

Muscle wasting in ageing and chronic illness

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Abstract

Purpose As life expectancy increases, muscle wasting is becoming a more and more important public health problem. This review summarizes the current knowledge of pathophysiological mechanisms underlying muscle loss in ageing and chronic diseases such as heart failure and discusses evolving interventional strategies.

Recent findings Loss of skeletal muscle mass and strength is a common phenomenon in a wide variety of disorders associated with ageing and morbidity-associated catabolic conditions such as chronic heart failure. Muscle wasting in ageing but otherwise healthy human beings is referred to as sarcopenia. Unlike cachexia in advanced stages of chronic heart failure, muscle wasting *per se* is not necessarily associated with weight loss. In this review, we discuss pathophysiological mechanisms underlying muscle loss in sarcopenia and cachexia, highlight similarities and differences of both conditions, and discuss therapeutic targets and possible treatments, such as exercise training, nutritional support, and drugs. Candidate drugs to treat muscle wasting disease include myostatin antagonists, ghrelin agonists, selective androgen receptor molecules, megestrol acetate, activin receptor antagonists, espidolol, and fast skeletal muscle troponin inhibitors.

Summary Present approaches to muscle wasting disease include exercise training, nutritional support, and drugs, although particularly the latter remain currently restricted to clinical studies. Optimizing skeletal muscle mass and function in ageing and chronic illness including heart failure is one of the chapters that are far from finished and gains future potential for new therapeutic interventions to come.

Keywords Muscle wasting; Sarcopenia; Cachexia

Received: 23 March 2015; Accepted: 23 March 2015

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Introduction

As a normal phenomenon of the ageing human body, there is a gradual decrease in muscle mass accompanied by gains in fat mass and abdominal circumference. If this age-related loss of muscle mass in the limbs is marked—roughly defined as appendicular muscle mass two standard deviations below that of young adults of the same ethnic group—it is referred to as ‘sarcopenia’.^{1,2} Diagnosis of sarcopenia is increasing with increasing life expectancy in our progressively older societies in Europe and the USA.

However, the whole phenomenon of muscle wasting in these populations is even greater. Muscle wasting in ageing but otherwise weight-stable healthy human beings is endorsed by the magnitude of people who suffer from a weight loss due to a chronic disease, called ‘cachexia’.³

Cachexia is a multifactorial syndrome defined by continuous loss of skeletal muscle mass—with or without loss of fat mass—which cannot be fully reversed by conventional nutritional support and which may lead to progressive functional impairment and increased risk of death.⁴ While muscle wasting in sarcopenia is not usually associated with weight loss, use of the term cachexia in muscle wasting characterizes patients with involuntary weight loss associated with chronic inflammatory disorders such as chronic heart failure (CHF). Cardiac cachexia may involve a loss of not only muscle but also fat and bone mass.⁵ This pathological counterpart of muscle wasting rises as well with advances in medicine and a longer lifespan of patients having a chronic disease such as heart failure. As a result, muscle wasting due to both sarcopenia and cachexia is a condition we are increasingly facing.

At the clinical level, muscle wasting frequently translates into frailty—a poor ability to adapt to the environment, which increases disability^{1,6–10} and consequently welfare and healthcare costs. However, as of now, specific tools for diagnosing and managing loss of muscle mass/function are not widely implemented yet into everyday clinical practice. Therefore, this review outlines the pathophysiology of muscle wasting in the elderly for both sarcopenia and cachexia and discusses evolving interventional strategies.

