488 ± 27 vs. 436 ± 12mg, p = 0.06), and cardiac output (53.2 ± 7.1 vs. 40.7 ± 3.1ml/min, p = 0.07) were higher in C21 group on day 11, suggesting an attenuated cardiac impairment in this model of cancer cachexia. Whereas proteasome/caspase activity was similar among groups in gastrocnemius, myostatin expression in heart was reduced by 32% in C21 group (p = 0.03).
Conclusion: Selective AT2 receptor stimulation by C21 had beneficial effects on cardiac function in a rat model of cancer cachexia. This effect may have contributed to better outcome of animals treated by C21.

4-29

A non-steroidal selective androgen receptor modulator (TEI-SARM2) for treatment of muscle wasting diseases

Kanou Masanobu, Horie Kyohei, Takagi Ken-ichiro, Nakamura Katsuyuki, Jinbo Toshie, Sugiyama Hiroyuki, Yamana Kei
Pharmaceutical Discovery Research Laboratories, TEIJIN Pharma Ltd, Tokyo, Japan

Muscle wasting is a frequent concomitant condition with hip fracture, cancer cachexia and aging. TEI-SARM2, a novel non-steroidal selective androgen receptor modulator (SARM) is selected as a pharmaceutical candidate for treatment of muscle wasting diseases by its potent muscle anabolic activity, favorable pharmacological and pharmacokinetic properties in non-clinical studies. TEI-SARM2 is a novel non-steroidal scaffold structure, highly selective to AR among nuclear receptors, bound as a novel binding mode to AR and efficacious to increase muscle mass in normal and orchiectomized rats.
In this study, we evaluated the efficacy of TEI-SARM2 during progressive disuse muscle atrophy. Female Wistar rats were hindlimb unloaded for 14 days and received a daily oral administration of TEI-SARM2 ranging from 0.1 to 3 mg/kg or single subcutaneous administration of nandrolone decanoate (ND) ranging from 1 to 30 mg/kg. TEI-SARM2 could reduce unloading-induced muscle atrophy without any effects on ovary and uterus weight while ND also inhibited muscle atrophy with significant effects on ovary and uterus weight. Mechanistically, TEI-SARM2 and ND increased the local IGF-1 expression dose dependently in muscle. Furthermore, Bcat2 mRNA levels were decreased and Rheb mRNA levels were increased in TEI-SARM2 treated rats. These results indicate that in addition to anabolic activity to increase muscle mass, TEI-SARM2 also prevent unloading-induced decrease of muscle mass at least in part by



influencing the local anabolic factors. The potential efficacy of TEI-SARM2 in cancer cachexia models is now underway.
Taken together our results indicate that TEI-SARM2 is a novel promising drug candidate for muscle wasting diseases.

4-30

Go-sha-jinki-Gan (GJG), a traditional Japanese herbal medicine, protects against sarcopenia in senescence-accelerated mice

Keisuke Hagihara[1], Yuki Kishida[1], Miho Nakanishi[1], Kousuke Baba[1], Hideki Yoshikawa[2]
[1]Department of Kampo Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Department of Orthopaedic Surgery, Medicine Osaka University Graduate School of Medicine, Osaka, Japan

Background and aims: Sarcopenia is a major problem in physical function in older adults, however, no pharmaceutical treatment is available. Go-sha-jinki-Gan (GJG) is a traditional Japanese herbal medicine that is used to alleviate various age-related symptoms, especially motor disorders in Japan. Here, we investigated the effect of GJG on aging-associated skeletal muscle atrophy by using senescence-accelerated mice (SAMP8).
Methods: Seven-week-old male SAMP8 mice were divided into 2 groups: those fed a normal diet (n = 10) and those fed a normal diet supplemented with 4% (w/w) GJG (n = 10). As controls, 7-week-old male senescence-accelerated aging-resistant (SAMR1) mice were used. At 38 weeks, the mice were euthanized and tibiae were removed. Soleus muscles were stained with H&E and evaluated microscopically using WinROOF software. Fiber type distribution as a percentage was calculated using anti- SERCA1 ATPase. The sera of mice were evaluated using a mouse IGF-1 ELISA system. The soleus muscles were homogenized and analyzed by western blotting.
Results: No adverse effect was observed in the GJG group mice. Immunohistochemical and western blotting analyses clearly showed that GJG significantly reduced the loss of skeletal muscle mass and ameliorated the increase in slow skeletal muscle fibers in SAMP8 mice compared to SAMR1 mice. GJG elevated the levels of serum IGF-1 in SAMP8 mice, which improved the phosphorylation of Akt, GSK-3β and FoxO4. MuRF1 expression levels were suppressed by GJG in SAMP8 mice. The phosphorylation of AMPK and mitochondrial-related transcription factors such as PGC-1α were increased after GJG treatment. The expression levels of TNF-α were elevated in SAMP8 mice, whereas GJG suppressed its level.
Conclusions: GJG suppressed sarcopenia via normalizing signal transduction through the IGF-1-Akt axis, maintained the expression of mitochondrial-related transcription factors, and suppressed TNF-α in SAMP8 mice. GJG is a promising candidate for relief from sarcopenia.
(Yuki Kishida et al. Phytomedicine 2015,doi:10.1016/j.phymed.2014.11.005).

4-31

PACAP6-38, a functional CART antagonist, reduces adipose tissue depletion in MCG101-tumor bearing mice with anorexia-cachexia that display increased plasma CART concentrations

Ulrika Smedh, Jonathan R. Burgos, Britt-Marie Iresjö
Dept of Surgery, Sahlgrenska University Hospital, and Institute of Clincial Sciences at the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Background and aims: Cocaine-and amphetamine regulated transcript acts centrally to inhibit food intake, but its peripheral effects is less known. We measured CART in plasma of mice bearing MCG101 tumors that display anorexia-cachexia syndrome and tested whether PACAP6-38 can affect cachexia development by pretreatment with the functional CART antagonist PACAP6-38.
Methods: Mice were inoculated with MCG101 and food intake and body weights were monitored daily. The animals developed reduced food intake after 10 days, and were then injected once-daily with PACAP6-38, i.p. The mice were killed on day 14, blood was collected by heart puncture. Plasma concentratins of SAP, T3 and CART was analyzed by ELISA. Body composition was determined. CART in tumor tissue was analyzed with rtQPCR.
Results: Compared to sham-implanted animals, mice with MCG101 tumors had significantly reduced food intakes and body weights. Plasma CART was increased in tumor bearing mice and the levels correlated to plasma levels of SAP. Plasma thyroid hormones were changed in tumor-bearing animals. PACAP6-38 did not affect food intake or body weight in sham-treated animals. MCG101 bearing mice receiving PACAP6-38 had significantly higher total body fat deposits compared to vehicle-treated tumor mice. PACAP6-38 did not significatly change total body fat in tumor free animals.
Conclusions: MCG101 bearing mice display increased plasma CART levels, which correlate to SAP levels. The CART increase is not dependent on reduced food intake per se but a host response to tumor. Pretreatment with a functional CART antagonist reduces depletion of total body fat, but does not affect food intake or body weight, suggesting a possible new therapeutic target mechanism to lessen tumor-induced cachexia.

4-32

Effect of 3-hydroxy-3-methylbutyrate on protein metabolism in whole body and in selected tissues of laboratory rat

Milan Holeček, Miroslav Kovařík, Melita Vodeničarovová, Luděk Šišpera
Department of Physiology, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Czech Republic

Background and aims*:* 3-hydroxy-3-methylbutyrate (HMB) is a leucine metabolite with protein anabolic action which may be employed in treatment of proteocatabolic illness and in endurance training. We

examined the effects of exogenous HMB on protein synthesis and proteolysis in whole body and selected tissues of laboratory rat.
Methods: Rats were administered by HMB at a dose of 0.1 g/kg b.w. (s.c. and i.v., 1:1) or by saline (control). The parameters of whole-body protein metabolism were evaluated 24 hours later using L-[1-^{14}C]leucine and L-[3,4,5-^{3}H]phenylalanine. Changes in proteasome dependent proteolysis and protein synthesis in selected tissues were determined according the chymotrypsin-like activity and labeled leucine and phenylalanine incorporation into the protein. The results were analyzed using Mann-Whitney test.
Results: A decrease in whole-body proteolysis and protein synthesis was observed in HMB treated rats. Proteasome-dependent proteolysis decreased significantly in skeletal muscle, changes in heart, liver, jejunum, colon, kidney, and spleen were insignificant. Decrease in protein synthesis was observed in the heart, colon, kidney, and spleen, while an increase was observed in the liver.
Conclusions: We conclude that protein anabolic effect of HMB in skeletal muscle is related to inhibition of proteolysis in proteasome. Alterations in protein synthesis in visceral tissues may affect several important functions and the metabolic status of the whole body.
Supported by PRVOUK P37/02.

5-01

β-hydroxy-β-methylbutyrate (HMB) alters skeletal muscle proteins implicated in mitochondrial dynamics, autophagy and atrophy during resistance training (RT) rehabilitation after 10-days bed rest in older adults

Robert A. Standley[1], Giovanna Distefano[1], Suzette L. Pereira[2], Min Tian[2], Owen J. Kelly[2], Paul M. Coen[1], Nicolaas E.P. Deutz[4], Robert R. Wolfe[3], Bret H. Goodpaster[1]
[1]Translational Research Institute for Metabolism and Diabetes-Florida Hospital, Sanford Burnham Prebys Medical Discovery Institute, Orlando, FL, USA, [2]Abbott Nutrition, Columbus, OH, USA, [3]Center for Translational Research in Aging & Longevity, Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, AR, USA, [4]Center for Translational Research in Aging & Longevity in the Department of Health & Kinesiology, Texas A&M University, College Station, TX, USA

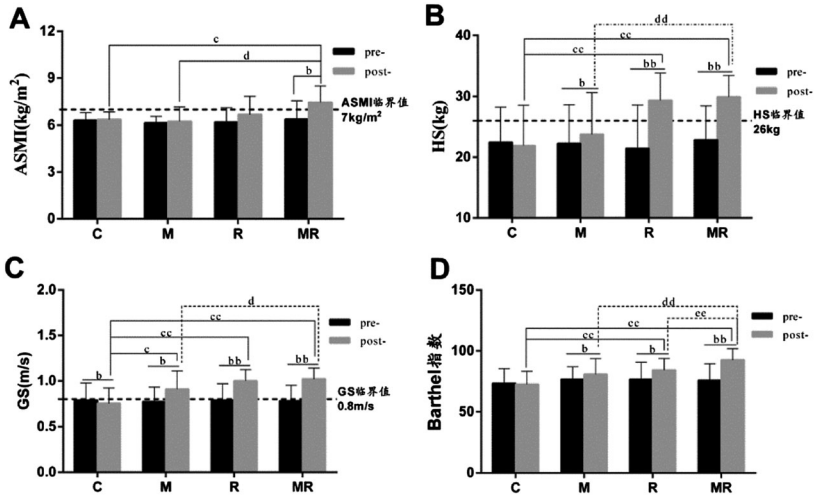
Loss of muscle mass during disuse is a serious health issue for older adults. HMB supplementation during 10d bed rest (BR) can preserve lean mass in older adults.[1] To elucidate the molecular mechanisms of HMB over bed rest/rehabilitation, we examined mediators of skeletal muscle mitochondrial dynamics, autophagy, and atrophy following 10d BR and 8 wks RT rehabilitation.
Nineteen older adults (60-76yr) completed 10d BR followed by 8wks RT. Subjects were randomized to either HMB (3g/d, HMB, N = 11) or placebo (CON,N = 8), and percutaneous vastus lateralis biopsies were obtained from a subset of these individuals (HMB N = 8, CON N = 8) before and after BR, and after rehabilitation. We measured proteins involved in mitochondrial content (OXPHOS), dynamics (Mfn-2, OPA-1, Fis-1, DRP-1), autophagy (beclin-1, LC3B, BNIP3), and atrophy (poly-ubiquinated proteins (poly-ub)) by western blotting.
After 10-days BR, OXPHOS protein levels and all measured mediators of mitochondrial dynamics and autophagy remained unchanged in both groups. Poly-ub proteins increased (36%) and decreased (23%) in the CON and HMB groups after BR ($p = 0.20$). Changes in Mfn-2 was associated with changes in total (TLM) and leg lean mass (LLM) after BR (TLM: $r = 0.54$, $p = 0.04$; LLM: $r = 0.65$, $p = 0.01$).
Following RT rehabilitation, OXPHOS content tended to be higher (80%) in HMB ($P = 0.06$); Fis-1 (53%), OPA-1 (44%), and Mfn-2 (98%) tended to be greater in HMB vs. CON ($P > 0.05$ to 0.25). DRP-1 increased (76%) in the HMB group after RT vs. CON ($p = 0.005$) and LC3BII/LC3BI ratio was lower (45%), independent of treatment group ($p = 0.042$).
In conclusion, HMB mainly decreased poly-ub proteins, and increased mitochondrial dynamics and content during exercise rehabilitation after 10-days BR in older adult. These data suggest a potential new mechanism of action for HMB on mitochondrial dynamics that contribute greater recovery following disuse.
Reference
1. Deutz NEP et al. *Clin. Nutr.* 32 (5): 704–712

5-02

Effects of Chinese massage and resistance exercise on ADL in elderly Chinese sarcopenic men

Zhao Y. Jun[1], He Y. Xiu[1], Zhang Y. Min[2], Guo Y. Hua[2], Dou Y. Li[2], P. Chen[3]
[1]Physical Education Department of HeBei Normal University, Shijiazhuang,Hebei, China, [2]Sport Department of Lv Liang University, LvLiang, ShanXi,China, [3]Sport College of BeiJing Normal University, Beijing, China

Background and aims: To investigate the effects of Chinese Massage and/or Resistance Exercise on skeletal muscle mass, strength and walking ability in Chinese Sarcopenic man.
Methods: A total of 60 men aged over 60 years were collected according to the Sarcopenia criterion defined by AWGS and randomly assigned into four groups averagely: Control(C), Chinese Massage(M), Resistance Exercise(R),or combined M and R group (MR). M group received a 40mins Chinese Massage program including YiJinJing and massage manipulation; R group attended a 40mins resistance exercise program which consists of bench squat and Thera-Band training with 60-80%1RM; MR group received Massage and resistance exercise alternately. All programs were carried out three times a week and for 8wks. Sarcopenic measurements, such as muscle mass(ASMI), strength(HS), gait speed(GS) and Barthel Index(BI), were collected at baseline and after the 8-week intervention.
Results: Within the groups, there were no significant difference in ASMI, HS and BI, excepting GS with a significant decrease in C group; There were significant increase in HS, GS and BI in both M and R group, whereas the ASMI had a slightly improvement with no significant difference; All four indicators had significant increase in MR group. Between the groups, there were significant increase of GS in M group, and HS, GS,BI in R group, and all four indicators in MR group compared with C group; There were also significant increase in all four indicators



in MR group compared with M group; Interestingly, just the BI had a significant increase in MR group compared with R group.

Conclusions: The combination of Chinese Massage and resistance exercise had a better beneficial effect than the using of CM or RE alone on physical function measured by gait speed, muscle mass and strength in Sarcopenic man, which can promote the activities of daily living.

5-03

Independent and combined effect of home-based resistance training and protein supplementation on muscle strength and physical function in dynapenic community-dwelling elderly with low protein intake: a randomized pilot study

Alessandra de C. Bastone[1], Luciana N. Nobre[2], Dayane D. L. Santos[1], Iramaya F. Rosa[1], Michelle D. Alves[2], Lunna H. T. Barbosa[2], Rômulo A. Gandra[1]

[1]Physical Therapy Department, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Minas Gerais, Brazil, [2]Nutrition Department, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Minas Gerais, Brazil

Background and aims: Dynapenia might be attributed to a combination of neural and muscle factors, and has been associated with adverse health outcomes in the elderly. Adequate dietary protein intake in combination with exercise, especially resistance training, is considered optimal for maintain or improve muscle function. Therefore, the aims of this study were to evaluate the effect of resistance training and protein supplementation, alone or in combination, on muscle strength and physical function in dynapenic community-dwelling elderly with low protein intake.

Methods: Forty-five elderly (≥60 years), with low handgrip strength (men <30 Kg and women <20 Kg), and low protein intake (<1.0 g/Kg body weight/day), were randomly assigned to one of three groups: resistance training (RT; *n*=15), protein supplementation (PS; *n* = 15), or resistance training and protein supplementation (RTPS; *n* = 15). Muscle strength was assessed as handgrip strength and physical function using gait speed, and "timed up and go" and "sit to stand" tests. The RT group attended a home-based progressive resistance training program three times a week, and the PS group ingested 40g of a protein mixture once a day for three months. The RTPS group associated both interventions.

Results: The intra-group analysis showed that the RT group (*n*=13; 77.39 ± 4.05 years) and the RTPS group (*n*=13; 75.31 ± 7.79 years) demonstrated significant improvements in handgrip strength and in all three physical function measures, whereas the PS group (*n*=14; 77.57 ± 5.03 years) showed a significant increase only in gait speed. The inter-group analysis showed no difference in the improvements demonstrated by the RT and RTPS groups, neither in the improvement in gait speed showed by the three groups.

Conclusions: Resistance training improved muscle strength and physical function in dynapenic community-dwelling elderly with low protein intake. The association with protein supplementation showed no additional benefit.

5-04

Benefits of an exercise program for the elderly aged 80 years and older: A preliminary study

Rita Paixão[1], Pedro Lopes, Maria Teresa Tomás[1,2]

[1]Physiotherapy Department, ESTeSL - Lisbon Higher School on Health Technology, Lisbon, Portugal, [2]CIPER - Interdisiplinary Centre for the Study of Human Movement, Lisbon University, Lisbon, Portugal

Background: Over the last decades the world elderly population has increased exponentially: from 2000 to 2050 people over 60 will double and those over 80 will quadruple. Loss of independence occurs as people age and is due to mobility restrictions, frailty, decreased functional fitness and cognitive abilities. Evidence has shown that appropriate programs and policies can keep older adults healthier and independent over time.

