Highlights from the 7th Cachexia Conference: muscle wasting pathophysiologial detection and novel treatment strategies

Nicole Ebner • Lisa Steinbeck • Wolfram Doehner • Stefan D. Anker • Stephan von Haehling

Abstract This article highlights preclinical and clinical studies in the field of wasting disorders that were presented at the 7th Cachexia Conference held in Kobe, Japan, in December 2013. This year, the main topics were the development of new methods and new biomarkers in the field of cachexia and wasting disorders with particular focus on inflammatory pathways, growth differentiation factor-15, myostatin, the ubiquitin proteasome-dependent pathway, valosin and the regulation of ubiquitin-specific protease 19 that is involved in the differentiation of myogenin and myosin heavy chain. This article presents highlights from the development of drugs that have shown potential in the treatment of wasting disorders, particularly the ghrelin receptor agonist anamorelin, the myostatin antagonist REGN1033, the selective androgen receptor modulators enobosarm and TEI-E0001, and the anabolic catabolic transforming agent espindolol. In addition, novel data on the prevalence and detection methods of muscle wasting/sarcopenia are presented, including the D3-creatine dilution method and several new biomarkers.

Keywords Cachexia • Muscle wasting • Sarcopenia • Therapy

1 Introduction

The term cachexia embraces a complex metabolic syndrome characterized by loss of body weight that may develop as a consequence of a chronic illness. Cachexia can affect muscle mass with or without the loss of fat mass; bone mineral density may be affected as well [1]. The term sarcopenia, on the other hand, describes the age-related loss of muscle mass and function. The development of preventive and therapeutic strategies against cachexia, sarcopenia and wasting disorders in general is perceived as an urgent need by healthcare professionals [2]. Over the last years, the Cachexia Conference has developed a platform for both clinicians and basic researchers to meet and discuss pathways as well as potential therapeutic targets from the fields of cachexia and wasting disorders [3]. The 7th Cachexia Conference was held in Kobe, Japan, from 9 to 11 December 2013, with over 350 participants from more than 30 countries attending. Some of the most appealing contributions to the conference are highlighted here.

2 Basic science

Numerous pathways are proposed to be involved in the development of cachexia and age-dependent muscle degeneration. This year, some elegant models were presented to better understand the mechanism behind muscle wasting and cachexia. Many factors are involved in muscle wasting, and many pathways are still unknown. Pro-inflammatory cytokines, in particular tumour necrosis factor-α (TNFα), interleukin-1, interleukin-6 and interferon-γ, are elevated in different diseases. Systemic inflammation and increased circulating TNFα levels have been implicated in various conditions accompanied by muscle atrophy [4]. Pro-inflammatory cytokines may induce muscle catabolism and proteinolysis signal in skeletal muscle. Constantin-Teodosiu et al. [5] (Nottingham University Medical School, Nottingham, UK) used a rodent model to show that acute endotoxaemia (lipopolysaccharide-induced) increases muscle protein expression of TNFα and inhibits pyruvate dehydrogenase.
complex. They showed that acute endotoxaemia increases muscle protein expression of TNFα and its downstream target pyruvate dehydrogenase kinase isomorf 4 in vastus lateralis muscle biopsy. One interesting candidate in the pathway of muscle wasting, presented at the conference, is the receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL). RANK and RANKL are members of the TNFα superfamily, and they are involved in the development of muscle dysfunction. Dumont et al. [6] (University Laval, Vienna, Austria) showed that inhibition of the RANK and RANKL pathway increases sarco/endoplasmic reticulum calcium adenosine triphosphatase (Ca²⁺ ATPase) activity and forces protein production in fast twitch skeletal muscle.