Diagnosis of muscle wasting

Sarcopenia

The alterations that occur with ageing affect all three entities mass, strength, and quality of the muscle.² The Society of Sarcopenia, Cachexia, and Wasting Disorders characterizes as sarcopenic ‘...a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group...’.^{11,12} Furthermore, ‘...the limitation in mobility should not be clearly attributable to the direct effect of specific disease...’,¹¹ thereby defining sarcopenia as an independent disease entity. However, as this term is somewhat loose, efforts are continuing to better classify this chronic muscle wasting disease due to ageing/senescence.¹³ According to the European Working Group on Sarcopenia in Older People, the clinical diagnosis of sarcopenia can be made in subjects with total or appendicular muscle mass ≥ 2 standard deviations (SD) below that of sex-matched and ethnicity-matched young adults and either low handgrip strength below 20 kg in women and 30 kg in men or a reduced muscle function such as reduced walking speed (< 1 m/s over 6 min).¹ The group defined three stages of sarcopenia: pre-sarcopenia with loss of muscle mass only, sarcopenia with loss of both muscle mass and distinct functions, and severe sarcopenia with loss of muscle mass and extensive loss of physical performance.²

However, a terminology named ‘Skeletal Muscle Function Deficit’ was recently suggested by the Foundation for the National Institutes of Health Sarcopenia Project to embrace the various evolving concepts of sarcopenia and age-related muscle dysfunction.² Herein, the relationship between mobility impairment (defined as gait speed ≤ 0.8 m/s) and muscle strength (measured by grip strength) is addressed, and strength cutpoints are determined (< 26 kg for men and < 16 kg for women) below which low strength is especially likely to contribute to slow gait.² Additionally, by relating these strength cutpoints to muscle mass [estimated by appendicular lean mass adjusted to body mass index (BMI)], cutpoints were determined (< 0.789 for men and < 0.512 for

women), below which low lean mass is especially likely to contribute to low muscle strength.² Of note, the thereby maintained cutpoints were found to have a predictive value on incident mobility impairment over 3 years of follow-up.¹⁴ Furthermore, the term ‘skeletal muscle function deficit’ helps to integrate functional deficits distinct from ageing such as diabetic polyneuropathy or secondary malnutrition and impairments in muscle strength or power that are independent of muscle mass.²

This is important because a more specific definition of age-related muscle wasting is highly desirable on practical grounds because specific criteria are critical for identifying candidate patients for clinical trials that test therapies aimed at reversing or alleviating the complications of sarcopenia and its associated manifestations.^{2,15} However, a current review article on sarcopenia argues ‘...that what we have...’ would be ‘...an amalgamated and often conflicted description, rather than a definition, of the sarcopenic condition...’.¹¹

Cachexia

In contrast to age-related muscle wasting, the term cachexia describes the wasting in patients with weight loss and chronic diseases such as CHF, cancer, chronic kidney disease, chronic obstructive pulmonary disease, neuromuscular disease, chronic infection, and metabolic disease-associated disease processes.¹³ In 2008, Evans *et al.* suggested a multidimensional approach to diagnose cachexia, incorporating weight loss of $> 5\%$ in the preceding year or a BMI of < 20 along with the presence of any three of the following: fatigue, anorexia, decreased muscle strength, laboratory evidence of anaemia (haemoglobin < 12 g/dL), hypoalbuminemia (< 3.2 g/dL), or elevated markers of inflammation (e.g. interleukin-6 or C-reactive protein).¹⁶ Recently, an international consensus on definition and classification of cancer cachexia confirmed this weight cut-off by stating that patients who have more than 5% loss of stable body weight over the previous 6 months, or a BMI of less than 20 kg/m^2 , and ongoing weight loss of more than 2% are classified as having cachexia.¹⁷ However, patients with sarcopenia and ongoing weight loss of more than 2% are now additionally classified as cachectic, too.¹⁷

Muscle wasting diseases

According to these overlaps and as the common phenomenon of both sarcopenia and cachexia is loss of muscle, a more integrative definition of age-related sarcopenia and chronic disease-related cachexia has been proposed recently, namely, the term ‘muscle wasting diseases’.¹⁸ This new classification allows a more general view on the clinical feature of muscle wasting. It distinguishes between muscle wasting in acute and chronic disease settings.^{15,18} The chronic one is the most

frequent form and can be classified by its aetiology (i.e. that they are due to an underlying chronic illness or ageing, which is then termed sarcopenia) and by disease severity or progression.¹⁸ Classification according to disease severity is used to describe pre-cachexia as well as any form of cachexia where, beyond muscle wasting, loss of fat tissue accompanies this wasting process that is extreme in the latter and typically associated with frailty.¹⁸

