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Therapeutic effects of androgens for cachexia

Luca Giovanelli, Doctor, Training Fellow in Endocrinology, Diabetes & Metabolism [a, b, c],
Richard Quinton, Doctor, Consultant & Senior Lecturer in Endocrinology [c, d, *]

[a] Department of Medical Biotechnology and Translational Medicine, University of Milan, 20100, Milan, Italy
[b] Department of Endocrine and Metabolic Medicine, IRCCS Istituto Auxologico Italiano, 20100, Milan, Italy
[c] Department of Endocrinology, Diabetes & Metabolism, Newcastle-upon-Tyne Hospitals, NE1 4LP, UK
[d] Translational & Clinical Research Institute, University of Newcastle-upon-Tyne, NE1 3BZ, UK

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Cachexia is a complex wasting syndrome, accompanying a variety of end-stage chronic diseases, such as cancer, heart failure and human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS). It significantly affects patients' quality of life and survival. Multiple therapeutic approaches have been studied over time. However, despite promising results, no drug has been approved to date. In this review, we examine and discuss the available data on the therapeutic effects of androgens and selective androgen receptor modulators (SARMs) for cachexia.

Introduction

Cachexia is a complex wasting syndrome, characterized by unintentional progressive weight loss (greater than 5% in 12 months or less) and severe wasting involving all somatic compartments; particularly skeletal muscle and adipose tissue, although bone can also be affected [1,2]. Whether cachexia should be viewed as a disease-specific complication or a common final catabolic process remains a matter of ongoing debate [3].

* Corresponding author. Endocrine Unit, Leazes Wing - Level 6, Royal Victoria Infirmary, Queen Victoria Rd, Newcastle-upon-Tyne, NE1 4LP, UK.
E-mail addresses: luca.giovanelli@unimi.it (L. Giovanelli), Richard.Quinton@ncl.ac.uk (R. Quinton).

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Its estimated prevalence ranges widely between 15 and 90%, depending on the underlying pathological condition [4] and potentially also the era in which data were collected. Although historically a ubiquitous finding in a variety of end-stage chronic diseases – including cancer, heart failure (HF), human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic liver and kidney disease – it now appears less prevalent in the developed world due to the secular obesity epidemic. As affected patients now start from a far higher median BMI at the onset of wasting, it takes that much longer for clinically discernible cachexia to become apparent, even though the rate of wasting is no different.

Cachexia greatly affects patients' quality of life (QoL) and survival [5,6]. In particular, sarcopenia, or loss of lean body mass (LBM), plays a key role in increasing frailty, hospitalization rate and mortality by reducing muscular strength and physical capacity [3]. Its pathogenesis is multifactorial, comprising anorexia, inflammation, increased protein catabolism and other metabolic alterations [7] [Fig. 1]. Since these mechanisms arise early on during the natural history of the underlying disease, an early diagnosis followed by timely intervention might be effective in preventing or delaying the onset of severe wasting.

Ageing strongly contributes to the decline in physical performance, especially in relation to sarcopenia [8], whose prevalence is substantial in most geriatric settings [9]. Indeed, sarcopenia can be considered the biological substrate of physical frailty, which is defined as an age-related decrease in homeostatic reserve [10] and, despite some shared common features, should be distinguished from cachexia. Ageing can exacerbate the muscle wasting associated with chronic illnesses and *vice-versa*. The relationship between the ageing process and skeletal muscle atrophy and dysfunction - mostly affecting fast fibres - is mediated via several phenomena, comprising DNA mutations, mitochondrial remodelling, lower antioxidant capacity and decline in male serum testosterone (T) - this latter principally arising from impairment of gonadotropin-releasing hormone (GnRH)-stimulated secretion of luteinizing hormone (LH), a reduction in Leydig cell numbers and responsiveness, an increase in sex hormone binding globulin (SHBG) levels and, potentially, greater aromatase activity [11,12].

Both research and everyday clinical practice in cachexia have largely focused on nutritional support, based on dietary supplementation with proteins, vitamins and minerals, which is not sufficient to delay or prevent progression of muscle wasting due to its multifactorial nature. Therefore, beyond treatment of the underlying disease, management of cachexia should be based on multimodal interventions, with