This year, the main focus of the conference was aimed at identifying new biomarkers of sarcopenia and muscle wasting. Some studies showed that the growth differentiating factor-15 (GDF-15) plays an important role in the pathways of muscle wasting and cachexia. GDF-15 is a protein belonging to the transforming growth factor beta superfamily that has a role in regulating inflammatory and apoptotic pathways during disease processes. The group of Lerner et al. [7] (AVEO Pharmaceutical Inc., Texas, USA) showed that GDF-15 induces significant weight, muscle and fat loss in mice. Human GDF-15 was administered subcutaneously to mice, and it was shown that treated animals have lower activity and decreased energy expenditure compared to placebo. Muscle strength measured as handgrip strength was significantly lower in GDF-15-treated animals; muscle strength in quadriceps, gastrocnemius and tibialis anterior muscles was also significantly decreased by GDF-15 administration. These findings suggest that GDF-15 induces weight, muscle, and fat loss and that it decreases the activity in mice and may be a promising target for therapeutic interventions in the field of cachexia and muscle wasting. To emphasise this relation, Tsai et al. [8] (St Vincent’s Hospital and University of New South Wales, Sydney, Australia) showed that overexpression of MIC-1/ GDF-15 in mice with advanced cancer results in anorexia and cachexia. These data suggest that monoclonal antibodies against this cytokine may prove to be an effective therapeutic approach for cachectic patients who present with a substantial elevation in their serum level of GDF-15. Another member of the transforming growth factor-β superfamily is myostatin. Myostatin is well characterized as a negative regulator of muscle growth and has been implicated in several forms of muscle wasting including severe cachexia [9]. Myostatin has high affinity to the activatin IIB receptor, and it has been shown that administration of soluble receptor of myostatin resulted in an improvement in body and muscle weight in mice. Cui et al. [10] (University of Maryland School of Medicine, Baltimore, MD, USA) showed that increased expression of activatin IIB receptor in non-human primate radiation induced cachexia. They showed that whilst levels of activatin IIB receptor were significantly increased, levels of myostatin were decreased in cachectic animals.

To understand the mechanism of wasting, some interesting animal studies and cell culture studies were presented in Kobe this year. 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. By using a mouse model, Picirillo and Goldberg [11] (Harvard Medical School, Boston, MA, USA) showed the critical role of valosin-containing proteins in muscle atrophy. Valosin-containing proteins act as a ubiquitin segregase that remodels multimeric protein complexes by extracting polyubiquitinated proteins for recycling or degradation by the proteasome. Therefore, they play an important role in extracting ubiquitinated proteins from myofibrils during atrophy. Surprisingly, inhibition of a valosin-containing protein (p97) caused rapid growth of myotubes (without enhancing protein synthesis) and hypertrophy of adult muscles. Thus, they concluded that valosin-containing proteins restrain postnatal muscle growth and are essentially involved in accelerated degradation of muscle proteins. Importantly, not only the extraction of ubiquitinated proteins but also deubiquitinating enzymes such as ubiquitin-specific protease 19 (USP19) are induced in various forms of atrophying muscle. Members of the ubiquitin-specific protease (USP) superfamily of cysteine protease seem to play a role in this context by protecting muscle cells from atrophy. The most intensively studied deubiquitinase is USP19. The group around Wiles et al. [12] (McGill University, Montreal, Quebec, Canada) analysed the effects of modulating USP19 isoform levels on L6 and C2C12 muscle cell fusion and expression of myogenic proteins. They found that a decrease of USP19 promoted muscle cell fusion and increased myotube diameter and expression of myogenin and myosin heavy chain. The opposite effect was found with overexpression of USP19. Thus, they concluded that the regulation of USP19 expression is required for normal differentiation of myogenin and myosin heavy chains and may act through regulation of endoplasmic reticulum stress during myoblast fusion. In this regard, Segawa et al. [13] (Teijn Pharma Limited) identified and characterized a novel USP19 inhibitor. They used a high-throughput screening assay to identify small molecule inhibitors of USP19. Indeed, USP19 inhibitor may be a new therapeutic target for the treatment of muscle atrophy.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcriptional coactivator that regulates the genes involved in energy metabolism. Costelli et al. [14] (University of Turin, Turin, Italy) investigated C57/BL6 mice to show that PGC-1α overexpression can prevent muscle wasting in an experimental cancer cachexia model. Interestingly, these authors showed that the enhanced oxidative capacity induced by PGC-1α overexpression in skeletal
muscle improves cancer-induced muscle wasting in female, but not in male, mice. They explained this effect by the different tumour mass, but further studies need to clarify the role of PGC-1α and the mechanism of how PGC-1α overexpression rescue muscle loss.

