MEETING REPORT

Journal of Cachexia, Sarcopenia and Muscle 2019; **10**: 218–225
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12408

Recent developments in the field of cachexia, sarcopenia, and muscle wasting: highlights from the 11th Cachexia Conference

Nicole Ebner[1,2]*, Stefan D. Anker[3,4,5] & Stephan von Haehling[1,2]

[1]*Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany,* [2]*German Center for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany,* [3]*Division of Cardiology and Metabolism, Department of Cardiology (CVK), Charité, Berlin, Germany,* [4]*Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany,* [5]*DZHK (German Centre for Cardiovascular Research), partner site Berlin, Charité, Berlin, Germany*

Abstract

This article highlights the updates from preclinical and clinical studies into the field of wasting disorders that were presented at the 11th Cachexia Conference held in Maastricht, the Netherlands, in December 2018. Herein, we summarize the biological and clinical significance of different markers and new diagnostic tools and cut-offs for the detection of skeletal muscle wasting, including micro-RNAs, siRNAs, epigenetic targets, the ubiquitin–proteasome system, mammalian target of rapamycin signalling, news in body composition analysis including the D3-creatine dilution method, and electrocardiography that was modified to enable segmental impedance spectroscopy. Of particular interest were the beneficial effects of BIO101 on muscle cell differentiation, hypertrophy of myofibers associated with mammalian target of rapamycin pathways activation, and the effect of metal ion transporter ZIP14 loss that reduces cancer-induced cachexia. The potential of anti-ZIP14 antibodies and zinc chelation as anti-cachexia therapy should be tested in patients with cancer cachexia. Big randomized studies were presented such as RePOWER (observational study of patients with primary mitochondrial myopathy), STRAMBO (influence of physical performance assessed as score and clinical testing), MMPOWER (treatment of elamipretide in subjects with primary mitochondrial myopathy), FORCE (examined differences in relative dose intensity and moderate and severe chemotherapy-associated toxicities between a strength training intervention and a control group), and SPRINTT (effectiveness of exercise training in healthy aging). Effective treatments were urothelin A, rapamycin analogue treatment, epigenetic factor BRD 4 and epigenetic protein BET, and the gut pathobiont *Klebsiella oxytoca*. Clinical studies that investigated novel approaches, including urolithin A, the role of gut microbiota, metal ion transporter ZIP14, lysophosphatidylcholine and lysophosphatidylethanolamine, and BIO101, were described. It remains a fact, however, that effective treatments of cachexia and wasting disorders are urgently needed in order to improve patients' quality of life and their survival.

Keywords Cachexia; Muscle wasting; Sarcopenia

Received: 17 January 2019; Accepted: 18 January 2019
**Correspondence to: Nicole Ebner, Department of Cardiology and Pneumology, University of Göttingen Medical Center, 37075, Göttingen, Germany. Email: nicole-ebner@gmx.de*

Introduction

The development of preventive and therapeutic strategies against cachexia and wasting disorders, such as sarcopenia, is perceived as an urgent need by health professionals and has instigated intensive research into the pathophysiology of these syndromes.[1–4] Unlike sarcopenia, cachexia is characterized by progressive weight loss affecting different body compartments, particularly muscle tissue and adipose tissue, although even bone mineral content may be affected.[5] Muscle wasting diseases such as sarcopenia, myopathies, and cachexia are associated with the decline in differentiation of muscle cells into functional myofibers. This leads to a decrease in mobility and poor quality of life. Over the last years,

the Cachexia Conference has developed into a forum for researchers from all fields of cachexia and wasting disorders. It is unique in several ways as it provides a platform for both clinicians and basic researchers to meet and discuss pathways and potential therapeutic targets as well as recent evidence from clinical trials. The 11th conference was held in Maastricht, the Netherlands, from 7 to 9 December 2018 with over 350 participants from more than 30 countries attending and over 200 abstracts being presented as posters.