This study aimed to determine the effects of a 6-week exercise program on body composition and functional fitness on a group of community-dwelling adults aged 80 years and older.
Method: 11 subjects (five male and six female), aged from 80-90 years, were selected from two community centres in Lisbon. Body composition and functional fitness were assessed at baseline and follow-up. Subjects performed aerobic, resistance, proprioceptive and flexibility exercises three times a week (once presential and twice home-based) for six weeks. The outcome variables were body composition (weight, BMI, abdominal, waist and hip circumference, waist-to-hip ratio, body fat and body lean percentage), functional fitness (aerobic capacity, agility and upper and lower-body strength, flexibility and grip strength).
Results: There were significant changes in waist circumference ($p = 0{,}029$), waist-to-hip ratio ($p = 0{,}041$), body fat percentage ($p = 0{,}026$) and body lean percentage ($p = 0{,}021$). No significant changes were found in the other parameters assessed, although individual analysis of results shows improvement for most of the participants.
Conclusion: Results of this preliminary study suggest that a 6-week exercise program may enhance body composition in the elderly aged 80 years and older. Funcional fitness parameters may need a more prolonged program consisting of two presential sessions in order to enhance adherence and results, despite increments for most of the participants, in order to achieve a statistical significance.

5-05

Effects of protein supplementation in obese sarcopenic women

Rosa Sammarco[1], Maurizio Marra[1], Marialuisa Di Guglielmo[1], Marianna Naccarato[1], Franco Contaldo[1,2], Fabrizio Pasanisi[1,2]
[1]Department of Clinical Medicine and Surgery Federico II University Hospital, [2]Interuniversity Centre for Obesity and Eating Disorders, (CISRO), Naples, Italy

Backgrounds and aims: Sarcopenic Obesity (SO) is usually defined as the combination of reduced fat free mass (FFM) with fat mass excess. Aim of this study was to evaluate the effect of two nutritional programs with different modulation of protein in females with SO.
Methods: 18 women, age 41-74 years, were studied during a 4 months hypocaloric diet. Obesity was diagnosed when fat mass $>35\%$ and sarcopenia was defined when FFM was $<90\%$ of the subject's ideal value. Patients were randomly assigned to different nutritional interventions: A) Conventional hypocaloric diet and B) hypocaloric high-protein diet (1.2-1.4 g/kg BW /day with 15 g/day of protein supplement). Resting energy expenditure (REE) was evaluated with indirect calorimetry, body composition with BIA, functional assessment by Handgrip test and Short Physical Performance Battery (SPPB) and quality of life by SF-36 questionnaire.
Results: Anthropometric measurements and body composition of the two groups of women showed not significant differences for age, weight, BMI, FFM and fat mass at entry. Weight decreased by 4 kg ($p<0.05$) in both groups whereas REE did not significantly change, even after correction for FFM, after 4 months of dietary treatment. Women with hypocaloric high-protein diet preserved FFM compared to conventional low-calorie diet (A vs B= -1.3 vs -0.5 kg, $p<0.05$). Muscle strength significantly improved in the group with protein supplementation (B: +1.6 kg); SPPB and SF-36 test scores did not change in both groups.
Conclusion: In our study, obese women with high-protein diet showed an increase in muscle strength after 4 months of high-protein diet. Dietary protein enrichment may represent a protection from sarcopenia risk following conventional hypocaloric diets. Further studies are required in larger groups to assess the relationship between dietary protein supplementation and increased lean body mass.

5-06

Multinuclear NMR Spectroscopic biomarkers for energy metabolism characterization in aging skeletal muscle

Harmen Reyngoudt[1,2], Benjamin Marty[1,2], Pierre-Yves Baudin[3], Noura Azzabou[1,2], Pierre G. Carlier[1,2]
[1]NMR Laboratory, Institute of Myology, Paris, France, [2]CEA/I2BM/MIRCen, Paris, France, [3]Consultants for Research in Imaging and Spectroscopy, Tournai, Belgium

The molecular mechanisms in the pathophysiology of sarcopenia are still widely unknown. Nuclear magnetic resonance spectroscopy (NMRS) enables to non-invasively monitor metabolic alterations in skeletal and cardiac muscle in vivo. While 31P-NMRS evaluates phosphate metabolism and pH, 1H-NMRS measurements gives an idea about the lipid composition. Both methods give specific information but can, however, be used complementarily. Phosphate metabolite changes in disease include a decrease in the phosphocreatine to ATP ratio which is a marker for healthy muscle tissue; and an augmentation of phosphodiesters reflecting altered rates of membrane turnover. These approaches have been performed in recent years in normal ageing populations. A correlation between PDE and age, an increase in lipid content and a prolonged PCr recovery have been observed in ageing subjects.
NMRS sequences were performed with dedicated sequences on standard clinical whole-body MRI scanners. A standard 31P-NMRS sequence, used in clinical routine, takes only around 5 minutes to acquire and can easily be added to the imaging protocol.
In the present study, we present 31P-NMRS results of a cohort of 100 healthy subjects covering two different age groups: young (23-33 years of age) and old (73-85 years of age). The substantial difference in age between these two categories will really enable us to establish the effects of age on the energy metabolism, as obtained by 31P-NMRS. These patients have also undergone additional quantitative NMRI imaging, including T2 mapping and fat fraction mapping, reflecting muscle water T2 and muscle fatty infiltration, respectively. Correlations between spectroscopic and imaging outcome measures will be performed. The combination of 31P-NMRS and quantitative NMRI imaging leads to a multi-parametric evaluation of individual subjects.

5-07

Leukocyte telomere length is associated with lean mass: Data from the Berlin Aging Study-II (BASE-II)

Antje Meyer[1], Bastian Salewsky[2], Elisabeth Steinhagen-Thiessen[1], Kristina Norman[1], Ilja Demuth[1]

[1]Research Group on Geriatrics, Charité-Universitätsmedizin Berlin, Berlin, Germany, [2]Institute of Medical and Human Genetics, Charité-Universitätsmedizin Berlin, Berlin, Germany

Background: Age-related loss of muscle mass is an increasing problem in in our aging society, affecting physical ability. Telomere length has been recognized as a marker of biological age on the population level.
Objective: Here we evaluated the rarely examined relationship between lean mass and relative leukocyte telomere length (rLTL) in 1,398 participants of the Berlin Aging Study II (mean age 68.2 ± 3.7 years, 49.6% men).
Methods: The determination of rLTL was carried out by real time PCR. Lean mass was estimated by dual X-ray absorptiometry and examined as leg lean mass (LLM), appendicular lean mass (ALM), and ALM corrected for body mass index (ALMBMI).
Results: Highly significant correlations ($p<0.001$) of rLTL and ALM ($r = 0.248$), ALMBMI ($r = 0.254$), and LLM ($r = 0.263$) were found. Associations remained significant in linear models adjusted for age, gender, BMI, low-grade inflammation, life style factors and morbidities: ALM ($\beta = 0.844$, $p = 0.009$), ALMBMI ($\beta = 0.032$, $p = 0.011$), and LLM ($\beta = 0.967$, $p<0.001$). Shorter rLTL, advanced age, female sex, sedentary lifestyle and elevated CRP level were associated with lower lean mass.
Conclusion: Short telomeres were associated with low lean mass. Our results indicate that rLTL may be a risk factor for loss of lean mass. To confirm the association between telomere attrition and loss of LLM and ALMBMI, which are highly relevant for physical ability, further research should examine this subject in a longitudinal context.
Funding: This study was supported by the German Federal Ministry of Education and Research under grant number 16SV5536K.

5-08

Dietary carotenoid intakes are associated with skeletal muscle mass but not grip strength in women

Ailsa A. Welch[1], Eirini Kelaiditi[1], Amy Jennings[2], Claire J. Steves[3], Tim Spector[3], Alexander MacGregor[4]
[1]Department of Public Health & Primary Care, Norwich Medical School, Norwich, UK, [2]Department of Nutrition, Norwich Medical School, Norwich, UK, [3]Deptartment of Twin Research & Genetic Epidemiology, King's College London, UK, [4]Department of Medicine, Norwich Medical School, Norwich, UK

Abstract: Background: Although age-related loss of skeletal muscle mass, strength and function are risk factors for sarcopenia, the role of micronutrients in preventing loss of skeletal muscle mass and function has been under investigated. Dietary carotenoids could moderate the mechanisms for loss of skeletal muscle mass and strength by their antioxidant activity thereby reducing chronic low grade inflammation, which is a risk factor for sarcopenia. Therefore, this study investigated cross-sectional associations between skeletal muscle mass and hand grip strength and specific dietary carotenoid intakes free-living women.
Methods: This study included 2570 women aged 18-79 years with fat free mass measured using dual-energy X-ray absorptiometry and hand grip strength measured using the Jamar hand grip dynamometer. Dietary carotenoids were calculated using a Food Frequency Questionnaire with a newly developed nutrient database. The fat free mass index (FFMI) (fat free mass in kg/height2) and grip strength were calculated according to quintile of individual carotenoids, using multivariate regression. Adjustments were made for age, physical activity, smoking habit, energy intake, HRT and menopausal status, as well as fat free mass for FFMI, and height for grip strength.
Results: Mean intakes of total carotene were 3,448 μg/d, of lycopene were 1,347 μg/d, of lutein were 2183 μg/d and of ß-cryptoxanthin were 200 μg/d. Mean (SD) FFMI was 15.0 (1.71) kg/m2. Significant positive associations were found between FFMI and carotenoids with extreme quintile differences of 0.26 kg/m2 for total carotene (P trend=0.003), of 0.23 kg/m2 for lycopene (P trend=0.027), of 0.19 kg/m2 for lutein (P trend=0.08), of 0.28 kg/m2 for ß-cryptoxanthin (P trend=0.014), in the fully adjusted models. No association was found between grip strength and intake of any of the carotenoids.
Conclusions: The positive and significant associations found between intakes of dietary carotenoids and skeletal muscle mass suggests that further investigation in intervention trials is warranted.

5-09

Clinical sarcopenia prediction score among older adults: results from Taichung community health study for elders

Yen-Ting Chen[1,2], Chia-ing Li[3], Tsai-Chung Li[4,5,6], Chih-Hsueh Lin[1,7], Chiu-Shong Liu[1,3,7], Wen-yuan Lin[1,7], Cheng-Chieh Lin[1,3,4,7,8]
[1]Department of Family Medicine, China Medical University & Hospital, Taichung, Taiwan, [2]Department of Public Health, College of Public Health, China Medical University & Hospital, Taichung, Taiwan, [3]Medical Research, China Medical University & Hospital, Taichung, Taiwan, [4]Institute of Health Care Administration, College of Public Health, China Medical University & Hospital, Taichung, Taiwan, [5]Biostatistics Center, China Medical University & Hospital, Taichung, Taiwan, [6]Graduate Institute of Biostatistics & Chinese Medicine Science, China Medical University & Hospital, Taichung, Taiwan, [7]Department of Family Medicine, College of Medicine, China Medical University & Hospital, Taichung, Taiwan, [8]Department of Healthcare Administration, College of Health Science, Asia University, Taichung, Taiwan

Background and aims: Sarcopenia is associated with adverse health outcomes, such as fall, disability, functional decline, and mortality, and became an important clinical issue in geriatric population. However, radiology equipment like dual-energy X-ray absorptiometry (DXA), bioimpedance analysis (BIA), computed tomography (CT) or magnetic resonance imaging (MRI) is necessary to estimate the volume of muscle mass according to current consensus definition of sarcopenia, and that makes large-scale screening difficult. This study aimed to develop a sarcopenic

prediction score that easily available in clinical outpatient services and able to arrange large-scale screening.

Methods: This population-based, cross-sectional study recruited 865 participants aged 65 years or older. Sarcopenia was defined according to the Asian Working Group for Sarcopenia (AWGS) consensus criteria, and lean soft tissue mass was determined by DXA. Medical records gathered at the outpatient clinic of a tertiary hospital in Taiwan were reviewed retrospectively, which included demographics, body measurement components, physical performance demographics, vital signs, and biological parameters. Multivariate logistic regression analyses and receiver operating characteristic curves were used for model development.

Results: The Clinical Sarcopenia Prediction Score was determined by using five predictors identified by multivariate logistic regression analysis. The predictors include age $>$ 80 years old, body mass index (BMI) $<$ 24, thigh circumference to waist circumference ratio $<$ 0.5, timed up-and-go test $>$ 10 seconds, and poor grip according to AWGS criteria. The area under the receiver operating characteristic curve used to predict sarcopenia was 82.6% (95% confidence interval 78.6%–86.7%).

Conclusions: The Clinical Sarcopenia Prediction Score, consists of five predictors, for the estimation of sarcopenia in older adults showed a relatively high accuracy. This score, based on age, body measurement components, and physical performance demographics, is easily performed among clinic outpatient services, and might be useful in large-scale screening for sarcopenic population.

5-10

Reduced muscle mass and loss of response to anti-TNF treatment in inflammatory bowel disease

Darcy Q. Holt[1,2,3], Boyd J. Strauss[3], Poornima Varma[1], Gregory T. Moore[1,3]

[1]Gastroenterology and Hepatology Unit, [2]Clinical Nutrition and Metabolism Unit, [3]Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia

Introduction: Inflammatory bowel disease (IBD) is associated with malnutrition, lower bone mineral density, lower body mass index and lower fat-free mass. There are limited data regarding the relationship between body composition and response to therapy in IBD.

Methods: A retrospective audit was conducted of all patients with IBD receiving anti-TNF therapy at our centre, in Melbourne, Australia. Patients with an accurate date for TNF commencement, an abdominal MRI or CT scan within 12 months of treatment induction, and adequate correspondence to determine end-points were included. Cross-sectional images were analysed using previously described techniques.[1] Loss of response (LOR) was defined by an admission or surgery post-induction, escalation of TNF dose or immunosuppressants for clinical LOR, emergence of a new fistula or rising Crohn's Disease Activity Index $>$150 (CDAI).

Results: 34 patients had Crohn's Disease, 1 had ulcerative colitis. 9 patients received adalimumab induction therapy, 26 received infliximab. 14 patients (45%) experienced LOR, with a median LOR-free survival of 1100 days. Patients in the lowest quartile of L3 skeletal muscle area were significantly more likely to have LOR, with a median LOR-free survival of 386.5 days compared with 1219 in the highest quartile ($p = 0.002$). Disease duration prior to anti-TNF therapy did not differ between groups ($p = 0.863$). Patients in the lowest quartile of visceral adipose tissue area had a median LOR-free survival of 636 days compared with 1100 days in the median 50% ($p = 0.046$). The median time to LOR was shorter for the lowest quartile of skeletal muscle area than for the lowest quartile of body weight or visceral adipose tissue area. CDAI, C-reactive protein, haemoglobin and albumin were not predictors of LOR. There was no difference in LOR-free survival between patients on weight-based dosing for infliximab or fixed-dose adalimumab. There was no correlation between weight and LOR in adalimumab-treated patients. Reduced muscle mass was prevalent: 100% of male subjects and 39% of female subjects had a CT-estimated ASMI more than a standard deviation below the young adult mean.

Conclusion*:* Reduced muscle mass is prevalent in patients receiving anti-TNF therapy for Crohn's Disease, especially in males. Both reduced skeletal muscle mass and visceral adipose tissue area are associated with earlier loss of response to anti-TNF treatment.

Reference

1. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;**33**:997–1006. Doi: 10.1139/H08-075.

5-11

Individualized moderate aerobic exercise improves physical endurance and prevents weight loss in collagen-induced arthritis

Rafaela C. do Espírito Santo[1,2,], Paulo V.G. Alabarse[1,2], Vivian O.N. Teixeira[1,2], Jordana M.S. Silva[1,2], Eduarda C. Freitas[1,2], Lidiane I. Filippin[1,3], Priscila S. Lora[1,4], Ricardo M. Xavier[1,2]

[1]Laboratório de Doenças Autoimunes, HCPA, Brazil, [2]Faculdade de Medicina, UFRGS, Brazil, [3]La Salle, Brazil, [4]UNISINOS, Brazil

Background: Rheumatoid arthritis (RA) patients suffer from joint pain and decreased physical capacity, muscle wasting and fatigue. Physical exercise can improve these features, but the most appropriate training program is unclear.

Aims: To evaluate physical endurance and weight changes in collagen-induced arthritis mice (CIA) submitted to an individualized moderate aerobic exercise in inclined treadmill.

Methods: Male DBA1/J mice were randomly divided into 3 groups: nonarthritic control with exercise (CO-EXE, n = 4), CIA with exercise (CIA-EXE, n = 5) and CIA not exercised (CIA, n = 4). Endurance exercise performance test was analyzed in all groups prior to booster injection each 15 days after protocol started. CO-EXE and CIA-EXE were

submitted to training on an inclined treadmill ($\theta = 5°$), 60 minutes a day, 5 days per week for 6 weeks at 60% of their own endurance velocity that induced fatigue. Variables analyzed were disease score, alteration of body weight (g) and fatigue velocity (m/min) as measure of exercise performance. Statistical significance was considered $p<0.05$.

Results: Clinical score of arthritis did not differ between CIA-EXE and CIA. Body weight was statistically significant different at week 6 when compared CIA (0.9 ± 0.7g) with CO-EXE (3.9 ± 0.4g) and CIA-EXE (2.6 ± 1.6g). Fatigue velocity was statistically significant different at 4 (CIA: 21 ± 3m/min; CIA-EXE: 28 ± 4m/min; CO-EXE: 35 ± 2m/min) and 6 weeks (CIA: 21 ± 5m/min; CIA-EXE: 28 ± 4m/min; CO-EXE: 35 ± 2m/min) of experiment, demonstrating that CO-EXE and CIA had, respectively, the highest and the lowest fatigue velocity.

Conclusion: individualized moderate aerobic exercise in inclined treadmill appears as an interesting intervention in RA to treat decreased physical endurance without altered disease score. Individualized moderate aerobic exercise in inclined treadmill had a positive impact on CIA exercise endurance, although more limited than in non-arthritic controls.

FINANCIAL SUPPORT: CAPES, CNPq, FAPERGS, FIPE-HCPA.