3 Muscle wasting and sarcopenia

The clinical problem of muscle wasting is mainly the fact that this clinical entity cannot be easily defined, and many different definitions have been used in different studies. Kim et al. [15] (University Seongnam, South Korea), for example, defined sarcopenia as appendicular skeletal mass divided by body weight (ASM/Wt), appendicular skeletal mass divided by height squared (ASM/Ht²) and total body skeletal mass divided by body weight (TSM/Wt). They included a total of 414 older adults (mean age, 65 years, and divided these subjects into two groups of older patients with (n=144) or without (n=270) diabetes mellitus. Interestingly, the prevalence of sarcopenia was not only higher in diabetic patients than in patients without diabetes but also varied by the definition used: (ASM/Wt = 23.7 % vs. 12.3 %, ASM/Ht² = 57.6 % vs. 41.5 %, TSM/Wt = 49.2 % vs. 20.0 %). Also, Povoroznyuk and Dzerovych [16] (Institute of Gerontology NAMS Ukraine, Kyiv, Ukraine) analysed the prevalence of sarcopenia and included 8,637 women of different age groups (age range, 20–89 years). Using dual-energy X-ray analysis (DEXA), they assessed lean and fat mass and found that fat and lean mass decreased with age; however, the prevalence of sarcopenia in women aged 65 and older was only 7 %.

Unfortunately, the definition of sarcopenia used for this analysis remains unclear. Prevalence values may also differ by the assessment technique used, and DEXA data may vary from bioimpedance measurements. Yamada et al. [17] (University Graduate School of Medicine, Kyoto, Japan) analysed 568 healthy men and 1,314 healthy women aged 65–89 years. Sarcopenia was defined as poor muscle function (low skeletal muscle mass measured with bioimpedance analysis, low 10-m walking speed and low handgrip strength). Interestingly, the prevalence of sarcopenia increased in both genders in subjects older than 75 years, but in subjects 65–75 years, the prevalence of sarcopenia was higher in women than in men [18]. Table 1 provides an overview of the different definitions of sarcopenia that have been used in different studies.

Another main aspect of the conference was the presentation of new methods for the measurement of skeletal muscle mass and loss. One interesting new method seems to be segmental bioelectrical impedance spectroscopy. Yamada and Kimura [19] (University of Wisconsin-Madison, Wisconsin, USA) presented data from 93 elderly men. They assessed intracellular and extracellular water and found that only intracellular water decreased by age compared to the extracellular component. Thus, intracellular water measurement can be used in a manner similar to the measurement of muscle strength (grip strength) to discriminate the elderly requiring care. There is a need for exact and new methods to discriminate between normal muscle function and muscle wasting. Therefore, measurements of skeletal muscle mass with different new methods were presented this year. Wilkinson et al. [20] (Royal Derby Hospital Centre, Derby, UK) tested the efficacy of deuterium oxide (D₂O) for measuring muscle anabolism in vastus lateralis muscle biopsies of eight young men (mean age, 22 years) over 8 days who undertook one-legged knee extensor resistance exercise. In the resting other leg, a decreased rate of myofibrillar, sarcoplasmic and collagen protein synthesis was noted compared to the exercised leg. To measure D₂O in body water and to estimate fat-free mass and fat mass, Walker et al. [21] (Texas A&M University, Texas, USA) described gas chromatography–tandem mass spectrometry as the most accurate method. In summary, the D₂O method is a valid but invasive approach to quantify muscle anabolism before any changes in muscle mass become detectable. However, the most amazing method was recently described by Stimpson et al. [22]. They described D₃-creatine dilution for the determination of total body creatine pool size and skeletal muscle mass. William Evans from Durham, NC, USA, presented this new direct, noninvasive method for the measurement of total skeletal muscle mass. In this method, a single oral administration of a stable (non-radioactive) isotope of creatine (30 mg D₃-creatine) is ingested, enters the circulation, and is actively transported into skeletal muscle and thus diluted in the skeletal muscle creatine pool. Creatine is converted into creatinine in an irreversible, non-enzymatic reaction and excreted in the urine. Thus, muscle mass can be determined from the enrichment of D₃-creatine in a single sample of urine. It was demonstrated that D₃-creatine analysis using liquid chromatography–tandem mass spectrometry (LC-MS/MS) produced results that were essentially identical to analysis by isotope ratio mass spectrometry and that the D₃-creatine dilution method can be used for longitudinal assessment of changes in skeletal muscle mass.