Basic science

This year, some interesting updates on signalling pathways and small molecules were presented. Especially, analysis of the genome including RNAs, micro-RNAs, the proteome, and microbiota was in the focus this year. So it was of special interest that Wand *et al*. (Emory University, Atlanta, GA, USA) presented data of muscle-derived exosome miRNA-26a in mice with chronic kidney disease. By using an engineered exosome vector, miRNA-26a generated in muscle satellite cells and injected into the tibialis anterior muscle of mice with chronic kidney disease, they impressively showed that overexpression of miRNA-26a in muscle prevents chronic kidney disease-induced muscle loss and cardiac fibrosis via exosome-mediated muscle-heart crosstalk. RNAs as novel regulators of gene expression in cancer cachexia were also presented by Damaraju *et al*. (University of Alberta, Edmonton, Canada). Several small nuclear RNAs (snRNA) or the introns can be ribozymes that are spliced by themselves. RNA can also be altered by having its nucleotides modified directed by small nucleolar RNAs (snoRNA) found in the nucleolus. The potential of miRNAs, piwi-interacting (pi)-RNAs, small interfering (si)-RNAs, sno-RNAs, and transfer (t)-RNAs is discussed in the recent literature[6,7] and was presented during the congress.[8–11] They profile and identify differentially expressed small non-coding RNAs (miRNAs, piRNAs, and mRNAs) from muscle biopsies (22 cachectic and 20 non-cachectic cancer patients). To validate representative sncRNAs, they used real-time PCR and to replicate their findings in independent muscle biopsies. Phenotyping of cases was based on the international consensus diagnostic framework for classifying patients as cachectic or not. A total of 453 piRNAs were identified, and five piRNAs were retained after stringent filtering as differentially expressed ($P < 0.05$ and fold change- 1.3). The identified miRNAs and piRNAs are associated with cachexia phenotype and have potential in developing targeted therapeutics. Paola Costelli (University Torino, Torino, Italy) gave an overview of the role of miRNA in muscle wasting. miRNAs and also other non-coding RNAs are modulated in the skeletal muscle of both tumour-bearing mice and cancer patients. In plasma-derived microvesicles, miRNAs seem to be less prone to changes. Nevertheless, further studies are needed to clarify the possibility to use miRNAs as biomarkers in cachexia. In this regard, Wang *et al*. (Columbia University, USA)[12] impressively showed a metal ion transporter ZIP14 that was up-regulated in cachectic muscles from five independent metastatic models as well as in patients with metastatic cancer. They showed that the cytokines tumour necrosis factor (TNF) and transforming growth factor beta (TGF-β) up-regulate ZIP14 in muscles, resulting in the accumulation of intracellular zinc. Zip proteins have been shown to import zinc into the cytosol from the plasma membrane or intracellular organelles. Zip14 is a member of the zinc transporter family, which is involved in zinc uptake by cells. Increased zinc in muscle cells degrades myosin heavy chain, a major determinant of muscle mass and function. They concluded that ZIP14 loss reduces cancer-induced cachexia. The potential of anti-ZIP14 antibodies and zinc chelation as anti-cachexia therapy should be tested in patients with cancer cachexia. One of these important pathways is the ubiquitin–proteasome system. The ubiquitin–proteasome system plays a critical role in skeletal muscle wasting. Studies from many groups over the past years have indeed identified many components in the ubiquitin conjugating system that are induced in atrophying skeletal muscle. Shavlakadze *et al*. (Biometrics Matters Limited, New Zealand)[13] gave an overview about targeting the mammalian target of rapamycin complex 1 (mTORC1) pathway for age-related disorders. They impressively showed that mTORC1 inhibition increases mass in sarcopenic muscle. The sustained mTORC1 activity in aging rat skeletal muscle results in up-regulation of mTORC1 pathway components and concomitant loss of muscle mass. Inhibition of mTORC1 with rapalogs is not detrimental to skeletal muscle and increased mass in selected muscle groups. Rapamycin and its analogues (rapalogs) are the first generation of mTOR inhibitors, which have the same molecular scaffold but different physiochemical properties. Rapalogs are being tested in a wide spectrum of human tumours as both monotherapy and a component of combination therapy. Low-dose rapalog treatment reverses several protein/gene expression signatures associated with sarcopenia. They concluded that multiple mechanisms can contribute to amelioration of the phenotype and accumulation of autophagic pathway components in treated tissue. They showed the increased adenosine monophosphate-activated protein kinase (AMPK)-α energy sensing pathway activity and possible improvement of metabolism together with the reduction of senescence marker levels which implicate enhanced satellite cell function. In this context, James Carson *et al*. (Center for Colon Cancer Research, University of South Carolina) showed that mammalian target of rapamycin (mTOR) signalling is activated after the dark cycle in wild-type mice and associated with the activation of protein synthesis but can be disassociated from protein synthesis in tumour-bearing mice. They showed interleukin-6 (IL-6) knockout (k.o.) mice suppressed insulin-like growth factor-1 and Akt/mTORC1 activation upon the initial resumption