5-12

Zinc alpha 2 glicoprotein (ZAG) increases lipolysis through a catalase-like effect in isolated adipocyte from cardiac cachectic patients

Stefano Tedeschi, Loredana Banti, Cinzia Galizia, Diana Poli, Elisabetta Pilotti, Simona Bianco, Gallia Graiani, Stefano Perlini, Rossana Rocco, Aderville Cabassi

Azienda Unità Sanitaria Locale di Parma, Parma, Italy

Background: Mechanisms of increased lipolysis in cardiac cachexia are not completely understood and probably involve oxidative stress. ZAG represents a marker of cachexia as well as a lipolysis stimulating factor. Hydrogen peroxide (H2O2) exerts insulin-like effect reducing lipolysis. Little is known on the interaction between oxidative stress and ZAG. Aim of the study was the evaluation of this interaction in adipose tissue from heart failure patients with (HFCX) or without cachexia (HF).

Methods: Thirteen patients (3 HFCX; 4 HF and 6 controls,CTR) underwent clinical and biochemical evaluation and were subjected to subcutaneous bioptic sampling. Adipose bioptic samples were processed to obtain freshly isolated mature adipocytes and basal glycerol release measured after 1,2 and 18 hours of medium (DMEM) incubation. A set of isolated adipocytes was first seeded in well culture plate and H2O2 measured in the medium every 30 minutes with Amplex Red flurometric method for 2h with or not recombinant ZAG (25 μg/ml). In another set of isolated adipocyte, glycerol release in the medium was measured after incubation with increasing H202 concentration (10-5-10-4M) and/or with norepinephrine (NE,10-5M), in presence or absence of ZAG (25 μg/ml) and/or catalase (from bovine liver, 100 U/ml).

Results: ZAG reduced H2O2 levels in all groups of patients after 2h of incubation with greatest reduction in HFCX where a significant lowering was evident after 1h incubation. Adipocytes from HFCX showed higher glycerol levels in response to NE compared to other groups. ZAG coincubation with NE increased glycerol release in HFCX (+71%). ZAG and H2O2 combination induced a reduction of glycerol levels after NE stimulation especially in HFCX. Catalase alone increased glycerol levels especially in HFCX.

Conclusion: ZAG lowered H2O2 release by adipocytes especially in HFCX. This could account for the facilitating effect of ZAG on NE-induced lipolysis in cardiac cachexia.

Govoni metti Histology and Embriology Unit SBIBIT Universita di Parma

5-13

Associations of pre-ESRD serum albumin levels and changes over time with mortality in the first 3 months of transition to dialysis: A transition of care in CKD study

Amanda Tortorici[1], Connie Rhee[1], Elani Streja[1], Melissa Soohoo[1], Jennie Jing[1], Danh Nguyen[1], Keith Norris[2], Joel D Kopple[2], Csaba Kovesdy[3], Kamyar Kalantar-Zadeh[1]

[1]UC Irvine,[2] UCLA, [3]Memphis VA Medical Center, USA

Background: Prior studies have shown that higher albumin (Alb) levels are a predictor of survival, but little is known about the association of Alb in the pre-ESRD prelude period with post-ESRD mortality outcomes. We hypothesized that higher Alb levels and a trajectory of increasing Alb in the final months of pre-ESRD period are associated with better post-ESRD outcomes in the first 3 months after transitioning to dialysis.

Methods: We investigated 18,702 US veterans who transitioned to dialysis between 9/2007-11/2011 with available serum Alb measurements within the 2 year prelude period (prior to transition to dialysis). We examined the association of 6 month averaged Alb and change in Alb over 2 years in the prelude period as a continuous predictor of all-cause mortality in the first 3 months post-ESRD, using restricted cubic splines and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region. We also adjusted for baseline Alb prior to transition in Alb slope models.

Results: Patients were a mean ± SD age of 68 ± 11 yrs, 2% female, 30% African-American, and 50% had diabetes as their primary cause of ESRD. There was an inverse linear association between Alb and 3-mo mortality risk, where patients with Alb >3.5 had a lower risk of mortality (Figure A). Also >75% of patients had a decreasing Alb in the 2 years prior to transition. Patients with a decline of less than 0.1 g/dL/year, no change, or an increase in Alb had lower risk of mortality (Figure B).

Conclusions: Greater and non-declining Alb levels in the pre-ESRD period were associated with lower post-ESRD mortality risk. Additional studies are needed to examine the pathophysiologic mechanisms underlying these associations.

5-14

Change in serum albumin and mortality risk in incident hemodialysis patients

Rieko Eriguchi[1], Connie M. Rhee[1], Yoshitsugu Obi[1], Elani Streja[1], Tae Hee Kim[1], Steven M. Brunelli[2], Joline L.T. Chen[1], Anna Mathew[3], Rajnish Mehrotra[4], Csaba P. Kovesdy[5], Kamyar Kalantar-Zadeh[1]

[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, Orange, CA, [2]DaVita Clinical Research, Minneapolis, MN, USA, [3]Hofstra North Shore-LIJ School of Medicine Hempstead, NY, USA, [4]Harborview Medical Center, University of Washington, Seattle, WA, USA, [5]University of Tennessee Health Science Center, Memphis, TN, USA

Background: Previous studies have shown that lower serum albumin levels, an important marker of nutrition and inflammation, are associated with higher mortality in hemodialysis (HD) patients. However, little is known about (1) the patient characteristics that predict change in serum albumin after HD initiation, and (2) the association between change in serum albumin and mortality.
Methods: Among 62,973 incident HD patients receiving care from a large US dialysis organization from 1/2007-12/2011, we examined variables that predicted increase in albumin in the first year of dialysis (>0g/dL/year) using logistic regression models. We also examined the association between change in serum albumin over the first year of HD and all-cause mortality.
Results: Patients were 62 ± 15 years old, among whom 44% were female, 34% were African-American, and 48% were diabetic. The mean change in albumin during the first year of HD was 0.27 ± 0.42g/dL/year. Asian and Hispanic race/ethnicity, as well as higher pre-HD systolic blood pressure, nPCR, and serum creatinine were associated with an increase in albumin. In contrast, older age; female gender; higher spKt/V, post-HD body weight, hemoglobin, calcium, phosphorus, ALP, iron saturation, and baseline albumin; and history of chronic heart failure and cancer were associated with decline in albumin. Patients who had a decline in albumin had a 2-fold higher mortality risk compared to those who had an increase albumin after adjustment for case-mix and laboratory tests: HR 2.02 (95%CI, 1.95-2.10; $p<0.001$). There was an inverse linear relationship between change in albumin in the first year of dialysis and subsequent mortality in cubic spline models adjusted for baseline albumin (Figure).
Conclusions: In incident HD patients, decline in serum albumin over the first year of dialysis therapy is associated with higher mortality risk.

5-15

Testosterone levels and mortality in a large U.S. dialysis cohort

Connie Rhee[1], Jerry Yu[1], Vanessa Ravel[1], Elani Streja[1], Rajnish Mehrotra[2], Matthew Rivara[2], Steven Brunelli[3], Csaba Kovesdy[4], Kamyar Kalantar-Zadeh[1]
[1]UC Irvine, Orange, CA, USA, [2]University of Washington, Seattle, WA, USA, [3]DaVita Clinical Research, Minneapolis, MN, USA, [4]University of Tennessee Health Science Center, Memphis, TN, USA

Background: In the general population, low circulating testosterone levels may lead to various adverse outcomes including higher risk of sarcopenia, cardiovascular disease, and mortality. Sarcopenia and cardiovascular disease are disproportionately prevalent in hemodialysis patients, and have been associated with higher death risk in this population. We sought to examine the association between testosterone levels and mortality in a national cohort of male dialysis patients in the US.
Methods: We examined a 5-year cohort (1/2007-12/2011) of male hemodialysis and peritoneal dialysis patients from a large US dialysis organization who underwent at least one or more total testosterone measurements. The association between baseline testosterone levels categorized as quintiles (0-<165, 165-<252, 252-<339, 339-<463, and ≥463ng/ml) and all-cause mortality were determined using Cox models with 3 hierarchical levels of adjustment: (1) Unadjusted (adjusted for quarter of study entry), (2) Case-mix (adjusted for unadjusted model covariates, age, sex, race/ethnicity, diabetes), and (3) Expanded case-mix models (adjusted for case-mix model covariates, duration of dialysis, cause of end-stage renal disease, dialysis access, congestive heart failure, atherosclerotic heart disease, serum albumin).
Results: Among 652 male dialysis patients, the mean ± SD and median (IQR) total testosterone levels were 323 ± 193 and 297 (190, 424) ng/ml, respectively, with a large proportion of patients with levels consistent with hypogonadism (defined as <231ng/dl) (Fig. 1A). Across all adjustment levels, we observe a graded association between higher testosterone and lower mortality risk (ref: 252-<339ng/dl): adjusted HRs (95% CI) 1.54 (0.88-2.70), 1.11 (0.61-2.01), 0.43 (0.21-0.89), and 0.40 (0.18-0.92) for testosterone levels of ≥463, 339-<463, 165-<252, 0-<165ng/ml) in expanded case-mix models (Fig. 1B).
Conclusion: Higher testosterone levels were associated with greater survival in male dialysis patients, independent of case-mix covariates. Further studies are needed to determine if loss of muscle mass and cardiovascular mechanisms underlie these associations, and if testosterone replacement ameliorates mortality risk in this population.

5-16

Low Basic Fibroblast Growth Factor (bFGF) levels are associated with cachexia in end stage renal disease patients

Rossana Rocco[1], Elena Cremaschi[1], Stefano Tedeschi[2], Pietro Coghi[1], Stefano Bianchi[3], Roberto Bigazzi[4], Giuseppe Regolisti[1], Enrico Fiaccadori[1], Paolo Govoni[5], Aderville Cabassi[1]
[1]Department of Clinical and Experimental Medicine, Cardiorenal Research Unit, Parma, Italy, [2]Cardiology Unit, Vaio Hospital, Azienda Sanitaria Locale Parma, Italy, [3]Nephrology Unit, PPOO Piombino, Cecina, Elba, USL 6 Livorno, Italy, [4]Nephrology and Dialysis Unit, Spedali Riuniti Livorno, Italy, [5]Department of Biomedical Science, S. Bi.Bi.T, University of Parma, Italy

Patients affected by end-stage renal disease (ESRD) can develop cachexia (ESRD-Cx). Fat loss mechanisms in uremic cachexia are still not completely understood. Fibroblast Growth Factors family include bFGF, whose effects on angiogenesis are well known; a new metabolic function of this factor has been suggested in promoting pre-adipocyte differentiation and potentially regulating adipose metabolism. Aim of this study was to investigate in ESRD patients with or without cachexia in comparison with healthy subjects (CTR) the relationship between bFGF and lipolysis markers.
Fifty-seven ESRD patients (age70 sd 13y) referred to Clinica Medica Nefrologia of Parma Hospital and to Nephrology Unit of Livorno

Hospital were included in the study. Patients were free from clinical or laboratory signs of acute infection, primary cachectic states and diabetes mellitus. Fourteen age-matched (age 72 sd 9y) CTR were also recruited. Basal laboratory tests, plasma neurohormonal and inflammatory markers including bFGF, TNF-alpha, IL-6,-8,-10 (Bio-Plex Pro Human Cytokine Plex Immunoassay), non-esterified fatty acid (NEFA) were measured. Forty-two% ESRD were on conservative treatment whereas 58% on hemodialysis. Patients were divided in ESRD-Cx (n=22,dry weight loss more than 5% in 6 months) and ESRD-nCx (n=35,without cachexia).

ESRD-Cx had lower albumin and prealbumin levels and higher NEFA vs ESRD-nCx. Higher levels of IL-6 were observed in ESRD-Cx as compared to ESRD-nCx and CTR. Basic FGF levels were significantly reduced in ESRD-Cx vs nCx group but higher vs CTR. In ESRD-Cx an inverse correlation was found between bFGF and NEFA (R2 0.20, p=0.03).

A significant lowering of bFGF level was associated to cachexia development in ESRD-Cx patients with a negative correlation between bFGF and NEFA. This observation could reflect a reduction of body fat mass with a lower secretion of bFGF by adipocyte or an increased lipolysis linked to a reduction in insulin sensitivity induced by low bFGF level in cachectic patient.

5-17

Insulin resistance is a key mediator of sarcopenia in advanced kidney disease

Serpil M. Deger[1,3], Jennifer R. Hewlett[1,2], Cindy Booker[1,3], Charles D. Ellis[1], Feng Sha[1], Naji N. Abumrad[4], T. Alp Ikizler[1,3]

[1]Vanderbilt University Medical Center, Division of Nephrology Nashville, Tennessee, USA, [2]Florida Atlantic University Charles E. Schmidt College of Medicine, Boca Raton, Florida, USA, [3]CSRD&D, Veterans Administration Tennessee Valley Healthcare System, Nashville, TN, USA, [4]Vanderbilt University Medical Center, Department of Surgery, Nashville, Tennessee, USA

Background: Protein energy wasting (PEW) and sarcopenia are hallmarks of chronic disease states. Patients with advanced kidney disease are especially prone to these abnormalities. Insulin is a potent anabolic hormone that regulates macronutrient homeostasis. The ability of insulin to stimulate glucose utilization is impaired in kidney disease patients but there are limited studies examining its effects on protein metabolism. We aimed to investigate the association between protein turnover and insulin sensitivity among 15 maintenance hemodialysis (MHD) patients and 15 matched controls using hyperinsulinemic euglycemic clamp (HEGC) followed by hyperinsulinemic euglycemic euaminoacidemic clamp (HEAC) technique combined with isotope tracer technique to assess whole body protein turnover kinetics.

Results: At baseline, whole body protein synthesis, breakdown and net balance rates were not significantly different between study groups (p=0.8). Net whole body protein balance was negative in both groups. During HEGC, both protein synthesis and breakdown rates decreased significantly in both groups (p=0.03 for MHD, $p<0.001$ for control). Net protein balance became more negative in MHD patients (p=0.03), whereas this change was not statistically significant in controls (p=0.07). During HEAC, protein synthesis rates significantly decreased in both groups (p=0.01 and p=0.05); however the change was numerically less in MHD patients. Whole body protein breakdown rates did not significantly change in either group ($p > 0.1$ for both). The net balance during HEAC became positive in both groups with significantly more increase in control subjects ($p<0.001$).

Conclusion: Patients with advanced kidney disease have impaired response to exogenous insulin administration. The impaired response is observed during both substrate depletion state (HEGC) and repletion of amino acids (HEAC) suggesting both anti-catabolic and potentially anabolic effects of insulin are impaired in the setting of advanced kidney disease. Further studies at the tissue level could help develop more effective interventions to prevent or treat PEW in MHD patients.

5-18

Exercise training improves systemic inflammatory markers in cancer cachectic patients

Emidio Matos-Neto[1], Joanna D.C.C. Lima[1], Raquel G.Figuêredo[1], Katrin Radloff[1]; Rodrigo X. Neves[1], Júlio Serrão[2], Flávio Tokeshi[3], Paulo S.M.Alcântara[3], José P. Otoch[3], Marília Seelaender[1]

[1]Cancer Metabolism Research Group, University of São Paulo, [2]School of Physical Education and Sport – USP, [3]University Hospital (São Paulo, Brazil)

Background: Inflammatory mediators play an important role in the development of cachexia, described as a chronic inflammatory syndrome. In contrast, exercise training has been suggested as an efficient anti-inflammatory strategy.

Aim: To evaluate, whether an exercise training protocol is effective in improving inflammatory markers in cachectic cancer patients.

Methods: patients with gastrointestinal carcinoma were enrolled in the following groups: Weight-stable cancer (WSC, n = 11), and cachectic cancer (CC, n = 5); and control (patients with umbilical hernia, Control, n = 11), submitted, after obtaining informed consent, to an aerobic exercise protocol, consisting of 6 weeks of walking on a treadmill with increasing volume and intensity, assessed individually after a submaximal test, to estimate each volunteer's VO_{2max}. Plasma analytes were quantified with Luminex xMAP technology.

Results: At the end of the six weeks, patients of all groups increased significantly their estimated VO_{2max} (Control: 24.49 ± 1.71 ml.kg.min, WSC: 16.23 ± 5.91 ml.kg.min and CC: 21.10 ± 4.96 ml.kg.min) when compared with baseline values (Control: 8.25 ± 2.43 ml.kg.min, WSC: 7.23 ± 3.37 ml.kg.min and CC: 5.28 ± 3.22 ml.kg.min), and decreased significantly the resting heart rate (Control: 76.4 ± 5.78 bpm, WSC: 74 ± 2.94 bpm and CC: 70.33 ± 5.17 bpm), compared to the first week (Control: 80.8 ± 3.59 bpm, WSC: 83 ± 2.52 bpm and CC: 81.60 ± 4.44 bpm). Plasma IL-6 and IL-7 were significantly higher in CC at baseline in relation to Control and WSC (Control: 3.47 ± 5.21 mg/mL; WSC: 3.54 ± 4.04 mg/mL; CC: 62.5 ± 130.45 mg/mL and Control: 1.0 ± 1.4 mg/mL; WSC: 0.9 ± 0.75 mg/mL; CC: 5.28 ± 7.74 mg/

mL, respectively) ($p<0.01$). The inflammatory cytokine content decreased continuously towards week 6, for both WSC and CC, when no statistical difference was found among the groups. IL-10 and IL-8 plasma content increased continuously over the exercise protocol, with significant differences at week 6 (Control: 1.13 ± 0.92; WSC: 2.3 ± 1.77; CC: 4.53 ± 4.94 mg/mL and Control: 20.99 ± 29.56; WSC: 26.64 ± 16.98; CC: 40.27 ± 38.49 mg/mL, respectively) ($p<0.01$) in relation to the 1st week (Control: 0.76 ± 0.61; WSC: 1.57 ± 1.55; CC: 1.48 ± 1.29 mg/mL and Control: 17.12 ± 27.02; WSC: 20.62 ± 13.32; CC: 14.20 ± 6.06 mg/mL, respectively) ($p>0.05$).

