Highlights of mechanistic and therapeutic cachexia and sarcopenia research 2010 to 2012 and their relevance for cardiology

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Submitted: 3 November 2012
Accepted: 6 November 2012

Arch Med Sci 2013; 9, 1: 166-171
DOI: 10.5114/aoms.2013.33356

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Abstract

Sarcopenia and cachexia are significant medical problems with a high disease-related burden in cardiovascular illness. Muscle wasting and weight loss are very frequent particularly in chronic heart failure and they relate to poor prognosis. Although clinically largely underestimated, the fields of cachexia and sarcopenia are of great relevance to cardiologists. In cachexia and sarcopenia a significant number of research publications related to basic science questions of muscle wasting and lipolysis were published between 2010 and 2012. Recently, the two processes of muscle wasting and lipolysis were found to be closely linked. Treatment research in pre-clinical models involves studies on a number of different therapeutic entities, including ghrelin, selective androgen receptor modulators (SARMs), as well as drugs targeting myostatin or melanocortin-4. In the human setting, studies using enobosarm (a SARM) and anamorelin (ghrelin) are in phase III. The last 3 years have seen significant efforts to define the field using consensus statements. In the future, these definitions should also be considered for guidelines and treatment trials in cardiovascular medicine. The current review aims to summarize important information and development in the fields of muscle wasting, sarcopenia and cachexia, focusing on findings in cardiovascular research, in order for cardiologists to have a better understanding of the progress in this still insufficiently known field.

Key words: cachexia, sarcopenia, muscle wasting, mechanism, therapy, cardiovascular illness, heart failure.

Introduction

The last decades have seen increasing interest in muscle wasting [1-5] and cachexia [6-16] research in chronic diseases and ageing. Indeed, both are significant medical problems with a high disease-related burden in terms of symptoms, quality of life and prognosis of patients [17-19] and with high socioeconomic expense [20]. Muscle wasting in general, sarcopenia, lipolysis and cachexia are very active research fields with great medical relevance [21-23]. New research is abundant and many comprehensive review articles have been written to cover the new findings on mechanisms and pathophysiology [24, 25] as well as symptoms [26, 27],

nutritional issues [28, 29], and new therapeutic options [30-33].

In this review we aimed to summarize the most important information on muscle wasting, sarcopenia and cachexia, focusing on findings in cardiovascular research, in order for cardiologists to have a better understanding of the progress in this still insufficiently known field. In order to reach a wide group of physicians and researchers, we have decided to publish this review simultaneously in two renowned journals (wide-scope and cardiologist ones).

Search strategy

We searched the electronic databases MEDLINE, EMBASE and SCOPUS (January 2010 to October 2012). Additionally, abstracts from national and international cardiovascular meetings were searched. The main search terms were: cachexia, sarcopenia, muscle wasting, mechanism, therapy, cardiovascular illness, and heart failure.

Muscle wasting is not only seen in chronically ill patients, but also prominent in acute and critical illness, including sepsis and septic shock [34], in hospitalized patients with acute and severe lung disease [35]. Patients with chronic heart failure were recently found to be affected by muscle wasting fulfilling the criteria of sarcopenia in 19.5% of a prospectively enrolled cohort of patients with stable disease [36]. Cachexia, on the other hand, is frequent in chronic kidney disease (CKD) [9, 37-39] and as part of the cardio-renal syndrome also affecting heart failure (HF) patients regularly [40-42]. Cachexia is also a significant problem in advanced heart disease itself [43] and related to comorbidities such as diabetes mellitus and chronic inflammation [44]. Abnormal cardiac parameters are seen in cachexia and may be associated with abnormal myocardial perfusion [45].

Much of the research on muscle wasting is focusing on regulators such myostatin [46], the ubiquitin-proteasome pathway [47], and free-radical production [48], but also on novel treatment approaches including the use of bile acids [49]. The latter has also been tested in humans with chronic heart failure (CHF) and showed improvements of endothelial function in arms and legs [50]. Limb anatomical changes may also cause peripheral neuropathy, which in turn has been shown to relate to poor quality of life [51]. Adaptive mechanisms in skeletal muscle are complex, involving the whole body, which develops anabolic/catabolic imbalance, anabolic failure and hypogonadism, as has been convincingly shown in CHF [52-54]. Other pathogenetic factors studied include sirtuin 1, which has been suggested to be a relevant mechanistic factor in the development of insufficient regeneration of skeletal muscle in cancer cachexia [55]. Desmin and tissue zinc redistribution are additional factors investigated for their role in muscle wasting [56, 57]. Other important fields of research are related to metabolic syndrome and insulin resistance [58-61] as well as heat shock protein 72 [62] and muscle stem cell function [63] and related telomere alterations [64]. The role of genetic factors is less well understood at this stage, but related research efforts are underway [44].

Research on lipolysis [65] is a young but strongly evolving field. There is strong interaction between lipolysis and muscle wasting [66-68]. This may also be relevant in heart disease [69].

Biomarker research in the field of muscle wasting is active [70, 71]. Serum creatinine levels are understood to be an unspecific marker of muscle wasting [72], but recently a more specific marker (C-terminal agrin fragment) was described [73]. As a result of a consensus conference that took place in Toulouse in 2011, recently a consensus paper on blood analysis based as well as imaging based biomarkers defining sarcopenia was published [74]. Before such biomarkers can be considered clinically (outcome) validated, successful clinical intervention phase III trials are needed.