of cage activity to recover muscle mass. Overall, there is a suppression of diurnal anabolic signalling in tumour-bearing mice, which is related to mTORC1 signalling being disassociated from muscle protein synthesis. Stretch activation of mTOR and protein synthesis is disrupted in by tumour-derived media and IL-6 in cultured myotubes. In tumour-bearing mice, mTOR activation is maintained, while the activation of protein synthesis is blocked. Muscle Akt/mTORC1 activity is suppressed after resumption of cage activity in IL-6 k.o. mice. There is a consistently strong relationship between tumour growth, circulating IL-6, and cachexia. Systemic IL-6 overexpression is sufficient to suppress basal and eccentric contraction-induced protein synthesis. Basal and contraction-stimulated protein synthesis is differentially regulated by skeletal muscle gp130 muscle signalling. The role of inflammatory signalling related to signal transducer and activator of transcription-3 and transcription factors nuclear factor-κB (NF-κB) for the suppression of basal and contraction-induced protein synthesis during the progression of cancer cachexia is not fully understood. Overall, there is a suppression of diurnal anabolic signalling in tumour-bearing mice, and further research is warranted to investigate the role of decreased physical activity and inhibited physical activity signalling for the suppression of muscle anabolic signalling during the progression of cancer cachexia. This opens new targets in the field of analysing the pathways of cachexia. Ratnam *et al*.[14] (Department of Cancer Biology and Genetics, The Ohio State University Wexner Medical Center, Columbus, OH, USA) gave an overview to the important functions of NF-κB in myoblast to stimulate activin and inhibit muscle differentiation. They impressively showed that NF-κB is activated in cachectic muscle in both paired box 7 progenitor cells and myofibers.[15,16] Other studies buttress the view that increased forkhead box protein O (FoxO) signalling and the activation of the transcription factors NF-κB, muscle RING finger 1 (MuRF1), and muscle atrophy F-box (MAFbx) in skeletal muscle play major roles during cachexia onset and progression.[17–19] MuRF1 and MAFbx are essentially involved in muscle atrophy development. Indeed, genes whose expression levels are commonly increased during multiple models of skeletal muscle atrophy, including cancer and sepsis, are MAFbx, MuRF1, and cathepsin, and there is evidence that each is a FoxO target gene. Inducers of MuRF1 and MAFbx expression are TNF, IL-6, and interleukin-1 (IL-1), and NF-κB appears to be the most important regulator of MuRF1 and MAFbx expression in the skeletal muscle.[5] In addition, recent experimental evidence pinpoint the atrophying effect of circulating activin A towards skeletal muscle, suggesting that activin A could predict poor survival in cancer patients by contributing to the loss of skeletal muscle mass. By using a model of primary human skeletal muscle cells, Loumaye *et al*. (Université Catholique de Louvain, Belgium)[20] presented the mechanisms involved in muscle atrophy induced by activin A. Activin A (100 ng/mL during 48 h) caused atrophy of differentiated skeletal muscle cells, characterized by a reduction of the myotube diameter associated with a decrease of the cellular content in slow myosin heavy chain. Activin A causes atrophy of human skeletal muscle cells by repressing transcription and activity of MEF2C leading to a decrease in MYH7 transcription and slow myosin heavy chain synthesis. Some factors known to increase MEF2C activity, such as exercise, should be assessed in order to prevent the atrophying effect of activin A on skeletal muscle and hence the development of cancer cachexia.

Giuseppina Caretti *et al*. (Universita degli Studi di Milano, Milan, Italy) showed the epigenetic targeting as a new field of development therapeutic avenues in muscle wasting. They interestingly showed that the epigenetic factor BRD 4 and the protein BET regulate cachexia through direct activation of the muscle atrophy programme. The pharmacological blockade of BET prevents the activation of catabolic genes associated with skeletal muscle atrophy and decreases IL-6. Moreover, BET proteins are required to coordinate an IL-6-dependent AMPK nuclear signalling pathway leading to the activation of the FoxO 3 transcription factor. Thus, BET proteins are a promising target to counteract cancer cachexia. Another potential field of development of therapeutically avenues in cancer cachexia is the gut microbiota.

Pötgens *et al*. (Université catholique de Louvain, Brussels, Belgium)[21] presented the role of gut microbiota. They identified *Klebsiella oxytoca* as one of the main Enterobacteriaceae species increased in cancer cachexia and demonstrated that these bacteria act as a gut pathobiont by altering gut barrier function in cancer cachectic mice. They propose a conceptual framework for the lower colonization resistance to *K. oxytoca* in cancer cachexia that involves altered host gut epithelial metabolism and host-derived nitrate boosting the growth of the gut pathobiont. They impressively showed the potential of targeting the gut microbial dysbiosis in cancer cachexia; moreover, they showed the role of *K. oxytoca* as a gut pathobiont. In this regard, Pötgens *et al*. (Université catholique de Louvain, Brussels, Belgium)[22] showed next-generation sequencing and ^{1}H-NMR metabolomics that can be used to characterize microbial ecosystem and metabolism of cachectic mice. Finally, the relevance of such biological pathways will be validated *in vivo*. Miller *et al*. (University of Edinburgh, Royal Infirmary of Edinburgh, UK)[23] showed plasma metabolomics in oesophago-gastric cancer patients. Eighteen patients were divided into two groups on the basis of percentage weight loss analysed with liquid chromatography–mass spectrometry. Metabolomic analysis identified 37 metabolites that were associated with weight loss. Metabolites with the highest fold change were lysophosphatidylcholine (ratio 1.78, P = 0.003) and lysophosphatidylethanolamine (ratio 1.79, P = 0.002). These highlight the role of increased lipolysis in cancer cachexia. Further studies are needed to validate lysophosphatidylcholine and lysophosphatidylethanolamine as early markers of cachexia in oesophago-gastric cancer. A number of elegant models were presented in order to improve our understanding of pathways involved in the wasting process. Muscle

wasting has received increasing research efforts in recent years.[24,25] Further research is warranted to investigate the role of decreased physical activity for the suppression of muscle anabolic signalling during the progression of cancer cachexia.[26] Feeding can activate cachectic muscle mTOR and protein synthesis. Stimulated contractions can attenuate muscle wasting and alter intramuscular cachectic signalling after the initiation of cachexia. Overall, there is a deficit in acute anabolic signalling induced by contraction signalling that is more pronounced than the response to feeding.[27]