Conclusions: Aerobic exercise training specially adapted for cachectic cancer patients is effective in reducing pro-inflammatory markers and increasing anti-inflammatory cytokine expression, improving cardiovascular function and causing weight loss cessation.

5-19

Investigating the role of body mass index (BMI) and serum albumin in the conversion ratio (CR) of other strong opioids to transdermal fentanyl (TDF) in cancer patients

Angelique Wong[1], Akhila Reddy[1], Jimin Wu[2], Diane Liu[2], Eduardo Bruera[1]

[1]Department of Palliative, Rehabilitation & Integrative Medicine, UT MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Biostatistics, UT MD Anderson Cancer Center, Houston, TX, USA

Background/aims: Cancer patients frequently undergo OR from other opioids to TDF. Recent reports suggest that BMI and albumin may play a role in the effectiveness of TDF. The accurate CR for OR from other opioids to TDF is unknown in patients with low BMI or albumin levels. Our aim was to compare the CR of morphine equivalent daily dose (MEDD) to TDF in cancer outpatients among different subsets of BMI.

Methods: We reviewed records of 22,532 consecutive patient visits at our Supportive Care Center in 2010-13 for OR to TDF. Data regarding symptoms and MEDD were collected in patients who returned for follow-up within 5 weeks. Linear regression analysis was used to estimate the CR between TDF dose and net MEDD (MEDD prior to OR minus MEDD of breakthrough opioid used along with TDF after OR).

Results: 129 patients underwent OR to TDF from other opioids. The mean age was 56 years, 59% male, and 88% had advanced cancer. There were no significant differences in patient characteristics, symptom scores, and reason for OR among patients with BMI of ≤25 (n=64) and > 25 (n = 65). In 101 patients with OR and no worsening of pain at follow-up, the median CR (range) from net MEDD to TDF mg/day was .01 (−0.02–0.04) and correlation of TDF dose to net MEDD was .77 (P<.0001). The CR was not significantly impacted by variables such as serum albumin and BMI. The median CR in groups with BMI <20, 20–25, ≤25, >25, 25-30, and >30 was 0.01 (Table 1.) with no significant difference among the groups. The CR of .01 suggests that MEDD of 100mg is equivalent to 1mg TDF/day or 40mcg/hour TDF patch (1000mcg/24hours).

Conclusions: The median CR from MEDD to TDF mg/day is .01 and did not vary a20ording to BMI or serum albumin level.

5-20

Comprehensive analysis of radiographic, clinical and inflammatory markers demonstrating the changes in lean muscle mass correlate with outcome in patients with metastatic pancreatic adenocarcinoma (mPDAC) who undergo taxane-based chemotherapy

Daniel H. Ahn[1], Chul Ahn[2], Veena Nagar[1], Anne M. Noonan[1], Matthew Farren[1], Gregory B. Lesinski [1], Michael Knopp[1], Tanios Bekaii-Saab[1]

[1]The Ohio State University Medical Center, Columbus, OH, USA, [2]The University of Texas Southwestern Medical Center, Dallas, TX, USA

Background: MPDAC is associated with a poor prognosis. The mechanisms of carcinogenesis in mPDAC are complex; involve multiple signaling pathways and inflammatory cytokines that may promote cachexia, a major cause of morbidity and mortality in mPDAC. The purpose of this study is to understand factors related to skeletal muscle changes, and its effect on outcomes in patients with mPDAC.

Methods: Patient and clinical data were obtained from a recently completed prospective clinical trial in mPDAC where all patients received first-line taxane-based chemotherapy. We examined changes in modified Glasgow prognostic score, neutrophil lymphocyte ratio, a 32-cytokine panel, weight, and skeletal muscle area (SMA), determined by validated methodology with computed tomography, at baseline and cycle 3. We defined > 6cm2 in SMA, correlating to 1kg of skeletal muscle gain (SMG), as significant. Univariate and multivariate Cox regression models were used to determine the association between laboratory, radiographic and clinical findings with progression free survival (PFS) and overall survival (OS).

Results: 66 evaluable patients were included. Independent of clinical response, a survival advantage was demonstrated in patients who experienced significant SMG (p = 0.023) and in patients with nominal SMG (p = 0.012). A nominal benefit in PFS was observed with SMG. Decreases in IFN-α (p = 0.024), IFN-γ (p = 0.001) and IL-6 (p = 0.042) were inversely significantly associated with SMG. A comprehensive analysis incorporating all relevant laboratory, radiographic and clinical assessments demonstrate a 4.62-month survival advantage in patients with favorable characteristics vs. those with poor prognostic factors (11.47 versus 6.84 months, p = 0.0029).

Conclusion: SMG or the reversal of cachexia confers an OS advantage in patients with mPDAC treated with taxane-based CT regardless of clinical response. A comprehensive assessment of SMA may help identify patients at greatest risk for muscle loss, which could predict for treatment response. This merits further investigation including in trials directed at reversing the process of cachexia.

5-21

Using computerized tomography for the assessment of skeletal muscle in clinical trials: Results from the Enobosarm trial

Carla M. Prado[1], Jingjie Xiao[1], Michael L. Hancock[2], Jeffrey Crawford[3], Richard J. Gralla[4], Mary Ann Johnston[2], Susan G. Small[2], Ryan Taylor[2], Mitchell S. Steiner[2], James T. Dalton[5]

[1]Department of Agricultural, Food and Nutritional Science, University of Alberta, AB, Canada, [2]GTx, Inc. Memphis, TN, USA, [3]Duke University Division of Medical Oncology, Durham, NC, USA, [4]Albert Einstein College of Medicine, Bronx, NY, USA, [5]University of Michigan, College of Pharmacy, Ann Arbor, MI, USA

Background and aims: Computerized tomography (CT) scans can be used for the secondary purpose of body composition analysis, providing direct assessment of skeletal muscle (SM). As a catabolic illness, a defining feature of cancer is muscle loss, an independent predictor of poorer outcomes. Here, we investigate the efficacy of an anabolic agent in promoting SM gain in patients with stage III or IV non-small cell lung cancer. Additionally, we explored the impact of SM gain ≥1kg as a previously suggested clinically meaningful cutpoint.
Methods: We used CT-assessed SM from participants enrolled in two Phase 3 trials of enobosarm, a nonsteroidal, selective androgen receptor modulator. Patients were randomized to placebo or enobosarm (3mg/day) at initiation of first-line platinum doublet chemotherapy (Power1 = platinum+taxane or Power2 = platinum +nontaxane) and continued through day-147. Change in SM is reported from baseline to day-84 and day-147.
Results: 83% of CT images available from tumor response assessment were exploitable for SM analysis. Enobosarm was associated with significant gain in SM. In Power1, median change in SM from baseline to day-84 differed ($p<0.0001$) between enobosarm (+0.5kg, n = 103) and placebo patients (-0.3kg, n=107) and was more pronounced at day-147 (+0.1kg and −0.8kg; $p<0.0001$). Similarly, in Power2, median change in SM from baseline to day-84 differed ($p = 0.03$) between enobosarm (+0.3kg, n = 101) and placebo patients (−0.2kg, n = 99) and was again more pronounced at day-147 (+0.5kg and −0.3kg; $p = 0.003$). The proportion of patients gaining ≥1kg SM in both trials was identical (27.5%).
Among all patients, a ≥1kg increase in SM was associated with longer median survival (+3.1 months, $p<0.01$) and meaningful improvements (≥10%) in stair climb power (SCP), $p = 0.046$.
Conclusion: CT analysis can be used as an opportunistic tool to assess SM change in clinical trials. Enobosarm promoted SM gain. SM gain ≥1kg was associated with prolonged survival and improved SCP.

5-22

Tumor-borne mediators trigger alterations in cardiac morphology, function and metabolism in cancer cachexia

Michaela Schäfer[1], Christian U. Oeing[2], Mauricio Berriel Diaz[1], Johannes Backs[2], Stephan Herzig[1]
[1]Institute for Diabetes and Cancer (IDC), Helmholtz Center Munich, Neuherberg, Germany, and Joint Heidelberg-IDC Translational Diabetes Program, Heidelberg University Hospital, Heidelberg, Germany, [2]Department of Cardiology, Angiology and Pulmology, University Hospital Heidelberg, Heidelberg, Germany, and DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Heidelberg, Germany

Cancer cachexia affects the majority of patients suffering from advanced cancers. Despite its clinical importance, the identity of tumor-borne signals and their impact on specific peripheral organ systems remain mostly unknown.
By using multiple mouse models for colorectal cancer-dependent cachexia, we show here that cardiac performance was impaired in cancer cachexia and that the cachexia-induced effects on the heart were mediated by tumor-secreted factors in a cell autonomous manner.
In an unbiased differential secretome analysis of colon cancer cells combined with high-throughput cardiomyocyte phenotyping we defined a set of tumor-secreted mediators with cachexia-inducing capacities. A signature of seven "cachexokines" was sufficient to mediate atrophy and aberrant fatty acid metabolism in primary cardiomyocytes. Amongst these seven candidates, Ataxin10 was found to represent a robust cachexia indicator as its serum levels were elevated in both murine and human cancer cachexia.
Taken together, our study demonstrates that cardiac dysfunction is an underestimated clinical feature of cancer cachexia and that alterations in fatty acid metabolism represent a distinct feature of the cachectic heart. In addition, this study provides an unbiased and functional screening setup for the investigation of tumor secreted factors with cachexia-inducing capacity. The Ataxin10-containing, heart-directed "cachexokine storm" provides a rational approach towards personalized predictive, diagnostic and therapeutic measures in cancer cachexia.

5-23

Hypermetabolism, cachexia and toxicity of anticancer treatments: A prospective study in 277 cancer patients

Anne Jouinot[1], Clara Vazeille[1], Jean-Philippe Durand[1], Nathalie Neveux[2], Anatole Cessot[1], Pascaline Boudou-Rouquette[1], Olivier Huillard[1], Jérôme Alexandre[1], Luc Cynober[2], François Goldwasser[1]
[1]Medical Oncology, Paris Descartes University, Cochin Hospital, AP-HP, Paris, France, [2]Clinical Biochemistry, Faculty of Pharmacy, Paris Descartes University, Cochin Hospital, AP-HP, and EA 4466, Paris, France

Background: Cancer cachexia is a major cause of death and is associated with treatment toxicity. Resting energy expenditure (REE) is often increased in cancer patients and may contribute to the alteration of nutritional status leading to cachexia. We investigated the relationship between REE, clinical and biological markers of cachexia and treatment toxicity.
Methods: In this prospective observational monocentric study, REE was measured by indirect calorimetry before treatment initiation. Measured REE was compared with predicted REE (Harris-Benedict) to define hypo- (REE<90%), normo- (90-110%) or hypermetabolism (>110%). We recorded daily energy intake, weight loss, performance status (PS), C-Reactive Protein (CRP), albumin and calculated Nutritional Risk Index (NRI). Toxicity was defined as any event leading to unplanned hospital admission or reduction in dose-intensity during the first cycle of treatment.

Results: A total of 277 patients were included: 56% male, median age 63 years. 76% had locally advanced or metastatic disease, 89% received chemotherapy and 11% targeted therapy; 29% were normo-, 51% hyper- and 20% hypometabolic.
Compared to normometabolic patients, hypermetabolic patients showed deeper energetic gap (intakes - REE: −57 vs +262 kcal/d, $p<10^{-3}$), altered PS (PS>2: 34% vs 17%, p = 0.008), higher systemic inflammation (CRP≥10mg/l: 45% vs 25%, p = 0.001) and lower NRI (NRI<97.5: 35% vs 19%, p = 0.013).
59 patients (21%) experienced a toxicity. Toxicity occurrence was associated with poor PS (2–3 vs 0–1: OR = 2.04, p = 0.029), low albumin (<35g/l: OR = 2.39, p=0.048), inflammation (CRP≥10mg/l: OR=2.43, p = 0.004), low NRI (<97.5: OR = 1.88, p = 0.048) and abnormal REE (vs normal: OR = 2.36, p = 0.023). REE demonstrated higher sensitivity (83%) than CRP (55%), PS (41%), NRI (38%) and albumin (17%) to predict toxicity.
Conclusion: Hypermetabolism correlates with clinical and biological markers of cachexia and with anticancer treatment toxicity. The measurement of REE might improve the detection of patients at risk for toxicity. These patients should benefit from early nutritional intervention.

5-24

Association of vitamin D deficiency with symptoms, weight loss, and prognosis in advanced cancer patients

Rony Dev[1], Egidio Del Fabbro[2], M.A. Cerana[1], Lindsey Pimental[1], Shalini Dalal[1], Eduardo Bruera[1]
[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Virginia Commonwealth University

Background: Vitamin D deficiency is common in patients with advanced cancer. We investigated the association of low serum vitamin D levels in advanced cancer patients with symptom burden, weight loss, survival and other indicators of a poor prognosis.
Methods: A retrospective review was conducted of 200 consecutive cancer patients evaluated in a Supportive Care Clinic. We investigated serum levels of 25(OH) vitamin D, vitamin B12, high sensitivity C-reactive protein (hsCRP), and weight loss. Symptoms were measured by the Edmonton Symptom Assessment Scale. Serum 25(OH) vitamin D<20 ng/ml was considered deficient.
Results: Patients were predominantly male (67%) and white (68%), with a median age of 60 (range, 27-91), BMI 26 (range, 15 – 54). Gastrointestinal (26%) and lung (21%) cancer were predominant. Mean of 3% weight loss (range, 2.8-11.4) and 75% of patients were noted to have >5% weight loss over the preceding 6 months. 108 patients (64%) were vitamin D deficient. Vitamin D deficiency (25(OH) vitamin D<20 ng/dl) was not associated with BMI, weight loss, or symptom burden as measured by the ESAS. Elevated hsCRP (>22.6), weight loss >5% were both significantly associated with poor prognosis, (P<0.001); while low BMI, vitamin D and B12 had no significant association with decreased survival.
Conclusion: Vitamin D deficiency (<20 ng/dl) is highly prevalent in advanced cancer patients evaluated in a supportive care clinic; however, no significant association with symptom burden, weight loss or survival was noted.

5-25

The d3-creatine dilution method for assessment of total body skeletal muscle mass: implementation in the Osteoporotic Fractures in Men (MrOS) Study

Peggy M. Cawthon[1], Katherine E. Peters[1], Kristine E. Ensrud[2], Jane A. Cauley[3], James Shikany[4], Deborah Kado[5], Marcia Stefanick[6], Steven R Cummings[1], Eric S. Orwoll[7]
[1]CPMC RI, San Francisco, CA, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Univesity of Alabama, Birmingham, AL, USA, [5]University of California, San Diego, CA, USA, [6]Stanford University, Stanford, CA, USA, [7]Oregon Health and Science University, Portland, OR, USA

Background: The novel d3-creatine dilution method estimates total creatine pool size, and thus total body skeletal muscle mass, by orally dosing individuals with deuterated creatine (d3-creatine) and then measuring labeled creatinine (d3-creatinine) in a morning void urine sample 3-6 days later. This method has been developed in small studies of in-patient housed participants; use in larger studies of community dwelling individuals has not been described. Herein we describe the successes and challenges of implementing the d3-creatine dilution measure in MrOS, a prospective, multi-site study of community-dwelling older men.
Methods: Enrollment for MrOS study Visit 4 began in May 2014 and is anticipated to conclude in April 2016. All surviving participants will be contacted to return to the clinic visit for repeat assessment of the main study measures. The d3-creatine dilution method is an ancillary project to the complex MrOS study Visit 4, with a separate consent and refusal option.
Results: In this very old population (vast majority are aged ≥80 years), we have had relatively few refusals (8.4%, N=87) with 943 men consenting to participation. Of the consenting men, 871 (92%) have provided usable urine samples. Each clinical center has developed successful strategies to implement this measure, such as the use of mail or phone based consent processes or the use of temperature controlled mailing boxes for returning the urine sample. Reasons for unusable urine samples include problems with timing of the d3-creatine dose (N = 28); problems with timing of the urine collection (N = 42); and shipping/mailing delays (N=2).Increased clinic reminders and instructions to participants about timing of the dose and/or urine collection improved the proportion of usable samples over time.
Conclusions: The d3-creatine dilution method can be successfully employed in large, multi-site cohort studies of community-dwelling adults, even in challenging populations such as the oldest-old.