Interventional studies in the pre-clinical setting are frequently reported and include studies investigating insulin-like growth factor [75], ghrelin and ghrelin analogues [76, 77], as well as specific androgen receptor modulators (SARMs) [78], and myostatin antibodies [79]. In addition, pre-clinical models suggest that treatments to block the effects mediated via the melanocortin-4 receptor may be useful in cachexia and muscle wasting [80]. The melanocortin-4 receptor antagonist BL-6020/979 is orally available and ready for human testing [17, 81]. The results so far are promising. Several other such compounds are in development [82]. Anabolic drugs are potentially of great relevance to HF where muscle wasting is highly prevalent [6]. Testosterone has already been tested and the results are promising [83].

In recent years, several interventional trials in humans have been performed, but for a number of them no final publications yet exist and we have to rely on meeting reports at conferences and press releases. Two promising drug treatment approaches are now in phase III clinical testing [84]. The SARM GTx-024 (enobosarm) [85] is being tested in two trials of 300 patients as to whether it can prevent or treat muscle wasting in non-small cell lung cancer. The two primary endpoints are changes in lean mass and changes in stair-climbing power [86]. The second trial program includes 2 trials of 477 patients each to investigate whether an orally available ghrelin (anamorelin) can positively impact on the disease progression of cachexia in non-small cell lung cancer [87]. The two primary

endpoints are changes in lean mass and changes in hand-grip strength, which will also have relevance in future heart failure trials. Results for these clinical trial programs are expected to be available in 2014.

From a cardiological standpoint, it is interesting to note that even cardiovascular drugs are now in clinical testing in cachexia. MT-102 is an anabolic/catabolic transforming agent with β1-blocking activity and it has direct anabolic and appetite stimulating effects in animal studies [88]. It is now being investigated in 132 patients with cachexia due to lung cancer or colorectal cancer [64]. Of interest, in the past also an angiotensin-converting enzyme inhibitor (imidapril) was investigated for use in cancer cachexia. Some promising results were obtained, but development programs were not completed due to lack of funding [89].

One treatment alone may not be sufficient to successfully treat sarcopenia or cachexia. Hence combination therapies have been proposed, including eicosapentaenoic acid and training exercise [90, 91], as well as anabolic steroids and exercise or more complex combinations such as megestrol acetate plus l-carnitine, celecoxib, and possibly also antioxidants [92, 93]. Nutritional studies have been a cornerstone of therapeutic research in cachexia and sarcopenia. Rozentryt *et al.* performed a clinical trial of nutritional intervention in cardiac cachexia [94]. A diet containing 600 kcal per day for 6 weeks (with relatively high fat content to reduce volume) increased weight during the treatment and the subsequent 12-week follow-up period (70% fat tissue, 30% muscle tissue) and had anti-inflammatory effects (reduction of TNF levels). This was accompanied by increases in cholesterol levels. Quality of life of patients improved for the 6-week period of the nutritional intervention, but decreased somewhat in the additional follow-up period.

Starting in 2008 [95], and with much more intensity in 2010 to 2012, a number of consensus-building activities to define cachexia and sarcopenia have been undertaken [96-99]. Also a more specific consensus document on the definition and stages of cancer cachexia has been published [100]. The reason for these activities is that it has been argued that treatments for cachexia (or sarcopenia) can only be developed when one can define it [101]. As much as this may be true, defining cachexia is not a simple task [102], and one can also postulate that at least as important as consensus definitions may in the long term be inclusion and exclusion criteria of trials per se. If they lead to regulatory treatment approval, then they will build the basis for approved educational initiatives that may likely develop more disease defining power than the consensus definitions ever could.

This may be similar to the situation regarding the definition of diastolic heart failure or HF with preserved ejection fraction [103, 104]. Guidelines and consensus papers will not be as powerful as the first successful therapies and the inclusion and exclusion criteria they used.

Journal and conference activities

Finally, the field of cachexia, sarcopenia and muscle wasting research is characterized by the development of several new scientific journals. In 2010, we founded the *Journal of Cachexia, Sarcopenia and Muscle* (JCSM). In 2011, the journal *Skeletal Muscle*, and in 2012 *The Journal of Frailty and Aging* (JFA) were founded. All these journals are free access or open access. Since 2000, six international cachexia conferences have taken place and reported extensively. Since 2000, the number of attendees has steadily increased from 150 to more than 400 in 2009 [105]. The next conference will take place from 8 to 11 December, 2013. Of even greater interest to those involved in treatment development in cachexia and muscle wasting in HF may be the 2013 Annual Congress of the Heart Failure Association of the European Society of Cardiology (Lisbon, 25-28 May, 2013), where on 28/29 May a trialist workshop on treatment development for cachexia and muscle wasting in heart failure and chronic obstructive pulmonary disease will be held.

Acknowledgments

Stephan von Haehling is consulting and has received honoraria for speaking from Professional Dietetics, Vifor, and Pfizer. Stefan D. Anker is consulting, and has received honoraria for speaking and/or attended advisory boards for Amgen Inc, Professional Dietetics, Psioxus Therapeutics, GTx, Helsinn, GSK, Sanofi, Regeneron, Novartis, Takeda, Servier, Chugai and Vifor. All other authors report no conflict of interest.

This paper is also published in parallel in *International Journal of Cardiology.*

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