The combination of new methods with new biomarkers was a fascinating aspect in the conference. The development of biomarkers for skeletal muscle wasting was one central point in the 7th Cachexia Conference. Emanuele Marzetti from Rome, Italy, presented the basics in the development of biomarkers for skeletal muscle wasting. The International Working Group on Sarcopenia emphasises the need for adopting a multidimensional approach to diagnose the condition and track its progression. Research is necessary to understand how sarcopenia intersects with muscle-atrophying disease conditions. Mark Hellerstein from Berkeley, USA, presented the advances in biomarkers for muscle biology. Hellerstein pleads for noninvasive laboratory tests that reveal the protein metabolism of skeletal muscle. Three

Springer
methodological developments were discussed: (1) muscle mass from a spot urine sample: the D3-creatine method with 2H3-creatinine as a muscle mass biomarker, (2) the turnover of muscle proteome assessed by the fractional synthesis rate and (3) “virtual biopsy” with plasma creatin kinase-type M for analysing muscle protein synthesis. In the last years, there has been enormous interest in the development of new biomarkers and new methods in the field of sarcopenia. When we look back to the 6th conference, the new animal model of sarcopenia, the so-called SARCO mouse, a transgenic mouse overexpressing the human enzyme neurotrypsin, was presented [3]. This enzyme produces C-terminal agrin fragment (CAF) from the peptide agrin, a synaptically located key player during the initial formation and maintenance of neuromuscular junctions. As a new and interesting biomarker to identify sarcopenia, CAF was recently described, even though this marker had not been validated in clinical studies [23]. This new diagnostic biomarker for sarcopenia has now been tested in clinical settings and was presented in oral presentations and poster sessions this year at the 7th Cachexia Conference. First, Stephan von Haehling from Berlin, Germany, gave an overview of new biomarkers for skeletal muscle wasting in chronic illness. He emphasised that new biomarkers are required to detect patients with a high pretest probability of being sarcopenic on sophisticated testing using, for example, DEXA. Next to laminin 211, myoglobin and actin, CAF was suggested as a potential candidate. Nadja Scherbakov from Berlin, Germany, presented CAF as a marker of muscle wasting in patients after acute stroke during early rehabilitation. These authors measured total CAF and the subfragment CAF110 in a total of 101 patients with acute ischaemic or haemorrhagic stroke and in 15 healthy controls. These results underscored the role of CAF as a marker of muscle wasting. In conclusion, CAF serum levels were elevated in patients after stroke, and CAF seems to be useful for monitoring muscle status [24]. In the Young Investigator Award Session, Lisa Steinbeck from Berlin, Germany, presented her research results from the Studies Investigating Co-morbidities Aggravating Heart Failure [25] with CAF as a novel diagnostic marker for muscle wasting in patients with chronic heart failure. These results may be clinically important because muscle wasting has recently been identified as an important comorbidity of heart failure patients that affects up to 20% of ambulatory patients with important clinical implications [26, 27]. The agrin breakdown products TotalCAF, CAF110 and CAF22 were evaluated in heart failure patients with muscle wasting compared to heart failure patients without muscle wasting. Since the assessment of CAF was associated with high sensitivity, CAF may be useful to identify patients with chronic heart failure and muscle wasting, prompting further investigations in these patients [28].

### 4 Nutrition

This year, a traditional Japanese herbal medicine, named rikkunshito, was presented, and Akihiro Asakawa from Kagoshima, Japan, gave an overview of how rikkushito improves anorexia/cachexia and influences ghrelin signalling. Rikkunshito consisted of eight herbs: Glycyrrhiza radix, Zingiberis rhizoma, Atractylodis lanceae rhizoma, Zizyphi fructus, Aurantii nobilis pericarpium, Ginseng radix. Active components of rikkunshito potentiated ghrelin secretion and receptor sensitization. The main pathway of rikkunshito is presented in Fig. 1. Mogami et al. [29] (University of Miyazaki, Miyazaki, Japan) presented data of rikkunshito administered to mice and showed that administration of rikkunshito resulted in increased plasma ghrelin levels and improved muscle weight. Thus, they suggested that rikkunshito improves anorexia and cachexia by enhancing ghrelin secretion via 5-HT2BR antagonism. By using a cancer cachexia rat model of implantation of a human gastric cancer-derived 85As2 cell line, Terawaki et al. [30] (National Cancer Center Hospital East, Kashiwa, Japan) showed that ghrelin administration resulted in ghrelin resistance in rats. Interestingly, administration of rikkunshito in this rat model showed that the ameliorative effects of cancer cachexia may be enhanced by the ghrelin receptor activity of rikkunshito.

| Definition | Screen | Definition |
|------------|--------|------------|
| IANA Sarcopenia Task Force | Gait speed <1.0 m/s | Low appendicular lean mass (<7.23 and 5.67 kg/m² in men and women, respectively) |
| EWGSOP | Gait speed <0.8 m/s | Low muscle mass (not defined) |
| SIG: Cachexia–Anorexia in Chronic Wasting Diseases | Gait speed <0.8 m/s OR Other physical performance measure | Low muscle mass (2SD) |
| Sarcopenia with Limited Mobility (SCWD) | 6-min walk <400 m OR Gait speed <1.0 m/s | Low appendicular lean mass 2SD 20–30 sex ethnicity |