5-26

A randomised feasibility study of Eicosapentaenoic acid (EPA) and Cox-2 inhibitor versus EPA, Cox-2 inhibitor, Progressive Resistance Training followed by essential amino acids high in leucine in NSCLC cachectic patients: Results from the ACCeRT study

Elaine S. Rogers[1], Rita Sasidharan[2] , Graeme M Sequeira[3] , Matthew R Wood[4], Stephen P Bird[5], Justin W L Keogh[6], Bruce Arroll[7], Joanna Stewart[8], Roderick D MacLeod[9]

[1]University of Auckland/Department of Medical Oncology, Auckland City Hospital, Auckland, New Zealand, [2]Department of Medical Oncology, Auckland City Hospital, Auckland, New Zealand, [3]School of Sport, Manukau Institute of Technology, Auckland, New Zealand, [4]School of Sport and Recreation, Auckland University of Technology, Auckland, New Zealand, [5]Sport and Exercise Science, James Cook University, Cairns, Australia, [6]Exercise and Sports Science, Bond University, Gold Coast, Australia, [7]Department of General Practice and Primary Health Care, University of Auckland, Auckland, New Zealand, [8]Department of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand, [9]HammondCare/Department of Palliative Care, University of Sydney, Sydney, Australia

Background: Cancer Cachexia (CC) is a common problem in Non-Small-Cell Lung Cancer (NSCLC). In CC there is a significant loss of adipose tissue and skeletal muscle mass. There is a need to utilise a multi-targeted approach to decrease the inflammation and to stimulate the skeletal anabolic pathways with the use of progressive resistance training (PRT).
Methods: ACCeRT is a feasibility, open-label study investigating Eicosapentaenoic acid (EPA) and Cox-2 inhibitor (Arm A) versus EPA, Cox-2 inhibitor, PRT followed by essential amino acids (EAAs) (Arm B) in a 1:2 randomisation.
Results: 20 patients enrolled, with 1 patient currently on study.
Results up to week 12; one patient in Arm A and B withdrew. Four patients in Arm A and B progressed before Week 12. One patient in Arm B changed to targeted therapy.
Three patients in Arm A completed questionnaire all scored 'strongly agree' to commence the PRT / EAAs. All patients in Arm B scored 'strongly agree/tend to agree' for the acceptability of the PRT sessions. Attendance for PRT sessions median = 92%.
No treatment related SAE's were seen. Full results with MRI, leg strength and QOL data will be presented.
Conclusion: The above combination has shown acceptability and stability of LBM and gain in some NSCLC patients with refractory cachexia. This combination deserves further evaluation in a larger phase II study.

	mean	Arm A (n=7)	Arm B (n=13)
Male / Female		5 / 2	8 / 5
Adenocarcinoma/ Squamous		4 / 3	10 / 3
Age at entry into study (years)	68.2	64-81	47-87
Weight loss pre-enrolment	9.01%	6.46% - 9.83%	6.29% - 20.29%

Mean change in Lean Body Mass (LBM) kg (range)				
		Week 3		Week 12
Arm A	n=4	-1.08 (-1.70 to +0.10)	n=2	+1.30 (+0.30 to +2.30)
Arm B	n=11	+0.53 (-2.20 to +3.00)	n=7	+0.66 (-4.20 to +6.80)

6-01

Nutritional and functional status, quality of life and caregiver burden of Alzheimer's disease patients

Odete Vicente de Sousa[1], Teresa F. Amaral[2]
[1]Hospital de Magalhães Lemos E.P.E., Porto, Portugal, [2]Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto, Portugal

Background: Several factors affect the nutritional and functional status and quality of life (QOL) of community-dwelling Alzheimer`s disease (AD) patients. However, the role of caregiver burden (CB) has not been comprehensively explored. The aim of this study is to explore the association between nutritional and functional status, QOL with CB in community-dwelling AD patients.
Methods: A cross-sectional study was conducted amongst 68 caregiver-patients dyads AD (patients: 25 men and 43 women; age: 77.5 ± 7.6; caregivers: 22 men and 46 women; age: 57.5 ± 21.7). Nutritional status was assessed using MNA, serum 25-hydroxyvitamin D3 [25(OH)D3] and bioimpedance analysis. Functional status using handgrip strength, gait speed, Lawton and Barthel Index was determined. Mental status was assessed by MMSE and QOL was evaluated through the Portuguese scale (QOL-AD). CB was measured using Zarit Burden Interview. Association between nutritional, functional mental and QOL status and CB was quantified through multivariable linear regression analysis.
Results: Thirty-three caregivers (48.5%) showed low CB and 24 (35.3%) high CB. Amongst high CB, 16 (34.8%) were female spouses, whose patients 14 (58.3%) were undernourished and 20 (29.4%) had 25(OH)D3 deficiency, 18 (75.0%) were severe dependent and 10 (41.7%) showed average QOL. Linear regression analysis showed that caregiver age and education, AD patient´s phase angle, gait speed and Barthel Index were the studied parameters most strongly associated with the CB, respectively (β = −0,465, 0.330, −0.358, −0.156, −0.284, and ρ = 0.008, 0.014, 0.002, 0.021, 0.033) regardless caregiver age, caregiver education, caregiver relatives, nutritional, functional and cognitive status and QOL (R2 = 0.662).
Conclusion: AD patient´s caregiver age and education, AD patient´s phase angle and functional status were the studied parameters independently associated with CB.

6-02

Hematopoietic stem cell transplantation in the elderly: nutritional and geriatric assessment

Andrea Z. Pereira[1], Juliana S.B. Barban[2], Ana Paula N. Barrére[2], Marcia Tanaka[2], Fabiana Lucio[2], Mariana Nicastro[2], Polianna M.R. Souza[1], Ludmila Koch[1], Silvia M.F. Piovacari[2], Nelson Hamerschlak[1]
[1]Oncology, Hospital Israelita Albert Einstein, S.Paulo, SP, Brazil, [2]Clinical Nutrition, Hospital Israelita Albert Einstein, S.Paulo, SP, Brazil

Introduction: Hematopoietic stem cell transplantation (HSCT) may improve outcomes of patients with hematologic malignancies not

curable with conventional therapies. Being in some diseases the only curative option. HSCT in elderly patients with good performance status and no comorbidities could, in fact, not only survive the transplant with reasonable risk, but also benefit in the same measure as younger patients. Objectives: To study and correlate nutrition and geriatric assessment in elderly patients undergoing HSCT.

Materials (or patients) and methods: A retrospective study of 17 elderly patients (>60 years) undergoing HSCT May 2012 to January 2014 in the Hematology-Oncology and Bone Marrow Transplantation Center at Albert Einstein Hospital in São Paulo, Brazil. All patients were evaluated approximately one month prior to HSCT. In the geriatric assessment were do ne hand-grip strength (HGS), questions about mobility and functional limitation. In the nutrition, we studied the Body Mass Index (BMI) (kg/m2), and serum levels of vitamin D, zinc and albumin.

Results: 17 elderly patients were observed in this study, mean age was 65,5 ± 3,8 years, BMI was 28 ± 6,0 kg/m2, HGS was 28 ± 8,5 kg; serum levels of albumin 3,2 ± 0,5g/dl(normal:3,5–5,0); serum level of vitamin D 23,4 ± 14 ng/ml (normal >20); serum levels of zinc 65,5 ± 18 mg/dl (normal: 66-132,5 mg/dl). We found the negative correlation between BMI and HGS (rp = 0,42). There were a significant and positive association between serum levels of zinc and albumin, and HGS and grades of mobility questions ($p < 0,05$). The serum levels of vitamin D weren`t significantly associated with geriatric factors.

Conclusion: Our study showed that the obese patients with more risks of complications in HSCT had more functional limitation. Besides low levels of zinc and albumin were associated with the worst results in the geriatric assessment. In the elderly the immobility and weakness can increased the complications after HSCT. The geriatric and nutrition assessment are important to improve HSCT results.

6-03

Assessment of nutrition and hydrate status in patients of palliative care unit - preliminary study

Teresa Małecka-Massalska[1], Monika Prendecka,[1] Iwona Homa[1], Przemysław Matras[2], Mariusz Teter[1], Beata Kolano-Janeczek[3]
[1]Department of Human Physiology, Medical University of Lublin, Poland, [2]Department of General and Transplant Surgery and Nutritional Treatment Medical University of Lublin, Poland, [3]Hospice of the Good Samaritan in Lublin, Poland

Background and aims: Nutritional status and body fluids balance affect quality of life and mortality of cancer patients treated in palliative care units. Provided that bioelectrical impedance analysis (BIA) is an objective tool of body components' evaluation such as: the extracellular mass (ECM), body cell mass (BCM) and their ratio (ECM/BCM), the method has been found to be a potentially useful indicator of nutrition status in many different disease entities (including cancer). The impact of a positive fluid balance on outcome of cancer patients has been well established. However, little is known which method is the best for objective monitoring of status and overload of fluids. Beside assessment of body components BIA allow to obtain: total body water (TBW), intracellular water (ICW), extracellular water (ECW) and ECW/ICW ratio. The present study was conducted to investigate the role of above parameters as an objective indicator of body fluid balance and nutritional status in patients of palliative care unit.

Methods: Study group consisted of 12 palliative women (cancer patients hospitalized in Hospice of the Good Samaritan in Lublin, Poland) and 15 healthy volunteers matched by body mass index, age and sex as a control group. Palliative patients and control group underwent a baseline nutritional assessment: subjective global assessment (SGA) and BIA.

Results: Between study groups, there were statistically significant differences in terms of: BCM ($p<0.0001$), %BCM ($p<0.0001$), ECM ($p = 0.0047$), ECM/BCM ($p<0.0001$), %ICV ($p<0.0001$), %ECW ($p<0.0001$), ECW/ICW ($p = 0,0003$).

Conclusion: Palliative patients have altered nutritional status and distorted fluid balance, which is reflected by change in body components and body fluids parameters measured by BIA. BIA could be alternative method to Subjective Global Assessment measurement and may provide more objective indicators of body fluid balance and nutritional status of patients with different cancers treated in palliative care units.

6-04

Nutritional associations with sarcopenia in an elderly Brazilian community study

Lucelia Campos Ap Martins[1], Lance A Sloan[2], Katia Cristina Portero McLellan[1,2]
[1]Sao Paulo State University - UNESP, Botucatu/SP, Brazil, [2]Texas Institute for Kidney and Endocrine Disorders – TIKED, Lufkin/TX, USA

Introduction: Sarcopenia is a generalized loss of skeletal muscle mass, that results in decreased strength, and commonly occurs with aging. It is caused by a combination of factors including sedentary lifestyle and inadequate diet.

Purpose: The aim of this study was to identify the associations of dietary intake with sarcopenia in elderly outpatients from a primary health care system.

Methodology: Cross-sectional study conducted with 136 individuals aged 60 to 89 years medically managed by the Primary Health Care of Bauru, São Paulo, Brazil. Anthropometric variables and dietary profile were assessed for all individuals. The skeletal muscle mass (SMM) was obtained by Bioelectrical Impedance (BIA) and muscle strength was assessed by grip strength (FPP). The definition for the diagnosis of sarcopenia used was muscle wasting with loss of muscle strength. Logistic regression model was performed to identify the associations of dietary intake with sarcopenia using a 5% significance level for the corresponding p-value.

Results: Individuals had a poor quality of diet (AHEI score <P75). This was characterized by low caloric diet; and low consumption of vegetables, fruits, whole grains, nuts, legumes, and eggs; and high consumption of red and processed meat, sodium, and trans fat. Low dietary protein (OR: 1.174; CI: 1.043 to 1.322) and low zinc intake (OR: 6.911; CI: 1.579 to 30.248) represented additional risk factors for sarcopenia.

Conclusion: Sarcopenia was associated with a poor quality diet with low caloric, protein, and zinc intake.

6-05

Caloric restriction in cancer cachexia: no benefit, no harm

Stef Levolger, Sandra van den Engel, Gisela Ambagtsheer, Jan N.M. IJzermans, Ron W.F. de Bruin
Department of Surgery, Erasmus MC – University Medical Center, Rotterdam, The Netherlands

Background: Caloric restriction has long been investigated for its positive effects on longevity. In recent years, it has been suggested to limit muscle wasting in sarcopenia. Cancer anorexia however already implies a certain level of caloric restriction. In this study we investigate the impact of 30% caloric restriction (30%CR) using a murine cancer cachexia model.
Materials and methods: Forty CD2F1 mice were obtained, and allocated randomly into four groups: C26 tumor-bearing (TB) + ad libitum food intake (DRI), TB+30%CR, non-TB (NTB)+30%CR, and matched intake (MI). TB groups were inoculated subcutaneously with $0.5x10^6$ C26 cells 14 days after initiating 30%CR. Bodyweight, food intake and grip-strength were recorded periodically. Gastrocnemius (GCM) muscles were resected and weighed 3 weeks after inoculation of tumor.
Results: Decreasing bodyweight was observed in the first week for both TB+30%CR (-10.5%, $p < 0.001$) and NTB+30%CR (-10.6%, $p < 0.001$) groups. At tumor inoculation, mean body weight in TB +30%CR animals was 88.6% of initial bodyweight compared with 106.9% in the TB DRI group. Bodyweight remained stable in the TB +30% CR group, i.e. 89.5% at sacrifice ($p = 0.186$), and was comparable to NTB+30%CR animals. TB DRI animals reached a mean bodyweight of 111.4% on day 28, followed by progressive wasting (-11% from day 28 to sacrifice, $p = 0.010$). Mean weight of GCM muscles was 129 mg (TB), 124 mg (TB+30%CR), 132 mg (NTB+30% CR), 158 mg (MI). One-way ANOVA with post-hoc Bonferroni correction showed that TB animals experienced increased muscle wasting compared with MI animals ($p = 0.008$). No differences in mean GCM muscle mass ($p > 0.999$) or mean grip strength (-7.9%[TB] and +15.3%[TB+30%CR]; $p = 0.038$) were observed between TB and TB+30%CR animals.
Conclusion: Caloric restriction does not protect against nor aggravate loss of muscle mass and strength in cancer cachexia, despite apparent changes in bodyweight.

6-06

Influence of high-fat feeding on the extracellular matrix in the aging rat

Robert Kob[1], Claudia Fellner[2], Thomas Bertsch[3], Astrid Wittmann[1], Cornel C. Sieber[1,4], Barbara E. Fischer[1], Christian Stroszczynski[2], L. Cornelius Bollheimer[1,4]
[1]Institute for Biomedicine of Aging, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nürnberg, Germany, [2]Institute of Radiology, University Hospital Regensburg, Germany, [3]Institute of Clinical Chemistry, Laboratory Medicine and Transfusion Medicine, Paracelsus Medical University, Nuremberg, Germany, [4]Department of General Internal Medicine and Geriatrics, St. John of God Hospital, Regensburg, Germany

Background: In sarcopenic obese subjects rather muscle quality than muscle mass is diminished. Several molecular pathological mechanisms might explain this relationship. One possible explanation would be that the amount or structure of the extracellular matrix (ECM) is altered by lipotoxic stress leading to a decline of force transduction. Therefore, in this study, the effect of a long-term high-fat diet on the collagen turnover was examined in Sprague-Dawley rats.
Methods: Beginning at 6 months of age male Sprague-Dawley rats ($n = 36$) either received standard rodent chow or a high fat diet for 15 month (HFD, 43 energy% of neutral fat). The HFD was based on lard and corn oil and contained lower quantities of carbohydrates but a similar protein content. At the end of the study, the collagen mRNA as well as protein levels were measured in the M. *vastus lateralis*. Additionally the activities of ECM-degrading matrix metalloproteinases (MMP) were analyzed using zymography.
Results: Even though the HFD leads to a decline of the quadriceps cross sectional area, there was no alteration of the collagen concentration detectable - neither on the mRNA nor on the protein level. MMP2 was the only member of the MMP family that could be detected in the muscle. In some animals, this enzyme revealed a strong activation regardless of the dietary group. Even though MMP2 had been shown to promote fibrotization by other groups, it was not correlated to the muscular collagen content in this study.
Conclusion: In the animal model of the aging HFD rat, no dysregulation of the collagen content as well as the MMP activity could be revealed. Therefore, we conclude that lipotoxic muscular atrophy did not alter the quality of the ECM.

6-07

Estimating risk factors in pre-cachectic patients with metastatic tumors: Yin and Yang

Maria Chalkia[1], Stephanos Tzanis[2], Meropi Kontogianni[3], Eleni I. Perdikouri[4], Michalitsa Makridou[4], Mariana Vlychou[2], Athanasios Migdanis[1], Ioannis Gioulbasanis[5]
[1]Technological Educational Institute of Thessaly, University of Thessaly, Larissa, Thessaly, Greece, [2]Department of Radiology, University Hospital of Larissa, Larissa, Thessaly, Greece, [3]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece, [4]Department of Oncology, University Hospital of Larissa, Larissa, Thessaly, Greece, [5]Chemotherapy Dept. Larissa General Clinic "E. Patsidis", Larissa, Thessaly, Greece

Background/Aim: According to the recent definition of cachexia, cancer patients are divided into 3 distinct groups. "Cachectic patients" may gain some benefit from nutritional support while "refractory cachectic patients" should be spared from any intervention. Concerning "pre-cachectic patients", diagnostic criteria are less clear and the time for initiation of nutritional

intervention has not been determined. Our aim was the evaluation of possible prognostic factors that might further discriminate pre-cachectic patients.
Methods: Newly diagnosed patients with metastatic primaries of the lung or the upper gastro-intestinal track, referred for initiation of systemic therapy, were eligible. All patients were assessed before the onset of chemotherapy and were classified as "pre-cachectic" according to the proposed criteria. Basic demographics were recorded as well as measurements indicative of nutritional status, inflammation, body composition and physical performance. Survival data were subsequently collected and the associations with the recorded parameters were evaluated.
Results: In total, 161 patients were recorded. Of them, 42 (26.5%) [76.2% males, median age 66 years (range 53-92)] fulfilled the criteria for "pre-cachexia" and were further evaluated. Thirty (71,4%) patients had primaries of the lung and 20 (47.6%) had a performance status (PS) of 0-1. Mean (±SD) values of BMI, albumin, CRP, fat-free mass (FFM), hand-grip strength (dominant arm) and gait speed were 24.5 (4.1)kg/m2, 3.7 (0.6)gr/dl, 5.5 (5.7)mg/dl, 43.7 (7.7)kg, 26,4 (10.2)kg, 1.1 (0.4)m/sec, respectively. Interestingly, 8 (19.1%) patients could be simultaneously classified as "pre-cachectic" and "sarcopenic". Overall survival was 9.6 months. Of the studied parameters, PS, albumin and gait speed were associated with survival (p-values= 0.024, 0.032 and 0.012, respectively).
Conclusions: Pre-cachectic patients represent a heterogeneous group in terms of nutritional risk and prognosis. Various aspects of nutritional status and functionality could be used to refine prognosis and determine the need for supportive interventions.

