Highlights from the 9th Cachexia Conference

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Abstract

This article highlights updates of pathways as well as pre-clinical and clinical studies into the field of wasting disorders that were presented at the 9th Cachexia Conference held in Berlin, Germany, December 2016. This year, some interesting results from clinical trials and different new therapeutic targets were shown. This article presents the biological and clinical significance of different markers and new diagnostic tools and cut-offs of detecting skeletal muscle wasting. Effective treatments of cachexia and wasting disorders are urgently needed in order to improve the patients’ quality of life and their survival.

Keywords Cachexia; Muscle wasting; Sarcopenia

Introduction

The development of preventive and therapeutic strategies against cachexia and wasting disorders, such sarcopenia, is perceived as an urgent need by healthcare professionals and has instigated intensive research into the pathophysiology of these syndromes.1,2 Cachexia is characterized by progressive weight loss affecting different body compartments, particularly skeletal muscle and adipose tissue, although even bone mineral content may be affected.3 Over the last years, the Cachexia Conference has developed into a respected forum for researchers from the 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 9th Cachexia Conference was held in Berlin, Germany, from 10 to 11 December 2016 with over 250 participants from more than 25 countries attending.

Basic science

This year, some interesting updates on signalling pathways were presented. 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. This year, Taillandier et al. (Unité de Nutrition Humaine, Clermont-Ferrand, France) focused on E2 enzymes that are either abundant or up-regulated in skeletal muscle wasting. They showed that the ubiquitin enzyme UBE2B is involved in contractile protein targeting. The autophagy family members include more than 30 components recruited to form the autophagosome. Among these, Atg8, which is soluble in the cytoplasm, is lipidated and cocked to the internal membrane. Therefore, the Atg protein is present during autophagy and is considered as a good marker to monitor the activity of the autophagy process.4 In this context, Kneppers et al. (Maastricht University Medical Center, Maastricht, The Netherlands) showed that parallel activation of autophagy and myogenic signalling exist during muscle mass recovery following disuse atrophy. The parallel changes in expression of autophagy and myogenic differentiation markers during early muscle reloading imply a co-ordinated regulation of these processes during recovery of muscle mass following atrophy.5 Musolinio et al. (University of Catanzaro, Rome, Italy) showed musculoskeletal changes associated with chronic constriction injury of the rat sciatic nerve. Interestingly, the modulation of anabolic and catabolic
pathways, focusing on autophagy, in skeletal muscle, using a model of atrophy induced by chronic sciatic nerve constriction showed that muscle atrophy induced by chronic sciatic nerve constriction might have different mechanisms than common muscle atrophic models. At 14 days post-sciatic nerve ligation, the chronic constriction injury group had significant decreases in body weight and body composition compared with naive animals. The ubiquitin E3-ligases atrogin-1 was decreased, suggesting that its involvement could occur at an earlier time point. Also, levels of p-Akt and total Akt were up-regulated, a result expected in a hypertrophic model. Guttridge et al. gives an overview to the important functions of transcription factors nuclear factor κB (NF-κB) in myoblast to stimulate activin and inhibit muscle differentiation. He impressively showed that NF-κB is activated in cachetic muscle in both PAX 7 progenitor cells and myofibres. Other studies buttress the view that increased FoxO signalling and the activation of the transcription factors NF-κB, muscle RING-finger protein (MuRF1), and muscle atrophy F-box (MAFbx) in skeletal muscle play major roles during cachexia onset and progression. 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 FoxO target genes. Inducers of MuRF1 and MAFbx expressions are TNFα, IL-6, and IL-1, and NF-κB appears to be the most important regulator of MuRF1 and MAFbx expressions in the skeletal muscle. Another new target for therapeutic interventions seems to be TAK1, which is required for the growth and maintenance of skeletal muscle mass. Kumar et al. (University of Louisville School of Medicine) showed that the inactivation of TAK1 in skeletal muscle causes loss of body mass and strength. Moreover, they impressively show that the inactivation of TAK1 stimulates slow-to-fast-type myofibre transition in soleus muscle and reduces the rate of protein synthesis in skeletal muscle in mice. They conclude that TAK promotes protein synthesis potentially through activation of mTOR. The loss of TAK1 causes oxidative stress and activates proteolytic pathways in skeletal muscle, and the inactivation of TAK1 leads to the activation of AMPK and Smad2/3 in skeletal muscle. TAK is essential for the overload-induced skeletal muscle hypertrophy. 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.