Table 1 Overview of the different definitions of sarcopenia
Yakabi et al. [31] (Department of Gastroenterology and Haematology, Kawagoe City, Saitama, Japan) tested orally administered rikkunshito at a dose of 1,000 mg/kg in tumour-bearing rats. They showed that rikkunshito inhibits the activity of the neuron of the solitary tract nucleus, suggesting that rikkunshito inhibits vagal input from the periphery to the central nerves. Suppression of the activity of the paraventricular nucleus in the hypothalamus results in a decrease of the sympathetic outflow from the central nerves to the periphery. Thus, they speculated that rikkunshito may act by a different mechanism in aged female mice. Kenji Kangawa from the National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan, who discovered in 1999 ghrelin, presented the way to the discovery and the main physiological effects of ghrelin. Ghrelin is a growth hormone secretagogue and is secreted mainly from the stomach into the bloodstream under fasting conditions. Ghrelin effects on food intake or body weight are mediated through the activation of appetite-inducing neuropeptide Y (NPY) in the hypothalamus or by blocking the appetite-reducing melanocortin receptors. Ghrelin activates NPY and agouti-related peptide, thus yielding stimulation of food intake. Different mouse models of cancer cachexia were used to define the effects of ghrelin and its pathways. For example, Chen et al. [34] (University of Texas, Houston, TX, USA) showed in tumour-bearing mice that ghrelin prevents muscle atrophy by decreasing inflammation, increasing Akt phosphorylation, activating myogenin and finally by downregulating the p38/C/EBFß/myostatin pathway. To translate results from animal studies into the clinical setting, Blum et al. [35] (Cantonal Hospital St Gallen, St. Gallen, Switzerland) presented the results of a dose finding trial of subcutaneous natural ghrelin to improve nutritional intake in patients with advanced cancer cachexia. In this study, the starting dose of ghrelin was 32 μg/kg twice daily, and it was followed by 50 % dose increases until they reached the minimal dose for maximal nutritional intake. This endpoint dose for maximal nutritional intake was 72 μg/kg. The positive effects on nutritional intake were amended with improvement of patients’ well-being. Ghrelin and ghrelin receptor agonists, such as anamorelin, showed appetite-stimulating and growth hormone-releasing effects and are likely to be useful for the treatment of muscle wasting. Temel et al. [36] (Massachusetts General Hospital, Boston, MA, USA) showed the results of the phase II study of anamorelin in patients with non-small cell lung cancer (NSCLC). This randomised, double-blind, placebo-controlled international study enrolled 226 patients and differentiated all in three groups of 50 mg anamorelin, 100 mg anamorelin and placebo. As early as 1 week after treatment initiation, beneficial effects on weight were observed in anamorelin-treated groups. Over 12 weeks of treatment with anamorelin, in both treatment groups (50 and 100 mg anamorelin), significant increases in body weight were observed compared to placebo. Also, improvements in handgrip strength and quality of life were observed in these treatment groups. They additionally showed that anamorelin had an overall favourable safety and tolerability profile in patients with NSCLC. Also, the design of a phase III study with anamorelin was presented by Abernethy et al. [37] (Helsinn Therapeutics, Inc., Bridgewater, NJ, USA). This study tested anamorelin at a dose of 100 mg once daily compared to placebo in 477 patients with NSCLC over 12 weeks of treatment. Anamorelin is still undergoing phase III investigation, and we are waiting for the results with regard to its efficacy and safety.