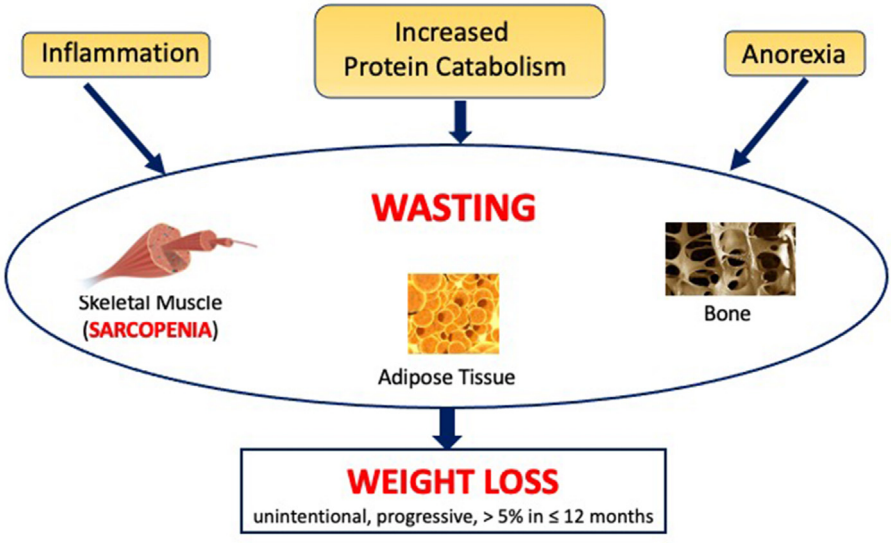

Fig. 1. Mechanisms and Manifestations of Cachexia.

physical exercise training currently appearing to offer the most promising approach to be deployed in parallel to nutritional interventions [13].

Focusing on the two main pathogenic processes, anorexia and catabolism, multiple attempts have been made to identify and validate medical therapies. These have included appetite stimulants, anti-inflammatory drugs, anabolic agents such as androgens and selective androgen receptor modulators (SARMs), and ghrelin (and its agonist anamorelin), which combines anabolic with orexigenic actions [Fig. 2]. Both the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2016 and the American Society of Clinical Oncology (ASCO) in 2020 have suggested pharmacological interventions to improve clinical outcomes in cachectic patients [14,15], but no drug is currently recommended for this purpose.

Overall, cachexia remains a great challenge in clinical practice despite secular changes in body mass index, and the development of preventive and therapeutic strategies and related clinical guidelines is considered to be an urgent healthcare need. As stated during the 11th Cachexia Conference (Maastricht, 2018), "we need personalized medicine to provide the right care to the right patient at the right time" [16]. The aim of this review is to summarize and discuss the available data on the therapeutic effects of androgens and SARMs for cachexia.

Practice points

- Cachexia is a complex wasting syndrome, characterized by unintentional progressive weight loss and severe wasting involving all somatic compartments.
- Prevalence ranges widely between 15 and 90%.
- It significantly affects patients' quality of life and survival.
- Pathogenesis is multifactorial, including anorexia, inflammation, increased protein catabolism and other metabolic alterations.
- Management of cachexia should be predicated on multimodal strategies.

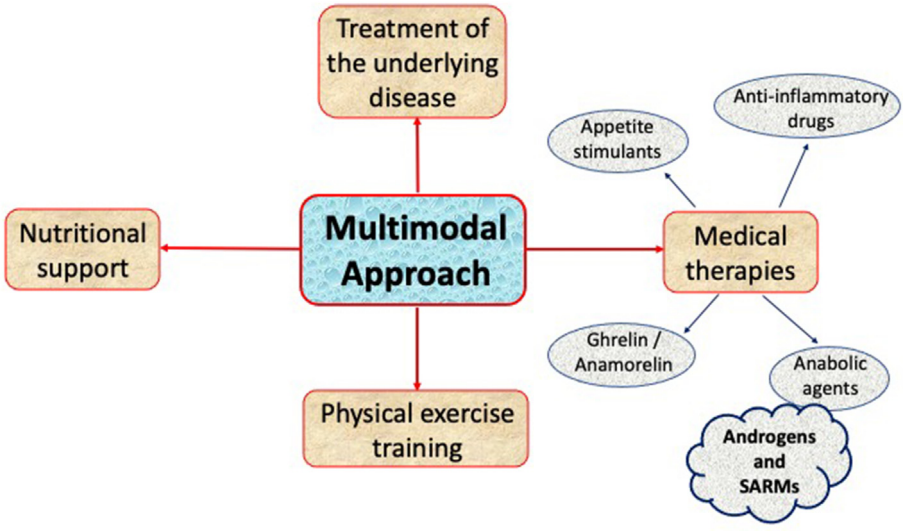

Fig. 2. Multimodal Management of Cachexia.

Role of androgens and SARMs in cachexia

T, the dominant male sex steroid, binds to the nuclear androgen receptor (AR) and, thereby, promotes a signalling pathway that ultimately results in the clinical features that define androgenicity, comprising anabolic effects on muscle, bone and bone marrow as well as the better known virilising effects on sexual function and reproduction [17].

Notably, any systemic chronic disease of sufficient severity can potentially suppress gonadotropin levels; a form of functional hypogonadism or "non-gonadal illness" (NGI), which is reversible once the underlying cause remits or is cured. However, it remains unknown whether this phenomenon is adaptive, maladaptive or neutral in its biological effects [18].

Based on these foundations, androgens have been identified and studied as a potential treatment for chronic disorders-associated muscle wasting.