6-08

Chronic pain and nutritional status in metastatic cancer patients: Interrelations and association with prognosis

Ioannis Gioulbasanis[1], Efi Moutafidou[2], Athanasios Migdanis[2], Eleni Lianou[1], Afroditi Letsiou[1], Meropi Kontogianni[3]
[1]Department of Chemotherapy, Larissa General Clinic "E. Patsidis", Larissa, Thessaly, Greece, [2]Technological Educational Institute of Thessaly, University of Thessaly, Larissa, Thessaly, Greece, [3]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

Background/Aim: Cancer patients often experience chronic pain (CP) as one of their presenting symptoms. Given the somatic as well as the psychological effect of CP, our aim was to evaluate the impact of CP on patients' nutritional status and prognosis.
Patients/methods: Patients with metastatic primaries of the lung and the upper gastro-intestinal (GI) track referred for initiation of systemic therapy were evaluated. All patients were asked whether they experienced CP before their first oncologic visit. Basic demographics, ECOG performance status (PS), nutritional status [Body Mass Index (BMI), presence of anorexia, weight loss history (WL), Mini Nutritional Assessment (MNA), Fat-Free Mass (FFM)] and systemic inflammation [Glasgow Prognostic Score (GPS)] were assessed at baseline and survival data were subsequently recorded.
Results: In total, 163 patients [136 (83.4%) males], median age (range) 67 (39-92) were evaluated. The majority (73%) had metastatic primaries of the lung and a PS of 0–1 [117 (72.7%)]. Forty-four (27%) reported CP at diagnosis. No differences emerged in relation to age or according to BMI and PS classification. However, in comparison with the rest of the accrued population, these patients reported more frequently anorexia and weight loss, had worst MNA and GPS scores and less FFM (p-values = 0.013, 0.007, 0.012, $<$0.001 and 0.036, respectively). In addition, these patients had significantly shorter overall survival (months) [10.2 vs. 17.2 (p = 0.006)].
Conclusions: CP at presentation is an adverse prognostic factor and is associated with increased risk of malnutrition. Given the constant prevalence of this symptom across BMI and PS categories, these patients should be independently considered for nutritional assessment.

6-09

Preliminary report on total parenteral nutrition (TPN) utilization and overall survival (OS) among patients in a tertiary cancer center

Wenli Liu, Khanh Vu, Todd Canada, Juhee Song, Sai-ching J Yeung
Department of General Internal Medicine, Clinical Pharmacy Services, Department of Emergency Medicine, Department of Endocrine Neoplasia and Hormonal Disorders, Department of Biostatistics, M D Anderson Cancer Center, USA

Background and aims: TPN is frequently prescribed to cancer patients. However, limited knowledge exists regarding description of utilization of TPN across various cancer types and OS in cancer patients receiving TPN. We aimed to characterize the utilization of TPN and measure OS in cancer patients in a tertiary cancer center.
Methods: We reviewed the Nutritional Support Team computer records of 4,105 consecutive patients who received TPN support at our cancer center from 08/01/08 – 08/01/13. Patients under 18 years old, nonmalignant diseases, and missing data were excluded. Data regarding cancer type, duration of TPN support, mortality rate, and first day of TPN support to death were collected.
Results: Of the eligible 3842 patients, the mean age at the time of initiation of TPN was 57 years and 56% were male. Gastrointestinal (31%) was the most common cancer type followed by gynecological and genitourinary (25%), hematological (24%), and thoracic/head and neck cancer (9%). The median duration (range) of TPN was 9 (0–1947) days. Hematological cancers had the lowest median age at cancer diagnosis (51 years; $P<0.0001$) and age of TPN initiation (56 years; $P<0.0001$) and also had the longest median duration (range) of 10.5 (0–1221) days ($P<0.0001$) compared to other cancer types. However, patients with hematological malignancies also had the lowest OS of 55 days ($P<0.0001$) compared to other cancer types (Fig. 1.). Patients with Gynecological/genitourinary (830 days) followed by gastrointestinal cancer (603 days) had the longest OS.
Conclusions: This preliminary report is part of the largest study in cancer patients who received TPN support and highlights the differences of TPN utilization among different cancer types and the association with OS.

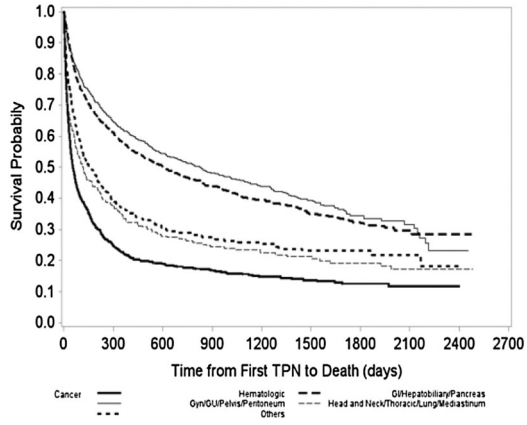


Figure 1 Kaplan-Meier curve for overall survival from initiation of TPN by cancer type.

6-10

A retrospective study on postoperative nutritional support in pancreatic surgery

Lisa Ellegård, Cecilia Engström Mattisson
Department of Surgery, Sahlgrenska University Hospital, Göteborg, Sweden

Background: Pancreatic cancer is one of the most aggressive malignancies, where only some improval has been observed in survival over the last decades. It includes a considerable risk of malnutrition, both due to the cancer itself, the fact that the organs involved are part of the digestive system and because of further impact of extensive surgery. Postoperative nutritional support is an important part of enhancing early recovery after surgery.
Aim: To provide a retrospective overview of the use of postoperative nutritional support in pancreatic surgery, which can be used to evaluate the effects of new guidelines.
Methods: Retrospective clinical study with collection of pre- and postoperative data in 115 patients undergoing pancreaticoduodenectomy, total pancreatectomy and distal pancreatectomy at Sahlgrenska University Hospital during 2012 and 2013.
Results: After pancreaticoduodenectomy, 73 % of the patients received postoperative nutritional support, for a mean duration of 19.3 days. The nasogastric tube remained inserted for 6.6 days after surgery. Patients were allowed liquids freely after 8.0 days. Length of hospital stay after pancreaticoduodenectomy was 26.6 days. There were significant differences in nasogastric tube duration, days until liquids and length of hospital stay between the different procedures. There were no significant differences in BMI
Conclusions: In 2012-2013, the majority of patients still received postoperative nutritional support, the nasogastric tube remained inserted for several days and patients were not allowed liquids freely until later in the recovery. New fast track guidelines similar to those in colorectal surgery are progressively implemented and Sahlgrenska University Hospital is benchmarking this, since little is found in the literature regarding pancreatic surgery in specific. This retrospective study may help us evaluate the effects of new guidelines, to enhance the postoperative treatment and strive for early recovery after surgery.

6-11

Impact of home ertificial nutrition on survival and quality of life in advanced cancer patients

Enrico Ruggeri, Federica Agostini, Luana Fettucciari, Marilena Giannantonio, Raffaella Pannuti, Franco Pannuti
ANT Foundation, Bologna, Italy

Background: Cachexia is up to 50% in advanced cancer patients, resulting in weight loss, reduced quality of life (QoL) and shortened survival time, and it is the leading cause of death for 20%.
Aim: Evaluate the importance of home artificial nutrition (HAN) on preventing death from cachexia and on improving QoL in advanced cancer patients assisted at home by ANT (Tumors National Association) Foundation in Bologna, Italy.
Materials and methods: Clinical and nutritional parameters: sex, age, tumor site, QoL evaluated using the Karnofsky Performance Status (KPS), duration of life, nutritional status, oral food intake, indications for HAN, daily regimen of HAN, survival after starting HAN. Criteria of patients' selection: inadequate caloric intake ± malInutrition; life expectancy ≥6 weeks; suitable psycho-physical conditions; informed consent. Statistics: m ± sd, Pearson correlation.
Results: Since 1990 ANT Foundation assisted at home 33489 advanced cancer patients. HAN has been administered to 725 patients (2.2%), 430 M, 295 F (age: 65.8 ± 12.8). Tumor site: head-neck and gastrointestinal tract in 88% of cases. Mean BMI: 19.2 ± 2.9. Caloric intake: <50% of total energy expenditure in all patients (negative caloric-protein balance). Enteral nutrition: 304/725 patients (41.9%), main indication: dysphagia. Parenteral nutrition: 421/725 patients (58.1%), main indication: gastro-intestinal obstruction. All patients had died at the end of the study. 78% of patients (563/725) survived ≥6 weeks. Mean duration of HAN was 17.6 ± 20.4 weeks, strongly correlated (r = 0.258) with KPS at the study entry. KPS was unchanged in 65% and increased in 24% of patients after one month of HAN, correlated with longer survival ($p<0.0001$). Caloric-protein intake with HAN (32 ± 8 Cal/Kg, 1.3 ± 0.4 Prot/Kg) allowed a significant weight gain ($p<0.0001$), more in patients with high KPS.
Conclusions. HAN can prevent death from cachexia in 78% of patients. The survival increases proportionally to improvement of the quality of life due to HAN.

6-12

Assessment of nutritional status in elderly patients during weight loss

Nadja Vasiljevic, Branko Jakovljevic, Milos Maksimovic, Jagoda Jorga
Institute of Hygiene and Medical Ecology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia

Background and aims: Obesity and overweight are common public health problems also among elderly people. Accordingly we evaluated nutritional status and especially fat free mass in the aim of

sarcopenia prevention among elderly participants undergoing diet therapy.

Methods: During the 2014 year we examine 1000 new patients at the Department of Nutrition, and among them there are 136 old age persons. The study sample consists of 19% of older male and 81% of older female patients. The age range of our sample is 60 to 84 years, and 21.5% are older than 70 years. Assessment of nutritional status was done by anthropometric measures and by In Body 720 body composition analyzer.

Results: According to anthropometric measures body mass index range was 26.2 -55.6kg/m^2. Overweight patients were 21.2%, 38,1% patients were with first degree of obesity, 25.4% patients were with second degree of obesity and 15.3% were with body mass index more that 40kg/m^2. Also, the relationship between obesity degree and morbidity was evaluated and reveal that body mass index correlated with the prevalence of hypertension, dyslipidemia, cardiovascular disease, endocrine disease, locomotor disorders, vascular disorders, and cholelythiasis more frequent. The findings indicated that duration of participation in weight program and a number of health checks undergone 43.8% of the elderly.

Conclusions: All of studied patient reduced their body weight at least 5% what is of clinical importance. Body fat mass and fat free mass were reduced and monitored regularly. In elderly population it is very important to monitor not only the body size but also the body composition, especially fat free mass changes during dietary treatment in the aim of preservation of muscle mass and sarcopenia prevention.

6-13

Impact of anticancer treatment on nutritional and functional status in cancer patients: A case control study

Shekhar Gogna, Priya Goyal

Department of Surgery, Pt. B D Sharma unversity of Healt Sciences, Rohtak, India

Background and aims: Etiology of cachexia is multifactorial and is related to local effects of tumor and anticancer therapies, reduced food intake due to systemic and psychological effects of the disease. The indicators of nutritional status are anthropometric variables such as body weight, BMI, hand grip dynamometry, mid arm circumfrenece and biochemical variables such as hemoglobin, serum albumin. These patients have poor nutritional and performance status. We aimed to establish improvement in both nutritional and performance status of patients after definitive anticancer treatment.

Methods: We did a case control study with the 100 disease and site specific cancer patients treated by surgery followed by adjuvant chemo/radiotherapy. Control group was formed by age and sex matched healthy volunteers. The nutritional and performance status were assessed before start of anticancer therapy and at 6 & 12 weeks after completion of the therapy in study group. Variables assessed pre and post treatment were hemoglobin levels, serum albumin, mid arm circumference, body weight, Body mass index (BMI) and hand grip dynamometry. Functional status was assessed by using Karnofsky performance scale (KPS). We also assessed the interrelationship among nutritional status and functional status.

Results: There was statistical significant increase in Body weight ($p<0.01$), BMI($p<0.01$), hand grip dynamometry($p<0.01$), improvent in midarm circumference and triceps thickness was present but not statistically significant. Hb, serum Albumin. KPS also improved staistically. On studying the interrelationship between nutritional and performance status we found early and linearly increasing improvement in KPS as compared to nutritional status.

Conclusion: We concluded that anticancer treatment does improves nutritional and performance status of cancer patient thus there is improvement in cachexia, fatigue and improvement in quality of life. Performance status improves earlier and helps to better the nutritional status also.

6-14

PG-SGA: The use of a nutrition assessment tool for triage in an interdisciplinary cancer cachexia clinic

Vanessa C. Vaughan[1], Helen Farrell[2], Paul A. Lewandowski[1], Peter Martin[1,2]

[1]School of Medicine, Deakin University, Waurn Ponds, Victoria, Australia, [2]Palliative Care Program, Barwon Health, Geelong, Victoria, Australia

Background/Aims: Cancer cachexia is a wasting condition effecting 50% of cancer patients, associated with decreased response to anti-neoplastic therapy, quality of life, and survival. The study aimed to establish if the nutritional status of patients on referral, as determined by 'Patient Generated Subjective Global Assessment' (PG-SGA) could be used to identify high-risk patients attending an interdisciplinary cachexia clinic.

Methods: A retrospective study was completed for non-active patients that attended the Barwon Health clinic between January 2008 and December 2013 (n=142). Patients with baseline PG-SGA scores were stratified to SGA-A: well nourished, SGA-B: suspected or moderately malnourished, or SGA-C: severely malnourished. Comparison of survival curves was carried out using the Log-rank (Mantel-Cox) test.

Results: 43 patients (25%) survived beyond study duration. Overall median survival was 136 days from first clinical appearance. Those patients within the SGA-C range had significantly shorter median survival interval (61 days) from their first clinical appearance compared to SGA-A (280 days, $P\leq0.001$) or SGA-B (183 days, $P\leq0.001$). The median survival from final clinical appearance was 71 days. SGA-C patients had significantly shorter median survival interval (42 days) from their final clinical appearance compared to patients in the SGA-A (158 days, $P\leq0.001$) or SGA-B range (80 days, $P\leq0.01$).

Conclusions: Given ease of administration, and significant survival distinction, PG-SGA may be a useful triaging tool to identify patients in need of immediate or intensive intervention. Increasing the

frequency that the questionnaire is administered would also assist in tracking the progress, and identifying patients in decline.

6-15

Effects of elastic-band resistance training and nutritional supplementation on circulating myokines, physical performance and muscle quality of institutionalized elderly - the Vienna Active Ageing Study (VAAS)

Barbara Wessner[1,2], Marlene Hofmann[1], Barbara Halper[1], Stefan Oesen[1], Bernhard Franzke[1,3], Eva-Maria Strasser[4], Karl-Heinz Wagner[1,3]

[1]Research Platform Active Ageing, University of Vienna, Vienna, Austria, [2]Centre for Sport Science and University Sports, University of Vienna, Vienna, Austria, [3]Faculty of Life Sciences, Department of Nutritional Science, University of Vienna, Vienna, Austria, [4]Karl Landsteiner Institute for Remobilization and Functional Health / Institute for Physical Medicine and Rehabilitation, Social Medical Center South, Vienna, Austria

Background and aims: Cytokines and other peptides that are produced and released by working muscles and that exert their effects on various body parts have been subsumed as "myokines".[1] As regular resistance exercise training and a balanced diet containing a sufficient amount of essential amino acids may counteract the age-related muscular decline, the aim of the current study was to investigate the influence of elastic-band resistance training and nutritional supplementation on circulating myokines (myostatin, GDF-15, activin A, follistatin, IGF-1), physical performance and muscle quality of institutionalized elderly.

Methods: Within the Vienna Active Ageing Study, 117 males and females aged 83.2 (65.0-97.4) years were randomly assigned to one of three intervention groups (RT = resistance training, RTS = resistance training combined with protein supplementation, CT = cognitive training). Myostatin, activin A, follistatin, IGF-1 and GDF-15, as well as muscle quality and functional parameters were tested at baseline and after 3 and 6 months of intervention (NCT01775111).

Results: Muscle quality increased in RT (+13%, p = .002) and RTS (+15%, p = .040) groups. Performance improved in RT and RTS for chair-stand test (RT +28%, p = .001; RTS +25%, p = .003), arm-lifting test (RT +23%, p = .002; RTS +51%, p=.000) and 6-minute-walking-test (RT +14%, p = .021; RTS +10%, p = .015). These changes were accompanied by changes in follistatin (RT: +12%, p = .028; CT: −7%, p = .030) and activin A (RTS: +52%, p = .042; CT: −10%, p = .011), while IGF-1, myostatin and GDF-15 levels were not affected.

Conclusion: Our data confirm that strength training improves physical performance and muscle quality even in very old adults. Interestingly, strength training leads to simultaneously enhanced levels of follistatin (a positive regulator of muscle mass) and activin A (a negative regulator). Future studies will investigate whether systemic levels of these mediators reflect the situation within skeletal muscles.

References

1. Pedersen BK. Muscle as a secretory organ. Compr Physiol.2013;**3**:1337-1362.

6-16

Reduced dietary intake of micronutrients with antioxidant properties negatively impacts muscle health in aged mice

Miriam van Dijk[1], Francina Dijk[1], Klaske van Norren[1,2], Richard Jaspers[3], Ardy van Helvoort[1], Sjors Verlaan[1] and Yvette Luiking[1]

[1]Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, the Netherlands, [2]Nutrition and Pharmacology, Wageningen University, the Netherlands, [3]Laboratory for Myology, MOVE Research Institute Amsterdam, VU University Amsterdam, the Netherlands

Background and aim: Inadequacies of micronutrients with antioxidant-properties are common among older adults and have been associated with higher risk of frailty, adverse functional outcome and impaired muscle health. However, a causal relationship is less well known. The aim was to determine in old mice the impact of reduced dietary intake of vitamins A/E/B6/B12/Folate, selenium and zinc on muscle mass, oxidative capacity, strength and physical activity (PA) over time.

Methods: 21-months-old mice were fed either AIN-93M or a diet low in micronutrients with antioxidant-properties (=LOWOX: 50% of mouse recommended daily intake of vitaminA/E/B6/B12/folate/selenium/zinc) for 4 months. Muscle mass, grip strength, PA, and general oxidative status (liver malondialdehyde (MDA)) were assessed. Moreover, muscle fatigue was measured on m. *extensor digitorum longus* (*EDL)* during an *ex-vivo* moderate exercise-protocol. Effects on oxidative capacity (succinate dehydrogenase (SDH) activity), muscle fiber type, number and cross-sectional area (FCSA) were assessed on m.p*lantaris (PL*) using histochemistry.