Body composition

Different techniques to measure body composition were presented during the congress including computer tomography scan, dual energy X-ray analysis (DEXA) and magnetic resonance imaging, D3-creatine dilution analysis, and bio-impedance analysis. In the last years, resistance training and the impact of different training modalities were more and more focused. Liberman *et al.* (Vrije Universiteit Brussels, Belgium)[28] showed the influence of short-term and long-term detraining on muscle strength and body composition after following a resistance training programme in older adults. Community-dwelling older adults (71 ± 5 years) participating in the Senior's Project Intensive Training (SPRINT) who were randomized into 3–6 months of 3 times per week intensive strength training [75–80% of one-repetition maximum (1RM); n = 31] or strength endurance training (40–50% of 1RM; n = 32) and of whom data at 1 year follow-up were available were included. Muscle strength and appendicular muscle fat ratio were assessed through 1RM measurements and bio-impedance at baseline and at 3, 6, and 12 months after baseline. The results showed that muscle strength increased significantly after 3 and 6 months of resistance training irrespective of training load (intensive strength training and strength endurance training: all $P < 0.001$). After short-term detraining, significant decreases were observed in strength endurance training and intensive strength training (both $P < 0.05$). After additional (long-term) detraining, no significant supplementary changes were found for muscle strength. From the same group, Bautmans *et al*. (Vrije Universiteit Brussel, Brussels, Belgium) showed that 6 weeks of strength endurance training attenuates senescence-prone T cells in peripheral blood in community-dwelling older women.[29] There is growing evidence that immunosenescence and its dysregulation may play a role in the development of sarcopenia. Therefore, targeting senescent cells is thought to be a promising way to prevent or alleviate age-related sarcopenia. Although exercise is recognized as a safe countermeasure for immunosenescence, few studies have explored its long-term effect on immunosenescence. The optimum training condition required to obtain beneficial results in older subjects is lacking. One hundred older women (aged 65 years and over) were randomized to two to three times per week training for 6 weeks at intensive strength training (3 × 10 repetitions at 80% 1RM, n = 31), strength endurance training (2 × 30 repetitions at 40% 1RM, n = 33), or control (flexibility training, n = 36). The results indicate that strength endurance training protocols with many repetitions might favour the reduction of senescence-prone T cells in older women. Whether strength endurance training might represent a potential novel strategy to delay the onset and impede the progression of immunosenescence requires additional investigation. One of the main topics this year is the screening tools for the assessment of sarcopenia and frailty and muscle wasting. Steven Heymsfield stated that 'the challenge is the integrated detection of muscle quality and muscle mass and muscle function'. Surprisingly, in this regard, Skrabal *et al*. showed (Medical University Graz, Graz, Austria)[30] measurements of appendicular muscle mass and fat measurements using 12-channel electrocardiography (ECG). The ECG was modified as to enable segmental impedance spectroscopy in six body segments (thorax, abdomen, and the four limbs). The impedance at different frequencies is used to calculate fat and muscle mass in all segments and can be corrected for extracellular fluid. After validation according to whole-body DEXA scan (123 male and 153 female participants) they showed measurements of ECGs from 976 male and 847 female participants (age range 9–97 years) demonstrating a continuous rise in appendicular muscle mass peaking at 25 years and a decline thereafter in both sexes. The slope of decline is much steeper in male participants, but in very old age, appendicular muscle mass is nearly identical in both sexes. However, the most amazing method to detect skeletal muscle mass was described by Stimpson *et al*.,[31] who showed the D3-creatine dilution method for the determination of total body creatine pool size and skeletal muscle mass. This interesting method can directly assess skeletal muscle mass or its change, during aging, inactivity, disease, or exercise. This method takes advantage of a number of aspects of creatine biology. More than 90% of the total body creatine pool is found in skeletal muscle. Newly synthesized creatine from hepatic and renal sources is transported into the sarcoplasm against a large concentration gradient. ^{2}H-labelled creatine is ingested as a 30 mg capsule and distributed to skeletal muscle. Creatine is converted to creatinine and excreted in urine. Importantly, the measurement with the creatine dilution method is not affected by shifts in body water that occur in many diseases associated with cachexia.

Clinical trials and new treatment targets

Maurizio Muscaritoli (Universita de Rome, Italy) stated that 'One of five patients with cancer dies from cachexia, not

from cancer'. He presented results of the prevalence of malnutrition study PreMIO. Malnutrition was defined as Mini Nutritional Assessment score < 17 ($n = 1925$). Among cancer site groups, malnutrition stages significantly increase with stage of cancer ($P < 0.001$). They showed that decreased nutrient intake, weight loss, and malnutrition are highly prevalent at all cancer stages. More than 20% of cancer patients die for the direct or indirect consequences of cachexia. Nutrition therapy does not affect tumour growth and changes in body composition, and depletion of muscle mass may increase the risk of treatment toxicity. The timely appropriated nutritional interventions may cost-effectively improve outcome in cancer patients. In regard to nutritional supplementation, Ispoglou *et al*. (Leeds Becked University, UK) presented findings with gel-based essential amino acids supplementation intake for addressing age-related sarcopenia in 10 elderly women. The whey protein and gel-based amino acids supplement provided nearly 7.5 g of essential amino acid or the equivalent of 15 g of high-quality protein. The mean age of the woman was 70 years. The whey protein isolate facilitated an increase in protein, whereas supplementation with essential amino acid-based gel increases in both energy and protein intakes. Kamyar Kalantar-Zadeh *et al*. (University of California Irvine, CA, USA) stated that the dialysis procedure is a perfect example of the integration of undernutrition and catabolism and how it leads to protein energy wasting, a single pathological entity. They summarized how cytokine activation, the increased muscle breakdown induced by dialysis, and reduced protein and energy intake lead to protein energy wasting. The dialysis procedure itself leads to increased inflammation with production of acute phase reactants, albumin, fibrinogen, and C-reactive protein. The state of undernutrition is associated with a depleted amino acid pool, amino acid loss into dialysate, and the synthesis of acute phase proteins, limited substrate availability for muscle protein synthesis, and other anabolic processes. Undernutrition-induced hypoalbuminaemia further aggravates this situation. The body therefore catabolizes muscle and tissue protein to release amino acids in plasma to maintain the amino acid pool. The muscle reacts to catabolism by activating local cytokine production. Thus, the dialysis procedure results in an increased inflammatory response that perpetuates the muscle catabolic effect in a vicious circle.