The new term makes no assumption about a particular pathophysiology of the disease process.¹⁸ However, distinct pathophysiological studies have been carried out up to now in both sarcopenic patients on one hand and cachectic patient populations on the other hand that may in synopsis shed further light on the pathophysiology of muscle wasting in general.

Pathophysiologic mechanisms contributing to sarcopenia

Numerous pathways are proposed to be involved in the development of age-dependent muscle degeneration.¹⁹ As a striking histological phenomenon of sarcopenia in the elderly, atrophy of muscle fibres, especially of the fast Type II fibres, a decrease in motor units, and an accumulation of fat within the muscle have been documented.^{1,18} First, immobility can trigger muscle wasting. However, muscle loss can lead to immobility as well.¹ Furthermore, there is a reduced anabolic drive in ageing leading to a decrease in synthetic capacity of the muscle.^{1,20} This is because ageing is associated with lower testosterone levels, insulin-like growth factor 1 (IGF-1), and insulin resistance, leading to decreased protein synthesis as testosterone, insulin, and IGF-1 are potent activators of the Akt pathway, resulting in increased muscle protein synthesis and decreased degradation by inhibiting Fox-O.^{1,21} Testosterone also stimulates myoblasts, inhibits myostatin, and increases satellite cells, which normally help in the repair of myocytes that are reduced with decreasing levels of testosterone in ageing.¹ However, there is still a lack of consensus regarding various aspects of sarcopenia. Alchin *et al.*, for example, defined sarcopenia as a problem of neuromuscular junction rather than describing the condition in terms of muscular pathology.¹⁵ Indeed, loss of lower motor neurons has been shown to play a role in tipping the balance towards muscle breakdown in the elderly.^{1,22} With ageing, motor units undergo successive reduction in numbers with limited adaptation, leading to a decline in motor control.¹⁵ When innervation of a myofiber is lost, a neighbouring motor unit will expand to re-innervate the myofiber in question, leading to an enlargement of the motor unit area.¹⁵ A significant fibre-type switching occurs when mainly Type II myofibers are re-innervated by slower Type I motor neurons.¹⁵ It is still a matter of debate whether this motor unit remodelling is a cause of sarcopenia or a secondary effect of impaired neuronal function and therefore a compensatory adaptive response to sarcopenia.^{15,23}

In a study by Ling *et al.*, motor unit characteristics with ageing were measured, taking surface representations of human quadriceps motor units electromyographically.²⁴ This study found an increase in the size of the motor units and furthermore a decline in the motor unit firing rate with age at contractions relevant to general mobility.²⁴ While these changes were slight until the age of 75, beyond this age, the effects were substantial. Motor unit alterations occurred later than the age of sarcopenic onset, thus indirectly referring to the condition as an initially muscular pathology.²⁴ On the other hand, a variety of other studies indicate that denervation, and by extension motor unit enlargement, occurs before myofiber degradation. Deschenes *et al.*, for example, analysed the neuromuscular junction of early aged rats by cytofluorescent staining to determine whether denervation is a precipitous neuromuscular junction of sarcopenic myofiber alterations.²⁵ In both the plantaris and soleus muscles, significant signs of denervation were observed with little change in myofiber phenotype, which adds weight to the hypothesis that the trigger factor for sarcopenia is pre-synaptic.²⁵ However, there is a third possibility that sarcopenia is a result of both pre-synaptic and post-synaptic degeneration.