**Body composition**

During the congress, several different techniques were presented to measure body composition. These included computed tomography scan, dual energy X-ray analysis and magnetic resonance imaging (MRI), D3-creatine dilution analysis, and bioimpedance analysis (BIA). Most surprising data in the field of daily activity measurements presented Rantanen et al. (University of Jyväskylä, Finland) with simple grip strength measurements. The force produced by the hand to press or squeeze correlates well with the results of other muscle strength tests, so it can be viewed as an easily applicable test of total body strength. The authors concluded that grip strength measurement can be used as a marker of physiological reserve during ageing. Grip strength declines by approximately 1–2% annually after midlife. Thus, it can be used as biomarker of ageing. Grip strength reflects the combined influences of genetic predisposition acquired modifications of physical constitution ageing processes chronic diseases. In this regard, Flores et al. (Universidad de Colima, Colima, Mexico) discussed the correlation between handgrip strength and muscle mass in 155 patients undergoing maintenance hemodialysis. Also Szulc et al. (University of Lyon, France) presented data of grip strength measured in the STRAMBO study. They showed that grip strength is associated with hormonal deficits and this remains true regardless of other confounders. The STRAMBO cohort consists of 811 men aged 60 to 87 years and grip strength was measured at baseline and after 4 and 8 years. The authors show impressively that increased high sensitivity C-reactive protein levels and poor physical performance are associated with accelerated grip strength decline.

However the most amazing method was described by Stimpson et al., the D3-creatine dilution for determination of total body creatine pool size and skeletal muscle mass. This interesting method can directly assess skeletal muscle mass or its change, during ageing, inactivity, disease, or exercise. This method takes advantage of a number of aspects of creatine biology. More than ninety percent of creatine is converted to creatinine and excreted in urine. Last year, Evans et al. (University of California, USA) presented results of a clinical validation study demonstrating that the creatine dilution method is strongly associated with whole body MRI-method. This year they presented that the creatine dilution method is also strongly associated with the dual energy X-ray analysis method. D3 creatine dilution method appears to be a valid non-invasive measurement for muscle mass and children. In some adults, a portion of the ingested D3 creatine label is filtered by the kidney and spilled into urine. By measuring creatine/creatinine ratio, a correction for spilled label is determined with an algorithm. Combined with dosing of 2H2O dosing, lean body mass and

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muscle mass can be measured non-invasively. Importantly, the measurement with creatine dilution method is not affected by shifts in body water that occur with many cachectic diseases.

Clinical trials and newly treatment targets

Li et al.16 (Acceleron Pharma, Cambridge, Massachusetts, USA) presented data of ACE-2494, a new growth differentiation factor (GDF) ligand trap. They used an immobilization mouse model to specifically induce tibialis anterior muscle atrophy and tibiae bone loss. A total of 30 mice were immobilized for 14 days and receive ACE-2494 (10 mg/kg) twice per week or vehicle. The results showed that ACE-2494 treatment resulted in enlarged muscle fibre size by over 28% and restored the loss in area bone mineral density. Thus, ACE-2494 restored and prevented muscle loss and can be used as a potential treatment for muscle atrophy and muscle disorders.16 Ábrigo et al. (Universidad Andres Bello, Chile, Santiago de Chile) showed that administration of angiostatin 1–7 as complex of hydroxyl polyamidoamine (PAMAM-OH) avoided the atrophic effects in skeletal muscle atrophy.17 Mice were immobilized and treated with angiostatin alone and in combination with PAMAM-OH or vehicle. They showed that only the combination of angiostatin with PAMAM-OH dendrimer can be an efficient method in therapy for treatment of skeletal muscle atrophy. Also, Rivera et al. (Universidad Andres Bello, Chile, Santiago de Chile) showed that angiostatin 1–7 decreased Lipopolysaccharide (LPS)-induced LC3II/LC3I ratio and suggested that angiostatin 1–7 is a new regulator of autophagy by mechanism dependent on MAPK.18 Interesting data in the field of the metabolic effects of a vitamin D and leucine-enriched breakfast were presented by Paddon-Jones et al.19 They showed that breakfast normally has the –7 is a new regulator of autophagy by mechanism dependent on MAPK.18 Interesting data in the field of the metabolic effects of a vitamin D and leucine-enriched breakfast were presented by Paddon-Jones et al.19 They showed that breakfast normally has the –7 is a new regulator of autophagy by mechanism dependent on MAPK.18 Interesting data in the field of the metabolic effects of a vitamin D and leucine-enriched breakfast were presented by Paddon-Jones et al.19 They showed that breakfast normally has the
cohort studies are recruiting patients, and we are waiting for the first results maybe in the next meeting.

**Conclusions**

From basic science, new therapeutic targets were shown including the TWEAK–Fn14–NF-κB–MuRF1–myosin heavy chain protein degradation cascade and the neutralization of tumour-derived parathyroid-hormone-related protein, as well as the influence and the role of the gut microbiota in the therapeutic management of cancer and associated cachexia. Effective treatments were REGN1033, ghrelin, and ghrelin receptor agonist anamorelin and enobosarm.