Mechanisms of action on key tissues

Muscle

Although T supplementation can achieve modest improvements in LBM among both frail and non-frail older men, evidence for a clinically useful effect on muscle strength and physical performance is weak and conflicting [19]. According to a meta-analysis of 59 randomized controlled trials (RCTs), enrolling 5078 males in total, T supplementation was associated with a significant reduction in fat mass and an increase in LBM; especially in younger subjects with metabolic disturbances [20]. Over past years, multiple studies have investigated the broad and complex range of mechanisms responsible for androgen action on skeletal muscle, such as dose-dependent hypertrophy of both type I and II fibres and increase in myofibrillar protein synthesis [21,22]. Androgens also encourage differentiation of mesenchymal multipotent cells into the myogenic lineage, while inhibiting their adipogenic differentiation [23]. In addition, there may be a neural component, influencing neurotransmitter synthesis and ultimately inducing recruitment of the larger and faster motor units [24].

In a relevant double-blind trial performed on older eugonadal men, Gharahdaghi and colleagues recently demonstrated that short-term administration of T therapy adjuvant to resistance exercise training (RET) is able to enhance muscle mass and performance [25], mirroring the experience of athletes aiming to achieve an illicit (for them) competitive edge in performance. Notably, the authors also elucidated the cellular processes underpinning this observation, collectively resulting in higher protein turnover and net protein accretion; thus overcoming age-related defects in adaptive responses to RET [26]. Specifically, myocellular ribosomal biogenesis and mRNA expression relating to T metabolism, along with insulin-like growth factor-1 (IGF-1) signaling and mitochondrial citrate synthase activity, were all upregulated.

Bone

Physiologically, T acts on skeleton both directly – by stimulating periosteal expansion and osteoblastic activation – and after aromatization into oestradiol, which inhibits bone resorption.

With regards to the effects of androgens on bone, the data mainly refer to T supplementation, whose benefits on BMD are well established in hypogonadal men. Concerning the effects on bone quality, in the Bone Trial – one of the seven Testosterone Trials enrolling older men with mild hypogonadism and features of metabolic syndrome – 1-year of TRT was found to increase trabecular volumetric BMD, as measured by quantitative computed tomography (QCT) [27], without any significant change in trabecular bone score (TBS), an indirect parameter for vertebral microarchitecture [28], compared to placebo. Recently, Ng Tang Fui and colleagues [29] performed the first RCT addressing the impact of T treatment on bone microarchitecture assessed by high resolution-peripheral QCT (HR-pQCT), which is more accurate than QCT. 2-Year administration of T undecanoate to men older than 50 years with early diabetes and T levels $\leq$14 nmol/L resulted in a less pronounced increase in volumetric BMD (possibly because most of these men were not actually biochemically hypogonadal), mainly affecting the cortical bone at both tibia and radius, consistently with previous findings from observational HR-pQCT studies [30–32]. Another recent study by Colleluori et al. [33] explored the skeletal response to TRT in men with average morning T < 10.4 nmol/L and Type 2 Diabetes (T2D) compared to their non-diabetic

counterparts. 18 months of intramuscular T cypionate led to a marked increase in circulating osteocalcin, possibly reflecting osteoblastic activation, as well as increased lumbar BMD and improved cortical bone geometry in the former group, in line with a previous study by Ghanim et al. [34]. Intriguingly, these findings suggest differential skeletal effects of T therapy depending on the underlying pathophysiology, i.e., mainly antiresorptive – mediated via conversion into oestradiol – or anabolic among those with high or low bone turnover, respectively [35].

Bone marrow

Animal and human studies suggest both direct and indirect stimulatory effects of androgens on bone marrow erythropoiesis [36]. More in detail, androgens are able to increase erythroid cell mass and their glycolysis-based metabolism [37]. They also encourage the renal production of erythropoietin (EPO) as well as the EPO-responsiveness of erythrocytes [38]. Moreover, by inhibiting the secretion of hepcidin, T may enhance the iron bioavailability and its incorporation into the red blood cells [39]. Lastly, the raised IGF-1 levels found in those receiving androgens could indicate a potential IGF-1 driven erythroid progenitor cells differentiation [40]. Notably, a few double-blinded RCTs specifically examining the impact of T replacement on anaemia in hypogonadal patients, have shown suppressed hepcidin with a significant increase both in haemoglobin and EPO levels [41,42].

Testosterone supplementation

A meta-analysis from 2006 provided compelling evidence that T supplementation increased muscle mass and strength in HIV-positive men with weight loss, as well as in older and/or glucocorticoid-treated men with low or low-normal T levels [23].

These observations have led to considerable pharmaceutical interest in applying T as an anabolic therapy to improve physical function and reduce the burden of disability in older men with mobility limitation. However, most trials have not demonstrated meaningful results [43–48], relating to limitations of sample size and statistical power; the inclusion of healthy older men without functional limitations; heterogeneity of T doses deployed and in the ascertainment of clinical outcomes, and relatively short duration of intervention (typically 3–6 months). Moreover, concerns relating to potential longer-term risks (erythrocytosis, cardiovascular and prostate events) have since restrained the enthusiasm of investigators.

In 2018, Bhasin et al. [49] analysed in detail the Physical Function Trial's findings, one of the seven Testosterone Trials (T-Trials) that aimed to determine the effects of T on mobility, physical function, falls and patient “global impression of change” in older men with limited mobility. Although a relevant improvement in walking ability was self-reported by all the participants, there was no impact on the key outcome of reducing falls.