Many studies of exercise training were presented. Caan *et al*. presented data from the Focus On Reducing Dose-Limiting Toxicities in Colon Cancer with Resistance Exercise (FORCE) study. They examined differences in relative dose intensity and moderate and severe chemotherapy-associated toxicities between a strength training intervention and a control group. A total of 180 newly diagnosed stage II and III colon cancer patients were included, and 36 patients were randomized into the training group. They received chemotherapy with fluoropyrimidine (5-fluoropyrimidine or capecitabine) ± oxaliplatin and patients received four to six in-person training sessions over the course of chemotherapy and completed two training sessions per week at home until the completion of chemotherapy. The complete results of the study will be presented during the next conference. Fancesco Landi (Universidad Católica de Roma, Roma, Italy) raised the question as to 'how much exercise is too much'? Maybe the exercise intervention trial SPRINTT[32,33] can give an answer. SPRINTT is a phase III, multicentre, randomized controlled trial aimed at comparing the efficacy in preventing mobility disability of a multicomponent intervention, based on long-term structured physical activity, personalized nutritional counselling/dietary intervention, vs. a healthy aging lifestyle education programme. A total of 1519 participants were included until November 2017 when the recruitment was finished, and the first results were shown. Also, some other new therapeutic molecules were presented this year. For example, Serova *et al*.[34] (Biophytis, Sorbonne Université, BC9, Paris, France) characterize a new small molecule, the drug candidate BIO101. Last year, the BIO103 was firstly presented, and this year, the newly BIO101 was shown. BIO101 is a pharmaceutical grade preparation of the ecdysteroid 20-hydroxyecdysone purified from stemmacantha carthamoides. BIO101 and BIO103 previously demonstrated its potential on muscle quality and function in different *in vitro* and *in vivo* models. The aim of this study was to characterize the impact of BIO101 on muscle cells differentiation. BIO101 increases phosphorylation of major kinases of AKT/mTOR pathway in C2C12 cells. The study impressively showed the beneficial effects of BIO101 on muscle cell differentiation and hypertrophy of myofibers associated with AKT/mTOR pathways activation. Moreover, they showed an increased desmin, myogenin, and myosin expression with BIO101 treatment and increases in mitochondrial mass and activity in response to BIO101 exposure. They conclude that BIO101 is believed to be responsible for improved muscle function, and these results support the clinical development of Sarconeos in sarcopenic patients. Yi-Ping Li *et al*.[35] (University of Texas Health Science Center at Houston, Texas, USA) showed the tumour-derived heat shock protein (hsp) 70/90 in cancer cachexia. Toll-like receptor (TLR) 4 has been shown to be a key mediator of muscle wasting induced by multiple types of cancer. Similarly, toll-like receptor (TLR) 4 k.o. mice were resistant to tumour-induced muscle wasting. Importantly, tumour-induced elevation of the circulating inflammatory cytokines TNF and IL-6 was dependent on tumour-released heat shock protein 70/90 and TLR4. They identified a regulatory mechanism that increases hsp70 and hsp90 involving up-regulation of Rab27B by the zinc transporter ZIP4. They impressively showed the effect of acetic acid intake on muscle quality and expressions of atrophy-related genes of aged rats. Maruta *et al*. (Okayama Prefectural University, Soja-city, Okayama, Japan)[36] showed that acetic acid increased

