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REVIEW

Research on cachexia, sarcopenia and skeletal muscle in cardiology

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Abstract
Background The awareness of cardiac cachexia, i.e. involuntary weight loss in patients with underlying cardiovascular disease, has increased over the last two decades.
Methods and results This mini-review looks at recent research in the cardiovascular literature that is relevant to the areas of interest of the *Journal of Cachexia, Sarcopenia and Muscle*. It identifies significant research in the last 3 years on the obesity paradox, the causes and effects of skeletal muscle wasting, animal models of cachexia and emerging treatment ideas in cardiac cachexia.
Conclusions Assuming a similar literature in the fields of cancer, chronic obstructive pulmonary disease, chronic renal failure and chronic liver failure, the emergence of cachexia as a vibrant area of clinical and experimental research seems assured.

Keywords Cachexia · Cardiology · Sarcopenia · Obesity · Skeletal muscle · Wasting disorders

The *Journal of Cachexia, Sarcopenia and Muscle* (JCSM) is young and covers a field in which it stands almost alone because of the relative newness of this field. The readership of JCSM comes from varied backgrounds with interests that span a variety of specialist fields (cancer, cardiovascular, pulmonary, renal, metabolic, musculo-skeletal, infectious disease, endocrine, GI, hepatic and intensive care) as well as across all levels of the research spectrum from fundamental science, translational medicine, clinical trials epidemiology and health service research. As a result, specialist knowledge may not be made easily available to JCSM readers and much cutting edge research may be lost in the specialist literature.

The current mini-review looks at recent research in the cardiovascular literature that is relevant to the areas of interest of JCSM. Modern readers rarely have time to read the literature outside their own disciplines so we felt it would be beneficial to bring to the attention of the readership of JCSM those recent relevant publications in the major cardiological journals over the last 2 years.

1 The epidemiology and risks of high and low body mass

Studies continue to confirm that normal, predominantly young and apparently healthy populations show adverse effects if their body weight increases to the obese range [1]. Central obesity may be a particularly adverse predictor of cardiovascular disease, possibly acting via both inflammatory and endothelial dysfunction mechanisms. In a cross-sectional study of 2,589 lean, moderately active participants aged 20 years and older in Inner Mongolia, inflammatory markers including C-reactive protein, soluble intercellular adhesion molecule 1 (also known as CD54) and soluble E-selectin were all significantly higher among individuals with a higher body mass index (BMI) and waist circumference. Increased waist circumference proved to be the stronger predictor of inflammation compared to BMI being the stronger predictor of endothelial dysfunction [2].

Although there an emerging consensus that weight loss, particularly to a low BMI, is a marker of an adverse outcome in heart failure (HF), the protective role of obesity remains the subject of conflicting reports and debate [3]. Trullàs et al. [4] examined the frequency and consequences of weight loss in 731 patients with HF from the Registro Nacional de Insuficiencia Cardiaca (RICA Registry). In contrast to earlier reports, the 419 (57.3 %) patients who lost weight during follow-up (or the

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152 [20.8 %] who lost at least 5 % of the baseline bodyweight) had similar survival rates and re-admission rates to those without weight loss. Zamora and colleagues [5] reported that the obesity paradox, where outcomes are improved in the obese patients, was only seen in those with a non-ischaemic aetiology for their HF, but it has also been described in all CHF patients undergoing surgery [6, 7]. Interest in obesity and the obesity paradox has been reported in a range of cardiovascular conditions including acute myocardial infarction [8, 9]; the latter report showing a U-shaped curve relating BMI to mortality in 2,157 patient with acute myocardial infarction (mean follow-up of 26 months), particularly in those patients with concomitant anaemia, who had a striking increase in mortality (adjusted hazard ratio [HR] 5.1, 95 % confidence interval [CI] 1.9–11.7 and 3.2, 95 % CI 1.5–7.0, respectively, for the lower and upper BMI categories). Atrial fibrillation has also been shown to be more common in the presence of obesity (either central or peripheral), even in the absence of an abnormal ECG on community screening [10]. In a population at lower risk of cachexia—a percutaneous transluminal coronary angiography population—from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry [3], patients were classified into a normal weight 34.7 % (354/1,019), overweight 45.9 % (468/1,019) or obese 19.3 % (197/1,019). In multivariable analysis, overweight, but not obesity, remained associated with a lower risk for all-cause mortality (HR=0.60, 95 %CI [0.42–0.86], p=0.005).

Perhaps one of the most surprising findings was the report by Doehner [11] in type 2 diabetes (the condition almost defined by a universal recommendation to lose weight) of a post hoc analysis of body weight and weight change in relation to outcome in 5,202 patients from the PROactive trial population who had T2DM and evidence of pre-existing cardiovascular disease. In this population, the lowest observed mortality was seen in patients with a mildly obese BMI of 30–35 kg/m^2 at baseline, and weight loss was associated with an increased total mortality (HR per 1 % body weight, 1.13 [1.11 to 1.16]; p<0.0001), with increased cardiovascular mortality, all-cause hospitalisation and the composite of death, myocardial infarction and stroke. Weight loss of ≥7.5 % body weight (seen in 18.3 % of patients) was the strongest cut-point to predict impaired survival (multivariable adjusted HR 4.42 [3.30 to 5.94]). Weight gain was not associated with any increased mortality. Even weight gain in patients treated with pioglitazone (mean+4.0±6.1 kg) predicted a better prognosis (HR per 1 % weight gain, 0.96 [0.92 to 1.00] p=0.037) compared to patients without weight gain.