Synthetic androgens

Although AR-binding is core to the pathway by which all androgens, including T, exert their actions, there are three potential ways by which synthetic androgens (also known as androgenic anabolic steroids) may exert actions that are disproportionately anabolic compared with native T. First, they may give rise to different patterns of post-receptor signalling; second, they may have different non-genomic actions via cell–surface interactions and, finally, their conversion to active metabolites 17,beta-Estradiol (E_2) and dihydrotestosterone (DHT) differs. Many of the physiological functions attributed to testosterone – including anabolic actions on cancellous bone and bony epiphyses, feedback inhibition of gonadotropin secretion and some aspects of libido – are actually mediated via aromatisation to E_2, and much of the virilising action of testosterone is mediated via DHT.

Despite concerns about side effects such as fluid retention and hepatotoxicity, synthetic analogues of gonadal steroids (oxandrolone, nandrolone, oxymetholone, fluoxymesterone) have been studied in patients with AIDS- and COPD-related cachexia; all showing improvements in body composition [50]. In a recent large systematic review and network metanalysis, Saeteaw and co-authors evaluated the relative efficacy and safety of pharmacological interventions for cachexia, by integrating evidence from

80 RCTs (10,579 patients, most of whom affected with cancer). Androgens were listed among those agents that significantly ameliorated both body weight and appetite [13].

SARMs

Due to their selective anabolic activity, SARMs have been heralded as the future of androgen treatment ever since their discovery towards end of the 20th century [51], but have not yet found any clinical treatment role. Even more than synthetic androgens, different tissue-specific AR expression patterns and transcriptional regulatory milieu allow these small molecules to function as either AR agonists or antagonists in different areas of the body [52] and, moreover, they are not at all metabolised to either E_2 or DHT [53].

Thanks to these properties, SARMs selectively elicit anabolic effects, while potentially minimizing the off-target effects of androgens (*e.g.* on prostate, heart and liver), which have been traditionally considered to outweigh benefits in vulnerable patients. Their excellent oral bioavailability with convenient dosing frequency provides them with another substantial advantage over T therapy. Moreover, the potential for transdermal administration – by circumventing hepatic metabolism – may mitigate unwanted effects of oral SARMs on high-density lipoprotein cholesterol (HDLc) levels, one of the few pitfalls observed to date [54].

SARMs have thus been explored as a promising treatment for a wide range of medical challenges, including cachexia and, indeed, early preclinical models documented beneficial effects on muscle wasting. For instance, GLPG0492 (Galapagos) was shown to be effective in treating immobilization-related muscle wasting in a pre-clinical model [55]. However, recent clinical studies have cast doubt over the clinical relevance of these findings.

Several phase I studies evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of the SARM GSK2881078. In a study by Clark et al. adverse events (*e.g.* decreases in HDLc) were noted in around half of the participants (albeit distributed evenly between the placebo and active treatment groups and thus indicating acceptable tolerability), and a potential therapeutic role for cachexia was shown [56]. In another phase I clinical investigation, subjects receiving the active drug achieved greater LBM gains than those on placebo, with lower doses achieving greater responses in females than in males even in the absence of any resistance training. Transient elevations in alanine aminotransferase (ALT) and reversible reductions in male T levels were observed [57]. A phase II trial is also currently underway to examine the safety of GSK2881078 and its effects on physical strength and function, in both postmenopausal women and older men affected with COPD and muscle weakness [54].

In a recent pre-clinical study by Muta and colleagues, a novel compound, S42, was seen to exert both anabolic and anti-catabolic actions on differentiating myotubes, hinting at the ability of SARMs to simultaneously prevent muscle loss and induce muscle gains [58].

GTx-024 (enobosarm), appeared to have a bright future as a therapy for muscle wasting, following preliminary clinical trials which demonstrated an improvement both in LBM and physical function in healthy younger and elderly men as well as in postmenopausal women [59]. Two years later, Dobs et al. conducted a double-blind phase II RCT on 159 male and postmenopausal female patients with cancer who had lost at least 2% of body weight in the 6 months before, in order to assess the efficacy and safety of enobosarm at two different dosages (1 and 3 mg). Significant increases in LBM were noted in both treated groups and the drug was well tolerated [60]. Unfortunately, results of the more recent phase III Prevention and treatment Of muscle Wasting in patients with cancER (POWER) I and II trials have tempered expectations. Although increases in LBM, measured by dual-energy X-ray absorptiometry (DEXA), were once again observed, there were no accompanying improvements in physical function – assessed as stair-climb power – in comparison to the placebo group [61–63], similar to findings of studies investigating androgens in male frailty [19,64].

These observations have proven the greatest barrier to gaining regulatory approval of SARMs for clinical use. Although the failure to achieve both primary endpoints may be due to confounding factors such as age, disease stage, baseline physical function and chemotherapy, the fact remains that, as stated by Ramage & Skipworth, "*the relationship between muscle mass and muscle function is complex and unlikely to be linear*" [63].