Additionally, a decrease in mitochondrial function and content has been described in aged muscles, and interestingly enough, this is prevented by exercise at least in animal models of sarcopenia.²⁶ Finally, muscle apoptosis has been documented to be increased.¹

Importantly, inflammatory pathways involving nuclear factor κ B (NF- κ B) are typically not activated in sarcopenia,^{1,4} and inflammation is believed not to contribute to this muscle wasting; resting energy expenditure is even decreased, and there is an increase in fat mass. These features are important to discriminate sarcopenia from cachexia, the latter being an extreme wasting disease characterized by weight loss, inflammation, and increased energy expenditure.¹⁸

Pathophysiologic mechanisms contributing to cachexia

Elevated resting energy expenditure is a major determinant in the development of malnutrition in cachexia. Resting energy expenditure describes the sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs.^{27,28} It is presumed that in cachexia, abnormalities in carbohydrate, lipid, and protein metabolism are major biochemical bases of elevated resting energy expenditure, while diet-induced thermogenesis and energy expenditure associated with exercise are not altered.²⁷

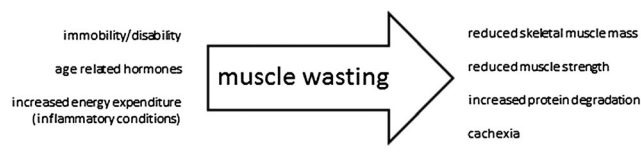
Some studies with cachectic patients show that part of the changes in metabolism can be attributed to altered absorption of nutrients¹⁶ as energy intake is one of the key components of energy balance. In cancer cachexia, for example, lipid and carbohydrate alterations in intestinal absorption have been

reported.⁴ Chemotherapy is, in part, responsible for the intestinal alterations.⁴ In the case of CHF, an increased sympathetic activity leads to a redistribution of blood flow away from the splanchnic circulation.²⁹ Thus, in CHF patients, a decrease in intestinal mucosal pH has been observed, indicating that intestinal ischaemia may contribute to malabsorption and thus trigger weight loss via decreased absorption of nutrients, with cachectic patients displaying a high loss of fat and protein via stool.³⁰ However, intestinal ischaemia with decreased absorption of nutrients is not the only reason for continuous catabolism in cachexia. Additionally, loss of gastrointestinal barrier integrity is thought to play a major role in an amplification of systemic inflammation in cachexia.^{29,31} Inflammation is purported to be a trigger in the pathogenesis of cachexia (Figure 1). Specifically, lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, is believed to interact with the damaged intestinal tract and to promote local and systemic cytokine release.²⁹ LPS can enter the circulation through the gut wall if barrier function is impaired in various diseases, not only cancer and CHF but also burn injury, sepsis, and liver cirrhosis, that lead to wasting.³² In the circulation of cachectic patients, LPS may activate monocytes and macrophages to release pro-inflammatory mediators, thus triggering an inflammatory state, which generates more energetic inefficiency. This is because cytokines are able to activate, for instance, mitochondrial-uncoupling proteins.^{32,33} Inflammatory cytokines including interleukin (IL)-1, IL-6, and tumour necrosis factor α induce myofibrillar breakdown by activation of the ubiquitin proteasome pathway, via NF- κ B-dependent and NF- κ B-independent mechanisms.^{1,34,35}

Down-regulation of anabolic factors/pathways including IGF-1, androgens, and satellite cell proliferation¹; increases in catabolic pathways/processes such as apoptosis,¹ autophagy,³⁶ and mitochondrial dysfunction³⁷; and the myostatin pathway¹ all may contribute to muscle mass and function loss in this setting. Cytokine-mediated release of cortisol and adrenergic hormones may furthermore lead to increased fat oxidation, atrophy, and hypermetabolism.¹

Some studies showed that the growth differentiating factor 15 (GDF-15) may play an important role in the pathways of muscle wasting and cachexia.^{38,39} GDF-15 is a protein belonging to the transforming growth factor β superfamily that has a role in regulating inflammatory and apoptotic pathways during disease processes.⁴⁰ In a mouse model, administration of human GDF-15 resulted in decreased energy expenditure and lower muscle strength.³⁸

Figure 1 Factors inducing muscle wasting leading to reduced mass and strength of skeletal muscle.