The influence of nutrition on protein kinetics in patients with cachexia is poorly understood. Takei et al. [38] (Tokyo laboratory, EN Otsuka Pharmaceutical Co, Tokyo, Japan) modified the physical properties of meat with homogeneous enzyme permeation-treated beef. They compared homogeneous enzyme permeation-treated beef with normally cooked beef. The beef protein content was 75 % higher in homogeneous enzyme permeation-treated beef, and they showed sufficient softness, good deformability and quick water dispersibility than in commercial beef. Serpe et al. [39]...
(University of Cagliari, Italy) assessed the effect of nutritional supplementation with a high title of omega-3 by krill oil on blood parameters and lipid profile. They included in this study 45 patients with stage IV cancer cachexia and 21 healthy controls. Patients received 3 g/day of krill oil capsules over 8 weeks. They found that supplementation of krill oil resulted in the reduction of triglycerides and total cholesterol and increases in high-density lipoproteins. Interestingly, inflammation markers such as interleukin-6 and tumour necrosis factor alpha were also decreased. This non-blinded, non-placebo-controlled study gives an impulse that krill oil can be tested in a nutritional study in patients with cancer cachexia. Nutritional therapy alone has no effect on the underlying catabolic process of cachexia, but it would be interesting to know the potential synergistic effect that could accrue from nutritional therapy in conjunction with different drugs. Giovanni Mantovani from Cagliari, Italy, stated that a combined therapy with anti-inflammatory anabolic/metabolic agents plus antioxidants may be able to improve the main nutritional, metabolic and physical activity variables as well as quality of life in patients with cancer cachexia [40]. A multi-targeted approach may be the way forward in the field of cachexia research.

5 Treatment of cachexia

Loss of skeletal muscle mass and strength plays a significant pathological role in the progression of a wide variety of disorders associated with ageing and catabolic conditions. Neutralization of myostatin activity results in skeletal muscle hypertrophy and prevents atrophy in adult skeletal muscle. Therefore, Bauerlein et al. [41] (Regeneron Pharmaceuticals Inc., New York, USA) tested the efficacy of the specific antagonist of myostatin, REGN1033. REGN1033 was tested in mice with weekly or biweekly subcutaneous injections ranging from 2.5 to 30 mg/kg treated for 21–28 days. The results showed that REGN1033 increases muscle mass, force, and physical performance outcomes in aged mice and prevents the loss of muscle mass. The pharmacodynamic effects of REGN1033 were further compared to the soluble decoy receptor body ActRIIB-hFc including a skin wound healing model. Thus, the use of antagonists of myostatin should be tested in clinical settings. Some clinical studies are now in phase III and the first results were presented. Selective androgen receptor modulators (SARM) have potential to increase muscle mass and improve physical function without the unwanted effects on the prostate, skin or hair that are commonly associated with testosterone or other nonselective, synthetic anabolic steroids. Enobosarm, a nonsteroidal SARM, has consistently demonstrated increases in lean body mass and better physical function across several populations along with a lower hazard ratio for survival in cancer patients. The phase III clinical trial was entitled “Prevention and treatment of muscle wasting in patients with cancer (POWER)” evaluating enobosarm for the prevention and treatment of muscle wasting in patients with NSCLC. Interestingly, this study enrolled patients with a mean weight loss of about 9 % within the previous 6 months, which is substantially higher than the commonly defined 5 % weight loss in 6 months for a clinical diagnosis of cachexia and far above the 2 % weight loss specified in the inclusion criteria [42]. A total of 159 patients were randomised and received at least one dose of the study drug (placebo, n=52; enobosarm 1 mg, n=53; or enobosarm 3 mg, n=54). The results showed that total lean body mass statistically significant increased from baseline to day 113, or end of the study, in patients who received enobosarm 1 mg (ρ=0.0012) and enobosarm 3 mg (ρ=0.046), but not in patients assigned placebo [43]. The POWER Study firstly established a SARM, enobosarm, as a new drug for the prevention and treatment of muscle wasting in cancer patients. Takagi et al. [44] (Teijin Institute for Biomedical Research) showed another new SARM (TEI-E0001) as a novel long-acting SARM. They showed that TEI-E0001 has excellent oral bioavailability and longer half-life in the blood, at least than other known SARMs. Moreover, after application in rats, they showed that TEI-E0001 has potent anabolic activity on the muscle and bone, reduced androgenic side effects and hormonal perturbation, and improved the dosing regimen.