Moreover it's worth noting that SARMs, because of their attractive side effect profile, ease of use and relative difficulty to be detected in comparison with other androgenic compounds, present a critical potential for abuse; not just be professional athletes [65,66]. Indeed, despite the lack of regulatory approval, agents purporting to be SARMs are readily available for purchase online [52], although many of these offerings contain several unapproved substances [67]. Conversely, the SARM ostarin (enobosarm) has been found as an undeclared ingredient of many dietary supplements. There have thus been increasing efforts focusing on isolating SARM metabolites for drug testing [68,69], with multiple SARMs having already been added by the World Anti-Doping Agency (WADA) to their "prohibited list" [70].

Practice points

- Given that testosterone has anabolic effects on muscle and bone and that any severe chronic disease can cause functional hypogonadism, androgens have been identified as a potential treatment for chronic disorders-associated cachexia.
- Studies investigating testosterone supplementation have yielded conflicting results, also because of concerns relating to longer-term risks.
- Synthetic androgens, which exert greater anabolic actions, have been shown to ameliorate body weight and composition.
- In view of their selective anabolic activity, SARMs have been explored as a promising treatment.
- According to preliminary clinical trials, enobosarm appeared to improve both lean body mass and physical function. However, more recent studies have not confirmed these findings.
- SARMs, due to their attractive side effect profile, ease of use and relative difficulty to be detected, present a critical potential for abuse.

Role of other anabolic agents in cachexia

Recombinant human growth hormone (rhGH)/recombinant human IGF-1 (rhIGF-1)

Given that GH/IGF-1 axis is a key regulator of muscle protein metabolism and also there is evidence of GH resistance in cachectic patients, rhGH has been considered a promising therapy for wasting syndrome. Several RCTs reported its efficacy (6 mg/d for 12 weeks) in increasing body weight and LBM, in the face of modest and transient impairment in blood glucose profile [71–73]. Instead, the combination between low doses of rhGH and rhIGF-1 was not generally associated with significant improvements. However, there is still much to be learned regarding rhGH therapy in cachexia, such as the optimal duration and regimen of treatment and its long-term impact on morbidity and survival [74].

Ghrelin/anamorelin

Ghrelin is a peptide hormone which combines anabolic with orexigenic and anti-inflammatory properties, partly mediated through GH release [75]. Interestingly, it has been seen to ameliorate chronic diseases-associated muscle atrophy by enhancing mitochondrial oxidative capacity and protein kinase B phosphorylation. It is also able to reduce energy expenditure, which is most frequently increased in cachectic subjects [76]. Anamorelin, an orally available human ghrelin receptor agonist with longer half-life, has been deployed in several RCTs focusing on cachexia management [77–80]. The treated arm experienced significant improvements both in LBM, weight gain, food intake and QoL scores, but without changes either in hand grip strength or overall survival, as compared to placebo. Two recent meta-analyses of these studies [81,82] have confirmed these

results, despite some limitations relating to high heterogeneity and limited sample size. Positive effects on muscle power were documented after intravenous administration of ghrelin in a small open-label study by Nagaya et al. [83].

Insulin

Insulin has been studied in cachectic patients due to its anti-lipolytic effects. Indeed, it was found to increase whole-body fat and survival, without any improvement in body weight, exercise capacity or QoL [84].

Bimagrumab

Myostatin is a transforming growth factor β superfamily member, able to inhibit skeletal muscle growth through activin receptor II B (ActRIIB). This has hence supported a role for anti-myostatin strategies in the treatment of muscle wasting [76,85]. In a clinical trial [86], Amato and co-authors demonstrated that a single intravenous dose of bimagrumab, an anti-ActRII monoclonal antibody, increased LBM and thigh muscles volume in patients suffering from inclusion body myositis, as compared to placebo. The most common adverse events were muscle spasms and only one patient required hospitalization relating to a flu-like illness. Notably, Lach-Trifilieff et al. [87] created the human antibody BYM338, featuring much higher affinity for ActRIIB than ActRIIA and thus determining greater muscle hypertrophy when administered in vivo. Combined with glucocorticoids, it was seen to significantly prevent muscle loss and preserve muscle function as well. Moreover, in a phase II RCT involving sarcopenic older adults, the anti-myostatin monoclonal antibody LY2495655 led to a significant improvement both in LBM and muscle power (expressed as stair climbing time, fast gait speed and chair rise with arms) [88].

Cancer cachexia

General considerations

In 2011, an international consensus statement defined cancer cachexia as “a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” [89]. Roughly two thirds of late-stage cancer patients suffer from cachexia. Prevalence varies across cancer types, up to 80% among the gastrointestinal ones.

Cancer cachexia negatively affects QoL, fitness for and responsiveness to chemotherapy; thereby contributing to the earlier death of a relevant proportion of patients [90].

The main clinical presentation is unintentional weight loss, accompanied by anorexia, systemic inflammation, insulin resistance and hypercatabolism. The wide spectrum of symptoms is mediated through a variety of both tumour- and host-derived factors. Muscle wasting is one of the particular hallmarks of cancer cachexia; also involving myocardial tissue with consequently impaired cardiac performance [91]. Nevertheless, the diagnosis can still be challenging due to confounding factors such as cachexia-like complications of cancer therapy and pre-existing sarcopenic obesity.