**Conflict of interest**

None declared.

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**References**

1. Ebner N, Steinbeck L, Doehner W, Anker SD, von Haehling S. Highlights from the 9th Cachexia Conference. J Cachexia Sarcopenia Muscle 2017;8:508–511. DOI: 10.1002/jcsm.12217

2. 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.

3. 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.

4. Polge C, Claustre A, Deval C, Béchet D, Combaret L, Attai D, et al. Identification of E2 enzymes involved in MuRF1-dependent skeletal muscle atrophy. J Cachexia Sarcopenia Muscle 2016;7:627, Abstract 1-03.

5. kneppers AAEM, Pansters NAM, Leemakers PA, Verdijk LB, van Loon LJG, Schols AMWJ, et al. Parallel activation of autophagy and myogenic signalling during muscle mass recovery following disuse-atrophy. J Cachexia Sarcopenia Muscle 2016;7:628, Abstract 1-05.

6. Musolino V, Bosco F, Nucera S, Giancotti LA, Ilari S, Lauro F, et al. New insights into muscle atrophy: role of autophagy in a model of chronic sciatic nerve conraction. J Cachexia Sarcopenia Muscle 2016;7:629, Abstract 1-08.

7. Talbert EE, Yang J, Mace TA, Farren MR, Farris AB, Young GS, et al. 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.

8. Lodda D, Pahuja A, Gees-Knörr C, Scheibe R, 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.

9. Kowalski K, Archacki R, Archacka K, Stremińska W, Paciorek A, Goląbek 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.

10. Marino FE, Risbridger G, Gold E. Activin-JC modulates cachexia by repressing the ubiquitin-proteasome and autophagic degradation pathways. J Cachexia Sarcopenia Muscle 2015;6:365–380.

11. 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.

12. Garagarza C, Flores AL, Valente A. Correlation between handgrip strength and muscle mass with biochemical and body composition parameters. J Cachexia Sarcopenia Muscle 2017;8:167, Abstract 1-54.

13. Szulc P, Chapurlat R. Accelerated grip strength decline in older men with sarcopenia. J Cachexia Sarcopenia Muscle 2017;8:217–223.

14. Stimpson SA, Leonard MS, Clifton LG, Poole C, Calder PC, Laviano A, Lononquist F, Muscarioti M, Ohlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease (COPD): a randomized, double-blind controlled trial. J Cachexia Sarcopenia Muscle 2017;7:174, Abstract 2-15.

15. Karaa A, Cohen BH, Goldstein A, Vockley J, Haas R. MMPOWER: the effect of treatment with elamipretide in patients with genetically confirmed primary mitochondrial disease. J Cachexia Sarcopenia Muscle 2017;7:170, Abstract 1-61.

16. Coats AJS, Ho GF, Prabhask K, von Haehling S, Tilson J, Brown R, et al. For and on behalf of the ACT-ONE study group. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). J Cachexia Sarcopenia Muscle 2016;7:355–365.

17. Ábrigo J, Márquez-Miranda V, Rivera JC, Araya-Durán I, Aravena J, Pacheco N, et al. New formulation based on anti-atropeic peptides and dendrimers for skeletal muscle atrophy treatment. J Cachexia Sarcopenia Muscle 2016;7:626, Abstract 1-01.

18. Rivera JC, Ábrigo J, Chion M, Bader M, Santos RA, Brandan E, et al. Endotoxin-induced autophagy dependent on Beclin1/Bcl2 complex is decreased by angiotensin-(1-7) in skeletal muscle. J Cachexia Sarcopenia Muscle 2016;7:626, Abstract 1-02.

19. Padon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009;12:86–90.

20. Calder PC, Laviano A, Lononquist F, Muscarioti M, Ohlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease (COPD): a randomized, double-blind controlled trial. J Cachexia Sarcopenia Muscle 2017;7:174, Abstract 2-15.

21. Ábrigo J, Márquez-Miranda V, Rivera JC, Araya-Durán I, Aravena J, Pacheco N, et al. New formulation based on anti-atropeic peptides and dendrimers for skeletal muscle atrophy treatment. J Cachexia Sarcopenia Muscle 2016;7:626, Abstract 1-01.

22. Coats AJS, Ho GF, Prabhask K, von Haehling S, Tilson J, Brown R, et al. For and on behalf of the ACT-ONE study group. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double blind, placebo controlled, international multicentre phase II study (the ACT-ONE trial). J Cachexia Sarcopenia Muscle 2016;7:355–365.

23. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. J Cachexia Sarcopenia Muscle 2015;6:315–316.