myoglobin, glucose transporter type 4 (GLUT4), myocyte-specific enhancer factor 2A (MEF2A), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) expressions through the activation of adenosine monophosphate (AMP)-activated protein kinase in cultured L6 myotube cells. They showed that treatment with acetic acid reduced lipid accumulation and enhanced glucose uptake in L6 cells. Moreover, they showed that expressions of atrogin 1, MURF1, and TGF-β genes were significantly lower, while MEF2A and mitochondrial DNA were increased in soleus muscle of acetic acid-administered rats. The most surprising in the field of new compounds was presented by Singh *et al*. (Amazentis SA, Lausanne, Switzerland). They present the new gut metabolite urolithin A. Urolithin A is a natural gut metabolite produced by host microbiota following transformation of precursors derived from diet. Interestingly, it is not found in food. Urolithin A restores mitochondrial function during aging.[37] During the mitochondrial life cycle, damaged mitochondria are removed by mitophagy for optimal cell function. Surprisingly, one out of three persons has the necessary gut microflora to produce urolithin A and at variable quantity due to the heterogeneity in gut microflora composition. Urolithin A was tested in 36 elderly participants (mean age: 66 years) with nine participants in each group (placebo, single intake of 250, 500, and 1000 mg) for 28 days. After a washout phase of 4 weeks, they started multiple doses for 28 days. Muscle biopsies were taken from each participant. They showed that orally administered urolithin A is safe when administered in both single and multiple ascending doses to healthy elderly subjects. They showed a decrease in plasma acylcarnitines which is indicative of improved mitochondrial function. The authors concluded that urolithin A impacts biomarkers of mitochondrial function. They impressively showed that orally administered urolithin A is bioavailable in plasma and skeletal muscle after single dosing and exhibits similar pharmacokinetics with increasing doses. Genes regulating key mitochondrial pathways are upregulated in human skeletal muscle after 4 week oral administration of urolithin A. Plasma acylcarnitines are lowered with urolithin A intervention. Long-term phase 2 interventional clinical studies have started in 2017 to investigate the effects of urolithin A on muscle and mitochondrial function. Szulc *et al*.[38] (University of Lyon, France) presented data of high-resolution pQCT (Xtreme CT, Scanco) measured in the STRAMBO study. They showed the influence of physical performance assessed as score and clinical testing (chair tests, standing with feed in side by side position with eyes open and closed, and 10-step tandem walk forward and backward). The STRAMBO cohort consists of 817 men aged 60 to 87 years. Physical performance together with grip strength was measured at baseline and after 4 and 8 years. They showed that in the osteopenic group, dynapenic obesity improved fracture prediction vs. traditional model [area under the curve (AUC) = 0.724 vs. 0.672, $P < 0.01$]. Dynapenic obesity was defined as the coexistence of fat fraction >24% and grip strength < 66 kPa (Vigorimeter Martin). They showed that dynapenic obesity was associated with fracture subtypes, e.g. peripheral fracture, AUC = 0.698 vs. 0.626, $P < 0.05$. Results of RePOWER: A Global Prospective Observational Study of Patients with Primary Mitochondrial Myopathy were presented by Michelangelo Mancuso (University of Pisa, Pisa, Italy).[39] RePOWER is designed to evaluate the genotypes and phenotypes identified in patients with primary mitochondrial myopathies and the regional differences in how patients with primary mitochondrial myopathies are managed. RePOWER also identified potential participants for MMPOWER-3 study. MMPOWER is a multicentre, randomized, double-blind, placebo-controlled study that included patients between 16 and 65 years of age with symptoms of mitochondrial myopathy and genetically confirmed mitochondrial disease. Primary mitochondrial myopathies are generally defined disorders leading to defects of oxidative phosphorylation affecting predominantly skeletal muscle. Secondary involvement of mitochondria was frequently observed in multiple neuromuscular diseases. The physiological functions of elamipretide[40] are the restoration of adenosine triphosphate production together with decreased reactive oxygen species emission and electron carriers back together with a higher membrane curvature resulting in normalized cardiolipin content. In the MMPOWER study, 30 patients in the elamipretide dosing groups (n = 9 with 0.01 mg/kg/h elamipretide, n = 9 with 0.1 mg/kg/h elamipretide, and n = 9 with 0.25 mg/kg/h elamipretide) compared with 30 patients in placebo group were included. The primary endpoint of distance covered during the 6 min walk test at day 5 was significantly higher in high-dose group (0.25 mg/kg/h) compared with the low dose and placebo. So they started the phase III of the randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of daily subcutaneous injections of elamipretide in subjects with primary mitochondrial myopathy followed by an open-label treatment extension. We are waiting for these results. Interestingly from the literature, elamipretide/bendavia was also tested in zebrafish lateral cell lines as a novel antioxidant, on gentamicin-induced hair cell damage.[41] The treatment of bendavia exhibited dose-dependent protection against gentamicin in both acute and chronic exposures. They found that bendavia at 150 μm conferred optimal protection from either acute or chronic exposure with ototoxin. Bendavia reduced uptake of fluorescent-tagged gentamicin via mechanoelectrical transduction channels, suggesting that its protective effects may be partially due to decreasing ototoxic molecule uptake. The intracellular death pathways inhibition triggered by gentamicin might be also included as no blockage of gentamicin was observed. These data suggest that bendavia represents a novel otoprotective drug that might provide a therapeutic alternative for patients receiving aminoglycoside treatment.

Conclusions

A number of definitions and diagnostic criteria for sarcopenia are available. Annemie Schols (Maastricht University, Maastricht, Netherlands) stated that 'We need personalized medicine to provide the right care to the right patient at the right time'. Sarcopenia and low muscle mass are associated with significantly increased health care costs and are associated with significantly increased risk of death in emergency abdominal surgery, cancer, and others. Prospective large studies are required in the field of cachexia, sarcopenia, and muscle wasting. From basic science, new therapeutic targets were shown including RNAsome, piRNAs, miRNAs, ZIP14, LysoPC, and LysoPE. The role of the gut microbiota in the therapeutic management of muscle wasting and cachexia and the potential epigenetic treatment targets were presented and discussed. Nevertheless, the definition of cachexia and sarcopenia as well as effective screening tools is of special interest. Big randomized studies were presented such as RePOWER, STRAMBO. MMPOWER, FORCE, and SPRINTT. Effective treatments were urothelin A, rapalog treatment, epigenetic factor BRD 4 and epigenetic protein BET, and the gut pathobiont *K. oxytoca*.