Longstanding controversies over both the definition and assessment methods of cancer cachexia have hampered efforts towards the development of any international standard of care guideline, which is still lacking. It should be noted that optimal treatment depends on the disease stage, as palliative options are necessarily prioritized over curative modalities at end of life. However, the multifactorial nature of cancer cachexia equally requires a multimodal approach, including drugs, nutritional support and an adequate program of physical exercise to achieve maximum benefit [85,92].

Several drug classes have been proposed to target the underlying pathophysiological processes – tumour-associated inflammation, catabolism and anorexia – and numerous trials have been conducted. Nevertheless, the usual limitations of small sample size and heterogeneity of their patient phenotypes apply, and have contributed to conflicting results of limited clinical applicability [89]. No

single approved therapy currently exists for cancer cachexia. Indeed, the proper staging of cancer cachexia is a prerequisite for optimisation of future clinical trial design, so as to permit the initiation of treatment it at an early stage; ideally even before weight loss can be detected. This emphasizes the need for identifying biomarkers to permit the early stratification of cancer patients with respect to the risk of developing cachexia [93,94].

Role of androgens and SARMs in cancer cachexia

Male cancer patients have a greater prevalence of T deficiency (50–90%) compared with age-matched controls, which may in turn contribute to fatigue, sexual dysfunction, impaired QoL, sarcopenia and – ultimately – reduced survival. However, the origin of gonadal dysfunction can be hard to disentangle in these patients. Multiple causes, such as chronic inflammation, pelvic radiation, chemotherapy and medications (*e.g.* opioids or corticosteroids), often coexist, leading to both primary and secondary hypogonadism [95].

Screening for hypogonadism also can be challenging. Because of poor sleeping patterns, T levels may not peak in the morning, hence giving falsely low values. On the other hand, increased levels of SHBG may lead to artefactually normal T concentrations, so free T should generally be calculated [50].

No guidelines exist for T supplementation in cancer patients. Only two small RCTs have evaluated the effects of T administration on cachexia outcomes in patients with advanced cancer [96,97]. In the first study, 4 weeks of intramuscular T improved sexual desire and performance status, but with no relevant impact on QoL [96]. In contrast, in a phase II study recently performed by Wright et al. enrolling both men and women, weekly injections of T enanthate were also associated with improved QoL [97]. Both two trials found therapy to be well tolerated.

Overall, although there is promising evidence for efficacy in some of its domains, the benefits of T replacement on cancer cachexia, particularly on weight and appetite, have yet to be evaluated in larger and adequately powered clinical trials.

Despite their side effects, synthetic androgens (oxandrolone, nandrolone, oxymetholone, fluoxymesterone) may benefit cancer patients, since they are able to counteract the progressive nitrogen loss related to muscle wasting [85]. In this context, Lesser and colleagues performed a prospective randomized phase III trial, comparing the effects of oxandrolone and megestrol acetate on weight, body composition and QoL in patients with cancer and weight loss receiving chemotherapy. Those treated with oxandrolone still lost weight overall, but gained LBM and improved appetite [98]. Nevertheless, no placebo-controlled studies have been published in peer-reviewed journals.

As stated previously, the SARM enobosarm was associated with significant improvements in LBM, physical function and QoL in a phase IIb RCT of cancer patients [60]. These positive results led to the design of phase III POWER trials, wherein cancer patients were randomized to receive either placebo or oral enobosarm 3 mg once daily for 147 days [61]. The two co-primary endpoints, LBM and physical function, were assessed by DEXA and as stair climb power, respectively. An increase in the former was reported, but as usual with no improvement in the latter [62,63]. These findings have likewise tempered initial enthusiasm for a potential role of SARMs as muscle-wasting treatments.

Cardiac cachexia

General considerations

In 1997, cardiac cachexia was identified as a strong independent risk factor for mortality in patients with chronic heart failure (HF) [99]. European Society of Cardiology (ESC) guidelines first mentioned cardiac cachexia in 2001 [100] and later recognized it as a comorbidity of HF in 2012 [101]. It was finally defined as “an involuntary non-oedematous weight loss of 6% or more of total body weight within the previous 6–12 months” [102]. This straightforward definition has enabled patients at risk to be identified in every body mass index (BMI) category.

Since then, moreover, weight reduction has no longer been routinely recommended across the board in overweight and obese subjects with pre-existing HF. Notably, these patients often present with fluid retention, which may hamper the diagnosis of cachexia in two ways: the elimination of oedema by diuretic treatment can be misinterpreted as significant weight loss, resulting in a false positive diagnosis and, conversely, progressive oedema can delay or even prevent the recognition of cachexia by masking the loss of tissue [103].

The prevalence of cachexia among HF patients ranges between 10% and 39%, depending on the study design, the diagnostic criteria of cachexia and the HF stage; being more frequent in advanced disease. The prognosis is dismal, with mortality reaching 50% in 18 months [103].