Systemic effects of tumours also lead to cardiac wasting, associated with left ventricular dysfunction, fibrotic remodeling and increased mortality. These adverse effects of the tumour on the heart and on survival may be mitigated by treatment with a β-blocker. Formoterol is a β2 adrenoeceptor-selective agonist which promotes muscle growth and results in skeletal muscle hypertrophy. Toledo et al. [45] (Universitat de Barcelona, Barcelona, Spain) presented the administration of formoterol (0.3 mg/kg) in cachectic tumour-bearing rats (Yoshida AH-130) which resulted in a reduction of muscle weight loss. Treatment of formoterol increases body mass and body water and interestingly showed no influence on heart weight and seems to improve heart function. Also, the anabolic catabolic transforming agent MT-102 (espinolol) showed these effects. Musolinio et al. [46] (Charité Medical School, Berlin, Germany) presented that the administration of MT-102 (3.0 mg/kg) in tumour-bearing rats (Yoshida AH-130) results in an improvement in functional cardiac parameters and that it significantly reduces cardiac wasting. Thus, formoterol and MT-102 (espinolol) seem to be prospective new drugs to treat patients suffering from cancer cachexia, particularly if patients show signs of declined cardiac function. Andrew Coats from Melbourne, Australia, presented the first results of the ACT-ONE trial with 87 patients from 17 centres. The ACT-ONE trial, a multicentre, randomised, double-blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent espinolol (MT-102)
recruited subjects with cachexia and NSCLC or colorectal cancer in stages III and IV [47]. Patients were randomised in a 3:1:2 fashion to one of two doses of espindolol (10 or 2.5 mg twice daily) or placebo and treated for 16 weeks. The results showed that only the high dose of 10 mg twice daily improves lean and fat mass after 16 weeks of treatment. Results of the functional data showed that only handgrip strength significantly increased after 16 weeks in the low-dose and high-dose treatment groups, but stair climbing power and 6-min walking distance were left unaffected. This study gives rise to the question whether or not β-blockers can be viewed as having a class effect in the treatment of cancer cachexia. To answer this question, Sandra Palus et al. [48] (Charité Medical School, Berlin, Germany) presented the results of testing different β-blockers in different doses in a cancer cachexia rat model. They showed that only espindolol at a dose of 3 mg kg$^{-1}$ day$^{-1}$ showed superior effect on survival in tumour-bearing rats compared to all other β-blockers. Espindolol showed the greatest wasting reduction.

6 Conclusion

In conclusion, it was shown from experimental studies that growth differentiation factor-15, myostatin, the ubiquitin proteasome-dependent pathway, valosin and the regulation of ubiquitin-specific protease 19 are essentially involved in the wasting process. There is further need for attractive biomarkers as therapeutic targets. As a new and interesting biomarker to identify muscle wasting, the C-terminal agrin fragment may provide some guidance in the clinical setting. For noninvasive measurement of skeletal muscle mass, the D$_{2}$-creatin dilution method can be applied repeatedly to measure total body creatine skeletal muscle mass change in longitudinal studies. Potential treatments of wasting disorders were discussed, including ghrelin and the ghrelin receptor agonist anamorelin, the myostatin antagonist REGN1033, the selective androgen receptor modulators enobosarm and TEL-E0001, and β-blockers formoterol and the anabolic catabolic transforming agent espindolol. But further studies are necessary to evaluate the mechanisms and long-term effects.

Acknowledgments The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia, and Muscle 2010; 1:7–8 (von Haehling S, Morley JE, Coats AJ, and Anker SD).

Conflict of interest Nicole Ebner, Lisa Steinbeck, Wolfram Doehner, Stefan Anker and Stephan von Haehling declare that they have no conflict of interest.

References

1. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008;27:793–9.

2. Marzetti E, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013;45:2288–301. doi:10.1016/j.biocel.2013.06.024.

3. 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. doi:10.1007/s13539-012-0061-y.

4. von Haehling S, Steinbeck L, Doehner W, Springer J, Anker SD. Muscle wasting in heart failure: an overview. Int J Biochem Cell Biol. 2013;45(10):2257–65. doi:10.1016/j.biocel.2013.04.025.

5. Constantin-Teodosiu D, Kanagaraj M, Constantin D, Chikhani M, Nixon A, Mallinson JE, et al. Acute endotoxaemia in humans increases muscle PDK4 protein expression and impairs nutrient-mediated increases in muscle PDC activity and whole-body glucose disposal. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-07.

6. Dumont N, Dufresne SS, Bouchard P, Lavergne E, Piette AB, Sarao R, et al. Inhibition of RANK/RANKL pathway greatly improves SERCA activity and force production in atrophic and dystrophic skeletal muscles. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-09.

7. Lerner L, Guillory B, Chen J, Winston W, Weiler S, Gyrus J, et al. Growth differentiating factor-15 (GDF-15) induces anorexia and cachexia in mice: a novel pathway for cachexia. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 2-02.

8. Tsai VW, Macia L, Johnen H, Kuffner T, Manadhar R, Jørgensen SB, et al. TGF-b superfamily cytokine MIC-1/GDF15 is a physiological appetite and body weight regulator. PLoS One. 2013;8:e55174. doi:10.1371/journal.pone.0055174.