Acknowledgements

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle.[42]

Conflict of interest

None declared.

References

1. Ebner N, Werner CG, Doehner W, Anker SD, von Haehling S. Recent developments in the treatment of cachexia: highlights from the 6th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 2012;**3**:45–50.
2. Ebner N, Steinbeck L, Doehner W, Anker SD, von Haehling S. Highlights from the 7th Cachexia Conference: muscle wasting pathophysiological detection and novel treatment strategies. *J Cachexia Sarcopenia Muscle* 2014;**5**:27–34.
3. Ebner N, von Haehling S. Unlocking the wasting enigma: highlights from the 8th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 2016;**7**:90–94.
4. Ebner N, von Haehling S. Highlights from the 9th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 2017;**8**:508–511.
5. Ebner N, Springer J, Kalantar-Zadeh K, Lainscak M, Doehner W, Anker SD, et al. Mechanism and novel therapeutic approaches to wasting in chronic disease. *Maturitas* 2013;**75**:199–206.
6. Narasimhan A, Ghosh S, Stretch C, Greiner R, Bathe OF, Baracos V, et al. Small RNAome profiling from human skeletal muscle: novel miRNAs and their targets associated with cancer cachexia. *J Cachexia Sarcopenia Muscle* 2017;**8**:405–416.
7. Narasimhan A, Greiner R, Bathe OF, Baracos V, Damaraju S. Differentially expressed alternatively spliced genes in skeletal muscle from cancer patients with cachexia. *J Cachexia Sarcopenia Muscle* 2018;**9**:60–70.
8. Paul R, Griffiths M, Kemp P. Does miR-675 control the sensitivity to inflammatory signalling in muscle to promote muscle wasting? *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 2–21.
9. Paul R, Griffiths M, Kemp P. miR542-3p suppresses mitochondrial gene expression and promotes muscle wasting in patients undergoing aortic surgery. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 2–22.
10. van de Worp WRPH, Schols AMWJ, Harel-Bellan A, Kelders MCJM, Dingemans AMC, Theys J, et al. Identification of miRNAs in skeletal muscle associated with lung cancer cachexia. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 2–24.
11. Powrózek T, Mlak R, Brzozowska A, Mazurek M, Gołębiowski P, Małecka-Massalska T. MiRNA-130a significantly improves accuracy of SGA nutritional assessment tool in prediction of malnutrition and cachexia in radiotherapy treated head and neck cancer patients. *J Cachexia Sarcopenia Muscle* 2018;1121–1184, Abstract 6–04.
12. Wang G, Biswas AK, Ma W, Kandpal M, Coker C, Grandgenett PM, et al. Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. *Nat Med* 2018;**24**:770–781.
13. Shavlakadze T, Zhu J, Wang S, Zhou W, Morin B, Egerman MA, et al. Short-term low-dose mTORC1 inhibition in aged rats counter-regulates age-related gene changes and blocks age-related kidney pathology. *J Gerontol A Biol Sci Med Sci* 2018;**73**:845–852.
14. Ratnam NM, Peterson JM, Talbert EE, Ladner KJ, Rajasekera PV, Schmidt CR, et al. NF-κB regulates GDF-15 to suppress macrophage surveillance during early tumor development. *J Clin Invest* 2017;**127**:3796–3809.
15. Talbert EE, Yang J, Mace TA, Farren MR, Farris AB, Young GS, Elnaggar O, Che Z, Timmers CD, Rajasekera P, Maskarinec JM, Bloomston M, Bekaii-Saab T, Guttridge DC, Lesinski GB. Dual inhibition of MEK and PI3K/Akt rescues cancer cachexia through both tumor extrinsic and intrinsic activities. *Mol Cancer Ther* 2016, **3**, pii: molcanther.0337.2016.
16. Saitoh M, Ishida J, Ebner N, Anker SD, von Haehling S. Myostatin inhibitors as pharmacological treatment for muscle wasting and muscular dystrophy. *J Cachexia Sarcopenia Muscle Clinical Reports* 2017, **2**(1), e37: 1–10
17. Lodka D, Pahuja A, Geers-Knörr C, Scheibe RJ, Nowak M, Hamati J, et al. Muscle RING-finger 2 and 3 maintain striated-muscle structure and function. *J Cachexia Sarcopenia Muscle* 2016;**7**:165–180.
18. Kowalski K, Archacki R, Archacka K, Stremińska W, Paciorek A, Gołąbek M, et al. Stromal derived factor-1 and granulocyte-colony stimulating factor treatment improves regeneration of Pax7−/− mice skeletal muscles. *J Cachexia Sarcopenia Muscle* 2016;**7**:483–496.
19. Marino FE, Risbridger G, Gold E. Activin-βC modulates cachexia by repressing the ubiquitin-proteasome and autophagic degradation pathways. *J Cachexia Sarcopenia Muscle* 2015;**6**:365–380.
20. Loumaye A, Lause P, Thissen JP. Activin A causes human skeletal muscle cell atrophy by inhibiting slow myosin heavy chain synthesis. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 4–03.
21. Pötgens SA, Brossel H, Sboarina M, Catry E, Cani PD, Neyrinck AM, et al. Bloom of