During the course of HF, the wasting of major body compartments appears to follow a characteristic pattern, typified by an earlier loss of LBM, which might not be associated with overall weight loss and leads to reduced exercise capacity and strength [104–106]. In advanced stages, fat becomes the predominantly wasted tissue. Beyond skeletal muscle, wasting also affects the myocardium, which may explain the intrinsic relationship between cachexia and decreased survival [107]. Studies investigating bone loss are scarce and controversial. The underlying catabolic–anabolic imbalance arises from a complex network of metabolic, immune and neurohormonal factors, which are mostly activated early but result in wasting at the inexorable stage of congestive HF [108].

Treatment for cardiac cachexia remains poorly defined. Optimizing HF treatment is certainly one of the mainstays, in particular with beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, targeting an imbalance of the renin-angiotensin-aldosterone system [109,110]. The most promising approach seems to involve a combination of nutritional counselling, exercise and pharmacotherapy. Nutritional advice includes avoiding excessive salt and fluid intake and replenishing deficiencies in trace elements, with the administration of omega-3 polyunsaturated fatty acids to selected patients. High-calorific supplements have also been used both to maintain and increase body weight, particularly the branched-chain amino acids isoleucine, leucine and valine. Prescription of aerobic exercise up to a level that provokes mild or moderate breathlessness is advocated by the ESC guidelines [102]; for instance, bicycle training has been seen to reduce skeletal muscle degradation [111–113]. From a pharmacological perspective, while no guidelines have been established, multiple options with potential benefit have been tested in small studies, aiming at the various pathophysiologic mechanisms of the syndrome, such as inflammation, metabolic-hormonal imbalance and gastrointestinal abnormalities. Therefore, further studies specifically focusing on the cardiac component of cachexia are needed.

Role of androgens in cardiac cachexia

Patients with HF have decreased circulating levels of T which may contribute to loss of skeletal and left ventricular muscle mass and deterioration in exercise tolerance.

Administration of T to these patients has long been documented to induce muscle growth and decrease peripheral vascular resistance and inflammatory cytokines and evidence for its use has been growing over the past 12 years. Indeed, T also acts as a direct vasodilator in systemic, coronary and pulmonary vessels, probably mediated by non-genomic mechanisms, as well as increasing oxygen transport by stimulating erythropoiesis. On the negative side, T promotes salt and water retention, which can be problematic in cardiac failure. Nevertheless, among approaches under investigation for cardiac cachexia, T has the strongest evidence base and is also mentioned in the ESC HF guidelines [102,110,111].

The first RCT to assess T treatment in HF was performed by Pugh and colleagues on 12 men. Oral T was well tolerated and associated with a relative increase in cardiac output and a reduction in systemic vascular resistance [114]. In the following year, the same group administered intramuscular T vs placebo to 22 patients with chronic HF and reduced exercise capacity as part of another double-blind RCT. After 12 weeks, the distance walked during the shuttle walking test improved significantly in the treated arm, as well as symptom scores from the Minnesota Living with HF questionnaire [115]. This study was followed by the largest trial published to date, involving 76 men with stable HF and impaired exercise tolerance, who were given either a 5-mg daily T patch or placebo. After 12 months, those receiving T showed increases in exercise capacity and improvements in New York Heart Association

(NYHA) functional class. No serious adverse effects were reported, apart from poor tolerance of the patch [116]. These positive results were confirmed in another RCT trial of comparable size, evaluating peak oxygen consumption and quadriceps strength [117]. The same researchers subsequently found similar improvements in 36 women with chronic HF [118].

A meta-analysis published in 2012 confirmed the overall beneficial effects of T treatment in both male and female HF patients, particularly on insulin resistance and exercise capacity, with a mean increase in the 6-min walking test, shuttle walking test and peak oxygen consumption between the T and placebo groups of 54.0 m, 46.7 m and 2.70 ml/kg/min, respectively [119]. However, limitations of most trials included small sample size, lack of specific identification of patients with cachexia and brief follow-up periods, ranging from 12 weeks to one year.

Moreover, downstream effects of T might represent a limiting factor, in that long-term administration of T promotes salt and water retention, although no harmful adverse events have been reported from replacement studies in HF, likely due to the lower doses used [110,111].

In the context of HF, no literature about SARMs is available. However, in view of the increased LBM obtained in cancer patients in the absence of off-target side effects (33–36), they might equally represent a reasonable therapeutic approach in cardiac cachexia.

HIV/AIDS - associated cachexia

General considerations

Cachexia is a debilitating and potentially life-threatening complication of HIV infection, associated with reduced strength and physical function, reduced ability to withstand opportunistic infections and increased mortality.

It was first officially recognized as an AIDS-defining illness in 1987, when the Centers for Disease Control and Prevention (CDC) provided a definition of HIV-associated wasting as “>10% involuntary weight loss plus either chronic diarrhoea (2 loose stools daily for >30 days) or chronic weakness and documented fever for >30 days (intermittent or constant) in the absence of a concurrent condition other than HIV infection that might explain these findings” [120].