9. 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. doi:10.1016/j.maturitas.2013.08.015.

10. Cui W, Bennett A, Zhang P, Kankey K, Taylor-Howell C, MacVittie TJ. Increased expression of protein catabolism and ActRIIB pathway in a non-human primate (NHP) radiation-induced cachexia model. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 2-04.

11. Piccirillo R, Goldberg AL. The p97/VCP ATPase is critical in muscle atrophy and for the accelerated degradation of most muscle proteins. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-08.

12. Wiles B, Miao M, Wing SS. USP19 regulates differentiation of muscle cells. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-04.

13. Segawa K, Tojo M, Kada E, Kimura T, Yamana K. Identification and characterization of USP19 inhibitors. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-05.

14. Costelli P, Pin F, Penna F, Conta F, Camperi A. PGC-1α counteracts cancer-induced muscle wasting in female mice. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 3-01.

15. Kim KS, Park KS, Kim MJ, Kim SK, Cho YW, Park SW. Higher prevalence of sarcopenia in older adults with type 2 diabetes. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-23.

16. Povoroznyuk V, Dzerovych N. Sarcopenia in Ukrainian women of different age. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-24.

17. Yamada M, Nishiguchi S, Fukutani N, Tanigawa T, Yukutake T, Kayama H, et al. Prevalence of sarcopenia in community-dwelling Japanese older adults. J Am Med Dir Assoc. 2013;14:911–5. doi:10.1016/j.jamda.2013.08.015.

18. Yamada M, Aoyama T, Arai H. Prevalence of sarcopenia in community-dwelling Japanese older adults. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-25.

19. Yamada Y, Kimura M. The application of segmental bioelectrical impedance spectroscopy in assessment of sarcopenia in elderly. J Cachexia Sarcopenia Muscle. 2014;5:abstract 1-29. doi:10.1007/s13539-014-0129-y.
20. Wilkinson DJ, Franchi MV, Brook MS, Narici MV, Mitchell WK, Atherton PJ, et al. The deuterium oxide (D₂O) stable isotope tracer is a powerful tool for monitoring short-term changes in skeletal muscle protein synthesis at rest and in response to exercise. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 1-03.

21. Walker DK, Thaden JJ, Deutz NEP. Fat-free and fat mass can be measured with D₂O dilution and gas chromatography–tandem mass spectrometry. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 2-13.

22. 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;3:217–23.

23. Hettwler S, Dahinden P, Kucsera S, Farina C, Ahmed S, Fariello R, et al. Elevated levels of a C-terminal agrin fragment identifies a new subset of sarcopenia patients. Exp Gerontol. 2013;48:69–75. doi:10.1016/j.exger.2012.03.002.

24. Scherbakov N, Ebner N, Knops M, Valentova M, Sandek A, Dahinden P et al. C-terminal agrin fragment as a marker of muscle wasting in patients after acute stroke during early rehabilitation. J Cachexia Sarcopenia Muscle. 2014;5:abstract 1-26. doi:10.1007/s13539-014-0129-y.

25. von Haehling S, Lainscak M, Doehner W, Poskowsky P, Rosano G, Jordan J, et al. Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Cachexia Sarcopenia Muscle. 2010;1:187–94.

26. Tacke M, Ebner N, Boschmann M, Jarius A, Valentova M, Füster S, et al. Resting energy expenditure and the effects of muscle wasting in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Am Med Dir Assoc. 2013;14:837–41. doi:10.1016/j.jamda.2013.08.008.

27. Steinbeck L, Ebner N, Valentova M, Sandek A, Bekfani T, Doehner W et al. C-terminal agrin fragment as a novel diagnostic marker for muscle wasting in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure. J Cachexia Sarcopenia Muscle. 2014;5:abstract 1-32. doi:10.1007/s13539-014-0129-y.

28. Mogami S, Tsubouchi H, Yanagi S, Miura A, Toshinai K, Yamada C et al. Rikkunshito, a Japanese Kampo medicine, ameliorates anorexia and Fos expression in the central nerve nuclei of autonomic nerves. J Cachexia Sarcopenia Muscle. 2013;4:295–343. abstract 5-01.

29. Palus S, Hartmann K, Braun T, Tschirmer A, von Haehling S, Doehner W et al. Beta-blocker for the treatment of cancer cachexia: are they all equal? J Cachexia Sarcopenia Muscle. 2014;5:abstract 4-19. doi:10.1007/s13539-014-0129-y.