Results: From 2 months on the diet, bodyweight of LOWOX-mice was lower compared to control-mice ($P<0.0001$) without difference in food intake, and mainly due to lower fat mass ($P<0.0001$). After 4 months, oxidative status of LOWOX-mice was lower, demonstrated by decreased vitaminE plasma levels ($P<0.05$) and increased liver MDA levels ($P = 0.018$). PA was significantly lower in LOWOX-mice ($P<0.001$). Muscle mass was not affected, although *PL*-FCSA was decreased (~16%; $P = 0.028$) while SDH-activity and muscle fiber type distribution remained unaffected. In LOWOX-mice, *EDL*-force production was decreased at lower stimulation frequencies ($P = 0.038$) and fatigue resistance was diminished ($P = 0.023$).

Conclusions: Reduced dietary intake of vitaminsA/E/B6/B12/Folate/selenium/zinc has major impact on muscle health as shown by decreased force production and PA, without effects on muscle mass. The reduced FCSA in combination with lack of effect on SDH-activity suggests that such dietary reductions cause muscle fiber atrophy and reduced muscle oxidative capacity resulting in reduced muscle fatigue resistance.

6-17

Diet composition as a source of variation in experimental animal models of cancer cachexia

Vera Mazurak[1], Kaitlin Giles[1], Chen Guan[2], R. Thomas Jagoe[2,3]

[1]Department of Agricultural, Food and Nutritional Science, University of Alberta, Canada, [2]McGill Cancer Nutrition Rehabilitation Program, Jewish General Hospital, Montreal, Canada, [3]Department of Medicine, McGill University, Canada

Background: A variety of experimental animal models are used extensively to study mechanisms underlying cancer cachexia, and to identify potential treatments. The important potential confounding effect of dietary composition and intake used in many preclinical studies of cancer cachexia is frequently overlooked. Dietary designs applied in experimental studies should maximize the applicability to human cancer cachexia, meeting the essential requirements of the species used in the study, matched between treatment and control groups as well as also being generally similar to human consumption.
Methods: A literature review of scientific studies using animal models of cancer and cancer cachexia with dietary interventions was performed. Studies that investigated interventions using lipid sources were selected as the focus of discussion.
Results: The search revealed a number of nutrient intervention studies (n = 44), with the majority including n-3 fatty acids (n = 16), mainly eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA). A review of the literature revealed that the majority of studies do not provide information about dietary design; food intake or pair-feeding are rarely reported. Further, there is a lack of standardization in dietary design, content, source, and overall composition in animal models of cancer cachexia. A model is proposed with the intent of guiding dietary design in preclinical studies to enable comparisons of dietary treatments within the same study, translation across different study designs, as well as application to human nutrient intakes.
Conclusion: The potential for experimental endpoints to be affected by variations in food intake, macronutrient content, and diet composition is likely. Diet content and composition should be reported, and food intake assessed. Minimum standards for diet definition in cachexia studies would improve reproducibility of pre-clinical studies and aid the interpretation and translation of results to humans with cancer.

6-18

Dietary quercetine supplementation inhibits cancer cachexia associated muscle wasting

Stef Levolger, Sandra van den Engel, Gisela Ambagtsheer, Jan N.M. IJzermans, Ron W.F. de Bruin
Department of Surgery, Erasmus MC – University Medical Center, Rotterdam, The Netherlands

Background: Cancer cachexia is characterized by progressive muscle wasting and associated with poor survival, delayed recovery after surgery and impaired quality of life. Quercitin is a flavonoid with reported antioxidant and anti-inflammatory effects. Recently quercetin has been reported to limit muscle wasting in an APC knockout cachexia model. We sought to validate these findings and optimize quercetin treatment in a murine cancer cachexia model.
Materials and methods: Custom CRM(P) diets supplemented with 250, 1000, or 2000 mg/kg quercetin (Q250, Q1000, Q2000) were obtained from SDS diets, corresponding with 35, 140, and 280 mg/kg/day mouse, respectively. Sixty CD2F1 mice were obtained, and allocated randomly into six groups: Healthy, Healthy +Q1000, Tumor-Bearing (TB), TB+Q250, TB+Q1000, TB+Q2000. Mice allocated in TB groups were inoculated subcutaneously with 0.5 x 10^6 C26 cells to induce cachexia. Simultaneously, all groups started their allocated diet. Bodyweight and food intake were recorded daily. Blood was collected weekly and at sacrifice on day 21 or when bodyweight loss exceeded 20%. Gastrocnemius (GCM) muscles were resected and weighed.
Results: TB animals receiving a standard CRM(P) diet experienced progressive weight loss in the three final days preceding sacrifice (Wilcoxon signed rank test p = 0.22). No decline in bodyweight was observed in animals receiving a quercetin supplemented diet. Food intake was comparable between all groups. Mean weight of GCM muscles were 175 mg (healthy), 172 mg (healthy+Q1000), 125 mg (TB), 171 mg (TB+Q250), 168 mg (TB+Q1000), 161 mg (TB+Q2000). One-way ANOVA with post-hoc Bonferroni correction was performed. TB animals receiving a standard CRM(P) diet experienced loss of GCM mass compared with healthy animals ($p < 0.0001$). No loss of muscle mass was observed in all dietary quercetin supplemented groups (all $p > 0.999$).
Conclusion: This study validates the efficacy of dietary quercetin supplementation in limiting bodyweight loss and muscle wasting in vivo.

6-19

Vitamins B9 (Folate), B12 & D deficiencies and hyperhomocysteinaemia in elderly diabetics of a primary care polyclinic in Singapore – serum folate strongly predicts muscle strength

Andrew K.H. Wee
SingHealth Polyclinics, Marine Parade Polyclinic, Singapore

Background and aims: Elderly diabetics are at risk of vitamin deficiencies, weakness and falls. As deficiencies of Vitamins D & B12 and Hyperhomocystineamia are well-known contributors to sarcopaenia, we conducted a pilot cross-sectional study of the association of these (with B9) with muscle strength-gait.
Methods: Stratified Sampling by Gender of polyclinic diabetics > 65 years. 56 subjects recruited. Hand Grip strength and Leg Quadriceps strength were measured in Kg force. Corresponding limbs were measured and the average was obtained. Mean muscle strength was then corrected for body habitus by using Body Mass Index (BMI) as denominator. The Timed up-and-go [TUG (sec)] and Tinetti POMA tests were used to measure gait. A history of "at least 1 Fall in the preceding year" was also asked.
Results: Multiple regression was used to predict Muscle strength (Grip and Quadriceps) from Vitamin & Homocysteine variables. Vitamin D, B12 and Homocysteine did not significantly predict muscle strength. However, 2 variables strongly predicted Average Corrected Grip Strength [$F(2,53) = 18.12$, $p<0.0001$, $R^2 = 0.41$]. Specifically, lnFolate ($B = 0.24$, $p = 0.003$) and Male gender ($B = 0.35$, $p < 0.001$). The Same 2 variable predicted Average Corrected Quadriceps Strength [$F(2,53) = 11.05$ $p = 0.0001$, $R^2 = 0.29$], lnFolate ($B = 0.28$,

p = 0.009) and Male gender (B = 0.36, $p < 0.001$). Log-regression showed that Quadriceps Strength separately correlated with a positive fall history, (OR = 0.12, p= 0.041).

Conclusion: Vitamin D, B12 and Homocysteine did not show an association with muscle strength, likely due to this pilot's small sample size. Despite this however, we were able to obtain a novel & very strong association of Folate levels with muscle strength. Defects in neuronal myelination, neurotransmitter formation and epigenetic DNA methylation are biologically plausible explanatory mechanisms. This warrants further study of Folate's role in sarcopaenia in public health.

6-20

Vitamins B9 (Folate), B12 & D deficiencies and hyperhomocysteinaemia in elderly diabetics of a primary care polyclinic in Singapore – A report on its prevalence and determinants

Andrew K H Wee
SingHealth Polyclinics, Marine Parade Polyclinic, Singapore

Background and aims: Diabetic elderly patients in the community are at risk of vitamin deficiencies, weakness and falls. We conducted a pilot cross-sectional study of the association of vitamin deficiencies (of B12, B9 and D) and hyperhomocysteinaemia with Muscle strength, gait and balance. We report the prevalence and salient determinants of deficiencies.

Methods: Disproportionate stratified sampling by gender of diabetic patients > 65 years was done at the polyclinic. Convenience sampling was employed and 56 subjects (28 of each gender) were recruited.

Results:

1) (24 subjects) 43% had Vitamin B12 deficiency of < 150 pmol/l
2) 20% had Vitamin B9 deficiency of < 13.4 nmol/l
3) 25% had Vitamin D deficiency of < 20 ug/l. Another 48% had D insufficiency (>20 and < 30 ug/l)
4) 52% had Hyperhomocysteinaemia of >15.0 umol/l

Multiple regression was used to predict Homocysteine from well-known variables. Three variables statistically significantly predicted Homocysteine levels, $F(3,52) = 13.77$, $p<0.0001$, $R^2 = 0.4427$. Specifically, lnFolate (B = -4.86, p = 0.012), lnB12 (B = −6.34, $p < 0.001$) and Estimated Glomerular Filtration Rate (ml/min) (B = −0.156, $p < 0.001$). Multiple regression was subsequently used to test the predictors of B12 levels. Four predictors were found [$F(4,51) = 14.53$, $p<0.0001$, $R^2 = 0.53$]. These were a Positive History of Vitamin B12 supplementation (B = 124.64, p = 0.001), Age (B = −5.64, p = 0.038), ln(LDL Cholesterol) (B = 159.27, $p<0.001$) and Cumulative Dose (grams) of Metformin Consumed in the preceding 12 months (B = −0.172, $p<0.001$)

Conclusion: Vitamin deficiencies and hyperhomocysteinaemia are indeed prevalent in diabetic elderly patients of primary care, with known variables strongly predicting them despite a small sample size. This data provides case-finding opportunity for needed research into the clinical significance of these deficiencies and treatment-prevention. The novel association of serum LDL Cholesterol with Vitamin B12 deficiency warrants further investigation.

6-21

Improvement of whole body nitrogen balance during the night in healthy elderly men following a pre-bedtime ingestion of a dietary supplement.

Leonidas G Karagounis, Laurence Donato-Capel, Kora Rade Kukic, Jean-Philippe Godin, Maurice Beaumont, Denis Breuillé
Nestle Research Center, Vers Chez les Blanc, Lausanne, Switzerland

Age-related sarcopenia is defined by a decrease in muscle mass and function resulting in compromised quality of life. Utilizing novel nutritional strategies to attenuate such losses is of great importance when trying to minimize the functional limitations in elderly individuals. The aim of our study was to test if a specific nutritional supplement ingested in the evening before going to bed would improve whole body nitrogen balance measured during the night.

We performed a randomized, double blind, mono-centric study in seventeen healthy elderly male subjects (55 to 70 y). Subjects consumed dinner at 18:00 h and a dietary supplement drink at 21:00h containing either 25 g milk protein, canola oil and maltodextrin (treatment group) or an isocaloric maltodextrin and canola oil drink (placebo group). In order to evaluate whole body nitrogen balance throughout the night, subjects ingested a drink of ^{15}NGlycine at 21:00 h. Amino acid, insulin and glucose concentrations were also measured in plasma at different time points throughout the night.

Increased amino acid concentrations were observed only in the treatment group, peaking at one and a half hours following ingestion. Hyper-aminoacidemia was maintained in the treatment group compared to the placebo group for the duration of the night (10h). In parallel, mean whole body nitrogen balance was greater in the treatment group (−0.13 ± 11.30 g prot/10h) compared to the placebo group (−12.22 ± 6.91 g prot/10h) ($P \leq 0.01$), signifying an attenuation in nitrogen loss the morning following an overnight fast.

We demonstrated for the first time that the ingestion of a dietary supplement containing 25g of milk proteins significantly improved the negative protein balance observed during the night. These findings suggest that pre-bedtime ingestion of protein may attenuate overnight losses of lean tissue in healthy elderly men.

6-22

Determination of ghrelin and its analogs in plasma samples by liquid chromatography-mass spectrometry

Jana Zemenová[1,2], David Sýkora[2], Blanka Železná[1], Lenka Maletínská[1]
[1]Institute of Organic Chemistry and Biochemistry v. v. i., AS CR, Prague, Czech Republic, [2]Department of Analytical Chemistry, University of Chemistry and Technology, Prague, Czech Republic

Background and aims: Ghrelin is the only known orexigenic gut hormone, it positively affects energy balance and also possesses anti-inflammatory effects. Ghrelin and ghrelin receptor (GHS-R1a) agonists are currently being investigated as potential therapeutics for treatment of cachexia. For drug designing and development a trustworthy analytical tool for the determination of the drugs is necessary. In this study we aimed to develop a new liquid chromatography – mass spectrometry (LC-MS) method suitable for the determination of ghrelin and other peptidic GHS-R1a agonists (designed and synthetized in our laboratory) in plasma samples.

Methods: Partition coefficients of the ghrelin analogs were determined and precipitation experiments were performed utilizing radiolabeled analogs of the compounds. Behavior of the synthesized peptides in solution was studied using dynamic light scattering. Quantification of the analytes was carried out utilizing LC-MS.

Results: The best recovery of the studied peptides from the plasma was accomplished when the plasma proteins were precipitation with sulfosalicylic acid solution. The recovery was higher for ghrelin analogs possessing short fatty acid moiety. As the fatty chain got longer the recovery decreased significantly. Matrix effect in plasma samples and ion suppression of MS signal were observed. The length of the fatty acid chain had also a significant impact on the behavior of the peptides in solution, their co-precipitation with plasmatic proteins, and partition coefficients.

Conclusions: We developed LC-MS method suitable for the determination of ghrelin and its synthetic analogues in plasma samples. We found out that the crucial part of the overall analytical method was the sample preparation step. Handling of lipidized peptides is very difficult. As a consequence a significant loss of material occurred in each step during sample preparation. This issue will be addressed in our future research.

Acknowledgements: This work was financially supported by RVO:61388963 (GA AS CR) and 13-14105S of GA CR.

6-23

Changes of fat content over time and survival in chronic heart failure patients

Jacek T. Niedziela, Piotr Rozentryt, Bartosz Hudzik, Natalia Niedziela, Wiktor Skowron, Aneta Ociessa, Lech Poloński, Mariusz Gąsior

3rd Department of Cardiology, Silesian Centre for Heart Disease, Zabrze, Poland

Background and aims: Chronic heart failure (HF) is an epidemic of the 21st century. Weight loss in HF worsens prognosis. Epidemiologic studies suggest protective role of fat tissue in HF. However, prospective data with direct repeated measurements of fat change over time are scarce. The purpose of our study was to investigate prospectively the impact of fat mass change on prognosis in HFs.

Methods: In patients with stable HF (without clinical signs of hypervolemia) two assessments of body composition were performed using dual-energy X-ray absorptiometry (DEXA). Patients were divided into 3 groups, according to fat tissue changes between DEXA examinations: fat loss (FL, fat tissue loss $>$ 2.5%), fat stable (FS, fat tissue changes ± 2.5%) and fat gain (FG, fat tissue gain $>$2.5%). Clinical, biochemical and functional characteristics were compared as well as a 5-year survival after second DEXA examination.

Results: 243 patients (age 51.6 years ± 11.5, 12.3% of female, NYHA 2.54 ± 0.7, LVEF 24.4 % ± 7.5, NT-proBNP 2677 pg/ml ± 3109, BMI 26.3 kg/m^2 ± 4.6) entered the study. The median interval between the DEXA examinations was 14.2 months (IQR 11.7-18.2). Fat loss and fat gain were found in 23% and 62.6% of patients, respectively. Groups were not different with respect of sex, BMI at both DEXA scans, NYHA, LVEF, NTproBNP, peak VO2, renal function, comorbidities and treatment. There were differences in age, total body mass change and HF duration between groups. Patients with FG had a better 5-year survival comparing to FS. There was a trend toward better prognosis in FG in unadjusted Cox analysis, however after adjusting for age and lean mass change or weight change we found no significant association of FG with mortality (Table).

Conclusions: We found no evidence for independent protective role of fat gain in HF.

	Fat loss n=56	Fat stable n=35	Fat gain n=152	p
Age	51.1 ± 12.4	56.7 ± 11.0	50.6 ± 11.1	0.03
Body mass change [%]	−5.2%	+0.6%	+8.2%	<0.0001
Fat change [%]	−13.6%	−0.2%	+31.9%	<0.0001
Lean change [%]	−1.7%	+1.3%	+2.2%	0.03
HF duration [months]	48.7 ± 40.7	57.1 ± 45.5	43.0 ± 45.6	0.03
5-year mortality [%]	50%	54.3%	36.8%#	0.1*

Hazard ratio ± 95% CI, p-value for 5-year mortality after second DXA

	Fat stable	Fat loss	Fat gain
Unadjusted model	1.0	0.91 (0.51–1.64), p=0.75	0.63 (0.38–1.07), p=0.09
Adjusted for lean change	1.0	0.87 (0.48–1.57), p=0.64	0.66 (0.39–1.11), p=0.11
Adjusted for body mass change	1.0	0.86 (0.47–1.57), p=0.62	0.71 (0.40–1.23), p=0.22
Adjusted for age and lean change	1.0	1.06 (0.58–1.95), p=0.85	0.79 (0.46–1.35), p=0.39
Adjusted for age and body mass change	1.0	1.07 (0.58–1.99), p=0.83	0.83 (0.47–1.47), p=0.52
Adjusted for age, body mass change and lean change	1.0	1.05 (0.57–1.94), p=0.66	0.82 (0.47–1.41), p=0.34

*-log-rank; #-log-rank p = 0.03 vs Fat stable group

6-24

The fat-free mass index and subjective global assessment in detecting malnutrition in head and neck cancers

Teresa Małecka-Massalska[1], Monika Prendecka[1], Agata Smoleń[2], Kamal Morshed[3]
[1]Physiology Department, Medical University of Lublin, Poland, [2]Epidemiology Department, Medical University of Lublin, Poland, [3]Otolaryngology, Head and Neck Surgery Department, Medical University of Lublin, Poland

Background and Objective: Worldwide, an estimated 644,000 new cases of head and neck cancer (HNC) are diagnosed each year, with two-thirds of these cases occurring in developing countries. Nutritional deficits have a significant impact on mortality, morbidity, and quality of life in patients with HNC. Bioelectrical impedance analysis (BIA) has been established as a valuable tool in the evaluation of body composition and nutritional status in many patients' conditions including cancer. BIA evaluates body component such as the fat-free mass (FFM). The fat-free mass index, determined by bioelectrical impedance analysis, has been found as a potentially useful indicator of nutritional status. Subjective Global Assessment is a subjective method of nutritional status in head and neck cancer. The study was conducted to investigate the association between the fat-free mass index and Subjective Global Assessment in head and neck cancer.
Methods: The observational study- a prospective cohort study. Otolaryngology Department, Head & Neck Oncology, Medical University. Patients were classified as either well-nourished or malnourished using the Subjective Global Assessment. Bioelectrical impedance analysis was conducted on a population of 75 patients with histologically confirmed head and neck cancer and the fat-free mass index was calculated. Receiver Operating Characteristic curves were estimated using the non-parametric method to determine the optimal cut-off level of the fat-free mass index.
Results: Well-nourished patients had a statistically significantly higher ($p = 0.005$) the mean fat-free mass index (11.01 kg/m^2) as compared to those who were malnourished (9.41 kg/m^2). The fat-free mass index cut-off of 8.935 kg/m^2 was 96% sensitive and 43% specific in detecting malnutrition.
Conclusion: FFMI is considered to be an indicator of nutritional status in patients with cancer. The FFMI cut-off level of 8.935 kg/m2 might be a new parameter of implementation in detecting malnutrition among patients with head and neck cancer. Further observations are needed to implement FFMI as a prognostic and nutritional marker in clinical practice.