Prior to the introduction of highly active antiretroviral therapy (HAART) in 1995, estimates of prevalence of wasting as the first AIDS-defining condition ranged up to 31% [121]. Since then, wasting has continued to be a concern in this population its incidence is has declined. In fact, wasting may even occur before progression to AIDS [122]. Although HAART has been an invaluable breakthrough, it has added metabolic problems of its own, which can make it harder to disentangle primary symptoms from adverse drug effects [123].

The pathogenesis appears to be multifactorial and remains incompletely clarified, but both a reduced caloric intake and an excessive proinflammatory cytokine response play a critical role in its development, along with other metabolic and endocrine factors (*e.g.* T deficiency and GH resistance) [124]. All these mechanisms lead to LBM loss, which is a salient feature of HIV-associated cachexia, produced by an imbalance between muscle catabolism and anabolism [74].

Role of androgens in HIV/AIDS-associated cachexia

20–25% of HIV-infected men on HAART have low T concentrations, with an even greater proportion having low free T due to high SHBG levels frequently encountered in these patients. HIV-related hypogonadism is associated with multimorbidity, progression to AIDS, frailty, depression, and loss of weight, muscle mass and exercise capacity [125,126]. A correlation between low free T levels and the development of wasting was observed in AIDS women as well, who unlike men, exhibit a disproportionate decrease in fat versus lean body mass [127].

In a systematic review of RCTs conducted on HIV patients with weight loss, 3–6 months of T replacement led to greater gains in body weight and LBM than placebo, especially when

injectable T esters were used [128], and a Cochrane review found similar results [129]. T administration has also been associated with improvements in maximal voluntary strength [130,131]. However, there are no data about the impact on physical function and risk of disability, or in relation to long-term safety. Indeed, in the study by Bhasin et al. [130], T and exercise training did not produce additive improvements when integrated. In another systematic review of RCTs, T therapy also had a moderate effect on depression [132]. Adverse event rates did not differ significantly between placebo and T groups. Nonetheless, considerable heterogeneity across trials (*e.g.*, in weight loss degrees, disease severity, T regimens) limit the strength of the inferences that can be drawn.

According to the Endocrine Society guidelines from 2018 [133], clinicians should consider short-term T treatment in HIV-infected men with low T concentrations and weight loss in order to induce and maintain body weight and LBM gain. Given that the evidence of benefit is limited to 6 months of therapy, shared decision making is needed regarding further continuation.

A few studies from the late 90s, using synthetic androgens in subjects with HIV-related wasting, reported gains in fat-free mass but not in muscle strength [130]. For instance, Gold and co-authors evaluated the safety and efficacy of nandrolone decanoate, a synthetic androgen of high anabolic potency, in 24 patients. Significant increases in weight, LBM and QoL scores were noted, in the absence of toxicity [134]. Oxymetholone encouraged similar improvements in a 30-week pilot study [135]. Oxandrolone, another oral anabolic steroid with a favourable anabolic/androgenic ratio, also induced meaningful weight changes and was well tolerated in a multi-centre RCT [136].

Glucocorticoid-associated cachexia

There is a high prevalence of T deficiency in glucocorticoid-treated men due to multilevel suppression of the hypothalamic–pituitary–gonadal axis. Typically, daily administration of more than 5–7.5 mg of prednisone or its equivalent is associated with an increased risk of hypogonadism and alterations in muscle and bone mass.

In two RCTs [137,138] performed on glucocorticoid-treated patients for COPD/bronchial asthma, T supplementation produced significant improvements in body composition compared to placebo, with a low frequency of adverse events. However, these inferences are weakened by the small size of these studies, their short duration and their inconsistent results.

In 2010, the Endocrine Society suggested that T therapy should be considered for men receiving high doses of glucocorticoids with low T levels, aiming to preserve LBM and bone mineral density [139], but this recommendation was removed from the latest edition of the guidelines [133].

Conclusions

Cachexia represents a major health and social burden, accompanying a variety of end-stage chronic diseases and greatly affecting patients' QoL and survival. It remains to date a great challenge in clinical practice, with progress required in terms of achieving timely diagnosis and developing evidence-based treatments. Apart from addressing the underlying disease, management of cachexia should be based on multimodal strategies. Indeed, although multiple medical therapies have been suggested, no drug is currently recommended. Among these, androgens and SARMs have been quite extensively studied with promising results. In this setting, the whole *raison d'être* of using synthetic androgens or SARMs in men is predicated on the basis that native T has undesirable or potentially dangerous effects. However, the more we learn about T therapy in men, the safer it appears, albeit its efficacy outside the core indication of organic hypogonadism remains elusive. On balance, despite a current standstill on the clinical application of SARMs, there remains considerable confidence about their potential, but standardized hard endpoints are required for future clinical trials. Moreover, a greater understanding of the mechanisms involved in tissue wasting - especially in cancer patients - might encourage the development of more targeted therapies, with a view to counteracting or even reverse the progression of cachexia.

Research agenda

- Cachexia still needs progress in terms of both timely diagnosis and evidence-based treatment.
- Further studies are needed to better substantiate pathogenetic mechanisms underlying cancer cachexia.
- Standardized hard endpoints are required for future clinical trials involving SARMs.
- More targeted therapies should be developed in order to counteract or even reverse the progression of cachexia.

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