2 The pathophysiology of adiposity and sarcopenia

Obesity, although usually being considered a sign of unfitness, can in chronic diseases be a good sign. Obesity has been shown to increase muscle strength in heart failure with reduced ejection fraction, possibly due to a form of training effect induced by the increased body weight carriage [12]. The role of sarcopenic obesity, where body mass goes up but fat-free mass declines, has more recently been investigated. de Simone [13] and colleagues showed that relative fat-free mass (FFM) deficiency (RFFMD) can also occur in obesity. In a population with a high prevalence of obesity, echocardiography was performed in 2,625 participants (1,694 women; 1,199 non-obese) of the Strong Heart Study cohort, free of prevalent cardiovascular disease and kidney failure. FFM was estimated by bioelectric impedance. RFFMD was found to be more frequent in women than men. Left ventricular hypertrophy was greater in those with RFFMD, even after adjusting for sex and diabetes (both p< 0.0001), an effect even independent of older age, greater BMI, higher systolic and lower diastolic blood pressure and waist/hip ratio, an effect thought to be more related to adiposity than central fat distribution.

3 The pathophysiology of symptoms and disease progression in cardiovascular cachectic conditions

Much research has been conducted on the obvious loss of appendicular skeletal muscle in cachectic conditions and the obvious deleterious effects this has on exercise tolerance [14]. Studies in patients with chronic HF show specific skeletal muscle deficits which cannot be explained by muscle size changes or physical activity levels alone [15]. The whole field of skeletal muscle changes in chronic HF has a long history, going back almost three decades. This has been recently reviewed [16]. Less has been published on the equally important loss of fat tissue [17, 18]. More recently, an appreciation that wasting and weakness can also occur in respiratory musculature both in chronic heart failure [19] and more recently described in pulmonary hypertension [20]. An even more surprising and potentially important finding has been the appreciation that cachexia and even cancer itself can damage the heart [21–23], leading to the potential for a cardiac non-cancer cause of death in advanced cancer, and the potential for novel interventions.

4 What causes cachexia and how can we treat it?

Poor nutrition is obviously a frequent co-morbidity in cachectic conditions; indeed, it could be argued you cannot diagnose cachexia with certainty without ruling out malnutrition by specific nutritional assessment and intervention first. Markers of poor nutrition in predicting a poorer outcome in chronic heart failure have been reported [24] including a report of lower cholesterol being independently

associated with worse outcome. This is frequent in many chronic illnesses including chronic HF. The role of nutritional assessment and intervention in the setting of heart transplant assessment has recently been reviewed [25] and guidelines published for heart and lung disease patients [26]. There has also been a lot of recent interest in the role of changes in small and large intestine function in chronic heart failure in the pathogenesis of wasting. [27–29].

The neurohormonal basis of weight loss in cardiac cachexia has been well evaluated [30, 31]. This as in severe heart failure, and indeed even in cancer cachexia [32], is associated with cardiopulmonary reflex abnormalities including Cheyne-Stokes respiration [33]. The mechanism is beginning to be evaluated such as the finding that angiotensin II, the classical heart failure-related neurohormone, plays a role in appetite suppression [34]. In addition to the classically defined cachectic cytokines [35], more recently attention has focussed on leptin [36] and other adipokines [37–39]. There is also an increasing interest in the role that insulin resistance may play in skeletal muscle dysfunction in chronic heart failure [40]. All of these remain interesting areas for the study of the pathophysiology of cardiac cachexia, and although we have some animal studies suggesting possible therapeutic strategies to treat the skeletal muscle changes of cardiac cachexia [41], human clinical trials remain frustratingly absent, and when there have been some, they have been almost uninterpretable by comparing multiple treatments simultaneously against an unproven control [42]. In recent reviews, the methods of measuring body composition have been evaluated [43, 44] and attempts to develop validated symptom questionnaires for cachexia are being progressed [45, 46]. These techniques are essential to make evaluation of interventions in phase 1 and 2 trials affordable.

A recent review highlighted progress being made in new treatments for cachexia, despite the fact that as yet only an appetite stimulant for AIDS-related cachexia has received approval in a cachectic condition in the European Union or the USA [47]. Dietary interventions must be attempted first, including nutritional support, and indeed in selected cases also with added exercise rehabilitation [48, 49]. Such diets have been shown to be effective in preventing cachexia in animal models [50].

The most promising areas for research in treatment of established cachexia include pro-anabolic therapies [51] although anti-catabolic and anti-inflammatory ideas may also show substantial promise. Ghrelin agonists which mimic a natural ligand for the growth hormone secretagogue receptor stimulate food intake and appetite as well as having indirect ant-inflammatory effects via cytokines [52]. Ghrelin may play an important role in cachexia [53, 54] as perhaps does the less well-studied counter-balancing hormone, obestatin [55]. Studies underway are looking at ghrelin or analogues in the treatment of cachexia caused by chronic HF, chronic obstructive pulmonary disease [56], cancer and renal failure. This area has recently been reviewed by Akamizu [52], Angelidis [57] and Ledderose [58]. Myostatin [59], a powerful inhibitor of skeletal muscle growth, is the subject of strategies to inhibit its activity and promote muscle growth [60–62]. Synthetic adrenergic receptor modulators are also under investigation and animal models of cachexia suggest the potential benefits of blocking the melanocortin system [63]. Novel anti-inflammatory approaches [64, 65] have also shown promise in some animal models of muscle wasting [66].

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