6-25

Malnutrition in rheumatoid arthritis: Bioelectrical impedance and body composition

Aisling O'Meachair[1], Brenda O'Connor[1,2], Cliona Lorton[2,5], Bernadette Brady[1,2], Pauline Ui Dhuidhir[2], David Joyce[2], Oliver Fitzgerarld[1,3,4], Douglas Veale[1,3,4], Declan Walsh[1,2,5]
[1]School of Medicine & Medical Science, University College Dublin, Dublin, Ireland, [2]Department of Academic Palliative Medicine, Our Lady's Hospice & Care Services, Dublin, Ireland, [3]Department of Rheumatology, Our Lady's Hospice & Care Services, Dublin, Ireland, [4]St. Vincent's Healthcare Group, Dublin, Ireland, [5]School of Medicine, Trinity College Dublin, Dublin, Ireland

Background and aims: Rheumatoid Arthritis (RA) is an inflammatory joint disease. In rheumatoid cachexia (RC) there is loss of fat free mass (FFM) with or without increased fat mass (FM); weight and Body Mass Index (BMI) may remain constant or increase. This can prevent recognition of RC. RC reduces function and life expectancy in RA. The primary aim of this study was to assess the feasibility and acceptability of Bioelectrical Impedance Analysis (BIA) to measure body composition of inpatients with RA. A secondary aim was to assess body composition in this group.
Methods: 10 consecutive participants (8 female), median age 72 years, were recruited from an inpatient rheumatology rehabilitation ward. Weight was measured and BMI calculated. FFM and FM were measured with BIA (Maltron BioScan 916) on 2 consecutive days and compared to published reference values. 4 ideal test conditions were identified (electrodes applied to right side of body, supine, bladder voided, fasting). Tests took place under real-world conditions and any divergence was noted. Participant acceptability was examined with a questionnaire.
Results: 9/10 participants were overweight or obese (BMI >25 kg/m^2 [n=5], BMI >30 kg/m^2 [n=4]). One person was underweight (BMI <18.5 kg/m^2). No reference values were available for 5 participants due to BMI. FFM was low and FM high or very high for the remaining 5.
Right side electrode placement was used in all tests. Bladder was voided for 15 and participant had fasted for 11 tests. No participant was assessed completely supine. All participants reported high device acceptability.
Conclusions:
- Device acceptability was excellent.
- Altered body composition, consistent with rheumatoid cachexia, was common.
- BMI was always abnormal. High BMI in RA may mask cachexia.
- Not all recommended test conditions were feasible in this study.
- Future studies should assess whether modified test conditions are valid.

6-26

Bioelectrical impedance analysis as an objective nutritional assessment's method in patients undergoing palliative care - preliminary study

Teresa Małecka-Massalska[1], Monika Prendecka[1], Radoslaw Mlak[1], Przemysław Matras[2], Mariusz Teter[1], Beata Kolano-Janeczek[3], Waldemar Wójcik[4]
[1]Department of Human Physiology, Medical University of Lublin, Poland, [2]Department of General and Transplant Surgery and Nutritional Treatment Medical University of Lublin, Poland, [3]Hospice of the Good Samaritan in Lublin, Poland, [4]Institute of Electronics and Information Technology Technical University of Lublin, Poland

Background and aims: Nutritional deficits have a significant impact on mortality, morbidity, and quality of life in cancer patients. Bioelectrical impedance (BIA) has been established as an easy-to-use, non-invasive, reproducible and thus valuable tool in the evaluation of body composition and nutritional status. BIA evaluates body components such as resistance (R) and reactance (Xc) by recording a voltage drop in applied current. The phase angle (PA) calculated as index of capacitance (Xc/R) has been found to be a prognostic indicator in several neoplasms: lung, pancreatic, colon and breast cancers. This study was conducted to investigate the role of Xc, R and PA as an malnutrition markers of cancer patients.
Methods: We evaluated 12 palliative women (cancer patients hospitalized in Hospice of the Good Samaritan in Lublin, Poland) and 15 healthy volunteers matched by body mass index, age and sex as a control group - between November 2014 and January 2015. Palliative patients and control group underwent a baseline nutritional assessment: subjective global assessment (SGA) and BIA. BIA was conducted at 50 kHz.
Results: Xc were found to be significantly lower in palliative patients than in the control group [medians (and 95%CIs) respectively: 2.12 (1.71–2.97) vs 5.55 (5.18–6.07), $p<0.0001$]. Similarly PA were found to be significantly lower in palliative patients than in the control group [medians (and 95%Cis) respectively: 18.55 (9.40–30.69) vs 49,68 (45.24–53.38), $p<0.0001$]. No significant differences were found during R analysis: $p = 0.4945$.
Conclusion: Palliative patients have altered tissue electrical properties expressed by bioelectrical impedance parameters. BIA could be alternative method to Subjective Global Assessment measurement and may provide more objectively assess nutritional status of patients with different cancers treated in palliative care units. However, further observations in larger sample sizes are needed to validate use of parameters of BIA as a nutritional marker or prognostic factor in clinical practice.

6-27

Body weight loss and survival in heart failure patients with type 2 diabetes mellitus

Jacek T. Niedziela, Piotr Rozentryt, Bartosz Hudzik, Natalia Niedziela, Wiktor Skowron, Aneta Ociessa, Lech Poloński, Mariusz Gąsior
3rd Department of Cardiology, Silesian Centre for Heart Disease, Zabrze, Poland

Background and aims: Patients with chronic heart failure (HF) and overweight or obesity live longer than normal-weight individuals. This, so called obesity paradox, does not exist in HF patients with type 2 diabetes mellitus (DM). Weight loss (WL) is not routinely recommended in HF, as it may worsen prognosis. On the other hand, moderate weight loss (about 7%) is recommended for overweight or obese patients with DM. The aim of this study was to assess whether DM modifies the impact of WL on mortality in HF patients.
Methods: 877 patients with HF were included in the study. Patients with stable body mass – body mass changes ± 2.5% (WS) and at least 7.5% weight loss (WL) were selected. Clinical parameters and 3-year outcome were compared between WL and WS groups for patients with and without DM separately.
Results: DM was found in 30.9% (n = 271) patients. 417 (47.5%) and 116 (13.2%) patients were included into WL ad WS groups respectively. WL was found more often in diabetic patients, comparing with those without DM: 53.5% vs 44.9% (p=0.018) respectively. There were no differences in the degree of WL, left ventricular ejection fraction, peak VO2, NT-proBNP levels, HF etiology or duration between diabetic and non-diabetic groups with WL.In non-diabetic group WL was associated with a higher 3-year mortality than WS: 38.8% vs 26.9%, respectively (log-rank p=0.047). Among patients with DM the prognosis in WL and WS groups was similar, with death rate 42.3% and 35.3%, respectively (log-rank p = 0.51). In the model adjusted for age, sex, BMI before HF, HF etiology and duration WL was associated with a higher risk of 3-year mortality only in non-diabetic patients: HR 1.88 (1.17-3.03), p = 0.009.
Conclusions: Weight loss in HF patients with DM did not worsen prognosis. Diabetes mellitus abolished protective effect of stable weight on long term survival.

6-28

Wasting and microbiota derangement induced by a peculiar "fed ad libitum", normocaloric diet providing 20% nitrogen but deprived of essential amino acids. An experimental model

Giovanni Corsetti[1], Claudia Romano[1], Evasio Pasini[2], Vincenzo Flati[3], Guerino Lombardi[4], Roberto Bevilacqua[5], Francesco S. Dioguardi[6]
[1]Department of Clinical and Experimental Sciences, Division of Human Anatomy and Physiopathology, University of Brescia, Brescia, Italy, [2]S. Maugeri Foundation, IRCCS, Cardiology Rehabilitation Division, Medical Centre of Lumezzane, Brescia, Italy, [3]Department of Biotechnology and Applied Clinical sciences, University of L'Aquila, Italy, [4]Department of laboratory Animals, IZSLER, Brescia, Italy, [5]C Pozzo Foundation, Milano, Italy, [6]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Background and aims: An experimental model of sarcopenia wasting and cachexia (SWC) was induced by a normocaloric diet. SWC is rapidly induced by the absence of essential amino acids (EAA) in quantitatively normal nitrogen intake.
Methods: Two groups of middle aged Balb/C male mice were fed according AIN93A-NIH7A rules for total nitrogen content. One group (n=11, NonEAA) was fed with a diet providing nitrogen as 100% NonEAA, second group (n=5, Controls) was fed with Purina chow. Both feed and water were provided *ad libitum*.
Results. NonEAA animals lost 30% of body weight (BW) after 21 days, although caloric intake was the same than in Controls. Organ weight/BW ratio in NonEAA vs Controls significantly increased in heart (1.01 ± 0.3 *vs* 0.66 ± 0.2), and decreased in kidneys (1.76 ± 0.2 *vs* 1.93 ± 0.1) and spleen (0.26 ± 0.05 *vs* 0.49 ± 0.12). In NonEAA group, *E.Coli* and fecal coliforms, multiplied and dominated the microbiota yet after 5 days, also increased were colonies of Mycetes. On the contrary, in gut flora of Controls, *Lactobacillus* was dominant.

In NonEAA group, serum albumin level decreased (22.6 ± 1.7 *vs* 28.7 ± 2.5 g/L), while the urea level increased (14.4 ± 3 *vs* 8.5 ± 2 mmol/L), compared to control animals.
In NonEAA were also altered blood white cells: neutrophils increased (59.2% ± 6 *vs* 23% ± 5), while lymphocytes (37.3% ± 6.7 vs 73.7% ± 5.2) and platelets (542 ± 279 *vs* 1028 ± 486 K/μL) decreased.
Conclusions: diets containing excess of NonEAA may induce SWC in experimental models. This model further underlines pivotal role of EAA in nourishing demanding patients. Microbiota derangement follows malnutrition, thus treating microbiota without contemporarily treating protein malnutrition would fail to reach its goals. The question is if the anatomical and hystochemical modifications, and peculiarly those of liver, heart, kidneys and spleen, as well as those of microbiota, may be reversed, and at what extent, by re-nourishing SWC induced by "qualitative" malnutrition.

6-29

Exercise attenuates body protein losses and enhances muscle protein turnover and sympathetic activity during body weight reduction

Tetsuo Yamada[1], Shin-ichi Kurasawa[1], Masami Matsuzaki[1], Akira Tanaka[2]
[1]Nutrition and Dietetics, Kanto Gakuin University, Yokohama, Japan, [2]Laboratory of Clinical Nutrition and Medicine, Kagawa Nutrition University, Sakado, Japan

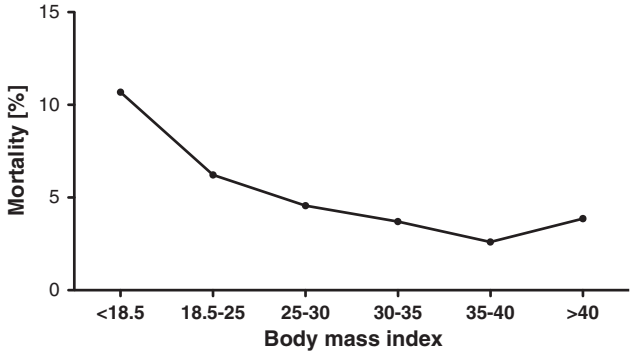
Background and aims: Insufficient energy intake causes muscle wasting, whereas exercise is effective to maintain and/or increase muscle mass. We investigated whether exercise attenuates the adverse effects of a reduction in body weight induced by dietary restriction.
Methods: Six adult male volunteers participated in two 10-day experiments. Each experiment consisted of two 5-day periods (total 10 days); the first half as an adjustment perio d and the second half as a treatment period. A wash out period was set between both of 10-day experiments. Dietary & exercise treatment was followed by dietary only treatment in half of the participants and the order was reversed for the other half (each group: n = 3). Actual energy intake during the adjustment period was 2,521 ± 124 kcal/day (mean ± SEM). During the diet only period (non-Ex period), the experimental diet comprised one-half of the energy intake consumed during the adjustment period (1,261 ± 62 kcal/day) and all foods were reduced in proportion to the energy intake. During the diet & exercise period (Ex period), the experimental diet comprised three-quarters of the adjustment period (1,891 ± 93 kcal/day) in a manner similar to the diet only period, and the amount of additional energy expenditure induced by exercise on a bicycle ergometer was one-quarter of the energy intake during the adjustment period (630 ± 31 kcal/day).
Results: Lean body mass significantly decreased during both the treatments and a significantly larger decrease was induced by the dietary only treatment, and basal metabolism was also significantly decreased after the diet only period. Significantly larger nitrogen and riboflavin losses were observed during non-Ex period. On the other hand, Urinary 3-methylhistidine, adrenalin and noradrenalin excretion levels were significantly increased during Ex-period.
Conclusions: During body weight reduction, exercise reduces body protein catabolism and brings larger muscle protein turnover and vigorousness compared to the dietary only treatment.

6-30

Nutritional status, nutritional intake, and mortality in adult hospitalized patients: results of a European-wide NutritionDay survey

Mitja Lainscak, Stefan D. Anker, Jerneja Farkas, Michael Themessl-Huber, Alessandro Laviano, Michael Hiesmayr, Karin Schindler

Background: Nutritional status and body weight trajectory are associated with outcome in patients with heart failure. To what extent this applies to hospitalized patients and whether there is association with appetite and nutritional intake during acute event is largely unknown. The NutritionDay survey is an ongoing multinational registry that collects comprehensive data about nutritional indices and in-hospital outcome. This analysis aimed to investigate relations between nutritional status, weight changes, nutritional intake, and all-cause mortality in patients with heart failure.
Methods: NutritionDay is a European-wide standardized one-day cross sectional survey of nutritional factors and food intake in hospitalized patients. Investigators reported heart failure for individual patients. Body weight changes within last 3 months, nutritional intake during last week and on the survey day were recorded; investigators reported about all-cause in-hospital mortality.
Results: HF was reported for 14616 patients (75±14 years, 51% men, median stay 17 days) with an average BMI of 26.68±6.55 kg/m^2. Overall, 6% had BMI <18.5, indicating malnutrition, and 25% were obese. Weight loss within last 3 months was self-reported by 48% of patients (most often 4-5kg – 7%). During last week, 31% reported to eat less than half of what they normally eat; on survey day, 54% ate half or less of their lunch/dinner. Enteral and/or parenteral nutrition was delivered to 13% of patients. During hospital stay, 694 (6%) patients died. More patients with weight loss died when compared to those with stable weight or weight gain (6% vs 3%, p<0.001). Low body mass index but not obesity was associated with increased mortality (Figure). Similar applied to poor food intake during last week or on study day and for enteral/parenteral nutritional support (p<0.001 for all).
Conclusions: Malnutrition, weight loss and poor food intake are common in hospitalized patients with HF and are associated with in-hospital mortality.



6-31

Nutritional screening is associated with muscle wasting in patients with chronic heart failure: insights from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

Masakazu Saitoh, Amir Emami, Nicole Ebner, Michiyoshi Hatanaka, Miroslava Valentova, Anja Sandek, Stefan D. Anker Stephan von Haehling

[1]Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany

Objectives: The mini-nutritional assessment short form (MNA-SF), in which lower values indicate potential malnutrition, is recommended to assess nutritional status in older people or patients with chronic disease such as heart failure. Malnutrition is one of the causes of muscle wasting in chronic disease. Our objective was to assess the diagnostic properties of MNA-SF in muscle wasting among ambulatory heart failure patients.

Methods and results: We assessed MNA-SF score in 130 patients (25 female, 66±12years) who were recruited at Charite Medical School, Berlin, Germany as part of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Muscle wasting was defined using the criteria for sarcopenia as an appendicular skeletal muscle 2 SD below the mean of healthy young reference group. A total of 19 patients (14.5%) presented with muscle wasting, and these patients indicated higher MNA-SF score than those without (12 points (interquartile range [8-13]) vs. 13 points [12-14], p=0.016). Single predictor logistic regression revealed that body mass index, age, and MNA-SF all predicted muscle wasting (all $p<0.05$). MNA-SF remained an independent predictor of muscle wasting after adjustment for age, body mass index, and sex (odds ratio 0.744 per 1 point increase, 95% confidence interval 0.570-0.970, p=0.03).

Conclusions: Patients with heart failure and muscle wasting are at increased risk of malnutrition. Additional analyses are required to verify whether muscle wasting alone leads to poor nutritional status, however, physicians should check both muscle and nutritional status in the patients with heart failure.

DOI: 10.1002/jcsm.12087