Enterobacteriaceae in cancer cachexia: *Klebsiella oxytoca* as a gut pathobiont contributing to intestinal dysfunction. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 3–22.
22. Pötgens SA, Delzenne NM, Bindels LB. Using NMR metabolomics to unravel the pathways underlying the host-microbiota crosstalk in cancer cachexia. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 3–21.
23. Miller J, Alshehri A, Stephens NA, Ramage MI, Wigmore SJ, Ross JA, et al. Plasma metabolomics in oesophago-gastric cancer patients: a pilot study. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 3–18.
24. Espinel-Bermúdez MC, Ramírez-García E, García-Peña C, Salvà-Casanovas A, Ruiz-Arregui L, Cárdenas-Bahena A, Sánchez-García S. Prevalence of sarcopenia in community-dwelling older people of Mexico City using the EGWSOP (European Working Group on Sarcopenia in Older People) diagnostic criteria. *J Cachexia Sarcopenia Muscle Clinical Reports* 2017, **2**(2),e9:1–9
25. Kamiya K, Hamazaki N, Matsuzawa R, Nozaki K, Tanaka S, Ichinosawa Y, Maekawa E, Noda C, Yamaoka-Tojo M, Matsunaga A, Masuda T, Ako J. Sarcopenia: prevalence and prognostic implications in elderly patients with cardiovascular disease. *J Cachexia Sarcopenia Muscle Clinical Reports* 2017, **2**(2)e41:1–13
26. Lønbro S, Farup J, Bentsen S, Voss T, Rittig N, Wang J, Ørskov M, Højris I, Mikkelsen UR Lean body mass, muscle fibre size and muscle function in cancer patients during chemotherapy and 10 weeks exercise. *J Cachexia Sarcopenia Muscle Clinical Reports* 2017, **2**(1),e26:1–8
27. Dagan A, Sella T, Urban D, Bar Y, Onn A, Segal G. Low alanine transaminase is not associated with increased rate of mortality in patients with advanced lung cancer. *J Cachexia Sarcopenia Muscle Clinical Reports* 2017, **2**(1),e16:1–8
28. Liberman K, Moreels B, Knoop V, De Dobbeleer L, Costenoble A, Njemini R, et al. The influence of short-term and long-term detraining on muscle strength and body composition after following a resistance training program in older adults. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 1–20.
29. Bautmans I, Dinh HC, Onyema OO, Beyer I, Liberman K, De Dobbeleer L, et al. Six weeks of strength endurance training attenuates senescence-prone T-cells in peripheral blood in community-dwelling older women. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 1–17.
30. Skrabal F, Skrabal K, Windhaber J. Detection of sarcopenia and cachexia during the recording of the routine 12 channel ECG (Combyn™ ECG). *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 4–01.
31. Stimpson SA, Leonard MS, Clifton LG, Poole JC, Turner SM, Shearer TW, et al. Longitudinal changes in total body creatine pool size and skeletal muscle mass using the D3-creatine dilution method. *J Cachexia Sarcopenia Muscle* 2013;**4**:217–223.
32. Cesari M, Landi F, Calvani R, Cherubini A, Di Bari M, Kortebein P, et al. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. *Aging Clin Exp Res* 2017;**29**:81–88.
33. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. *Aging Clin Exp Res* 2017;**29**:35–42.
34. Serova M, Didry-Barca B, On S, Latil M, Veillet S, Lafont R, Dilda P. BIO103 accelerates differentiation and enhances mitochondrial function in skeletal muscle cells. *J Cachexia Sarcopenia Muscle* 2018, **9**:1121–1184, Abstract 4–11
35. Zhang G, Liu Z, Ding H, Zhou Y, Doan HA, Sin KWT, et al. Tumor induces muscle wasting in mice through releasing extracellular Hsp70 and Hsp90. *Nat Commun* 2017;**8**:589.
36. Maruta H, Abe R, Ma Y, Isono C, Yamashita H. Effect of acetic acid intake on muscle quality and expressions of atrophy-related genes of aged rats. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 1–67.
37. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Félix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med* 2016;**22**:879–888.
38. Szulc P, Chapurlat R. Older men with dynapenic obesity have more fragility fractures—the prospective STRAMBO study. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 1–29.
39. Mancuso M. on behalf of the RePOWER InvestigatorsThe RePOWER registry: a global prospective observational study of patients with primary mitochondrial myopathy. *J Cachexia Sarcopenia Muscle* 2018;**9**:1121–1184, Abstract 1–05.
40. Daubert MA, Yow E, Dunn G, Marchev S, Barnhart H, Douglas PS, et al. Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide. *Circ Heart Fail* 2017;**10**:e004389.
41. Kuang X, Sun Y, Wang Z, Zhou S, Liu H. A mitochondrial targeting tetrapeptide Bendavia protects lateral line hair cells from gentamicin exposure. *J Appl Toxicol*. 2018;38(3):376-384
42. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle*. 2017;**8**:1081-1083