Finally, various disease-related, therapy-related, and patient-related factors such as pain, nausea, fatigue, and depression may additionally cause a reduction in appetite in these patients, further aggravating their given hypercatabolic state.^{1,41} The elderly, with co-morbidities, limited mobility, reduced nutrition, low IGF-1 and testosterone levels, and low muscle mass, seem to be especially prone to cachexia even at earlier stages of chronic disease.¹

Diagnostic tools for assessment of skeletal muscle

Skeletal muscle merits more attention in daily clinical work and has received only limited research endeavours so far.⁴² The availability of tools to easily detect muscle loss or even muscle wasting in affected patients would provide a means for daily clinical practice. The standard method for assessment of lean mass, which includes the muscle is dual-energy X-ray absorptiometry.⁴³ However, bioelectrical impedance analysis is an alternative that is widely available and much more suitable for fast and routine clinical application because of mobility and affordable technical application without use of radiation.^{44,45} A new recently validated method indicates a decreased rate of myofibrillar, sarcoplasmic, and collagen protein synthesis very early. This isotope-based method using the deuterium oxide (D₂O) method is a valid but invasive approach to quantify muscle anabolism before any changes in muscle mass become detectable.⁴⁶ Another method allows measurement of a stable (non-radioactive) isotope of creatine (D₃-creatine) that reflects total muscle mass in a single urine sample.^{47,48} Application of these methods seems to be suitable to assess and monitor muscle mass in patients with muscle wasting diseases.

Currently available treatment strategies targeting muscle function

The development of preventive and therapeutic strategies against sarcopenia, cachexia, and wasting disorders in general is an urgent need.^{49,5}

Despite differences in their pathophysiology, it is widely believed that both sarcopenia and cachexia are likely to respond to interventions and/or drugs that increase muscle mass and muscle strength.⁴⁰ Despite intensive research efforts in the field of muscle wasting during the last couple of decades, no effective treatment of muscle wasting exists, even though study of the molecular pathways involved in muscle wasting suggests many therapeutic targets. In addition, a large number of smaller clinical trials have been performed with mixed results. *Tables 1* and *2* give an overview

Table 1. Potential treatment of muscle wasting in elderly patients

Treatment	Study design	Study population: <i>n</i> in total (in treatment group), features	Intervention	Comparison	Outcomes (intervention group)	Reference
Nutritional supplementation	Randomized controlled trial	210 (105), hospital-admitted malnourished elderly patients (≥ 60 years)	Nutritional supplementation (energy-enriched and protein-enriched diet, oral nutritional support, calcium-vitamin D supplement, telephone counselling by a dietitian) for 3 months post-discharge	Usual care	<ul style="list-style-type: none"> • Increase in body weight in the intervention group; significant for the highest body weight category (mean difference 3.4 kg) • Decrease in functional limitations (more in the intervention group than in the control group) • No significant differences for physical performance, physical activities, fat-free mass, or handgrip strength • A rise in peak nocturnal growth hormone (prompted by each capromorelin dose) • Increase in body weight by 1.4 kg (capromorelin) at 6 months and decrease by 0.2 kg (placebo group) ($P = 0.006$) • Increase in LBM 1.4 vs. 0.3 kg ($P = 0.001$) • Improved tandem walk by 0.9 s ($P = 0.02$) in the pooled treatment vs. placebo groups • Improved stair climb by 12 months ($P = 0.04$) • Significant dose-dependent increase in LBM ($P < 0.001$, 3 mg vs. placebo) • Significant improvements in physical function ($P = 0.013$, 3 mg vs. placebo) and insulin resistance ($P = 0.013$, 3 mg vs. placebo) • Significantly improved 6-min walking distance ($P = 0.003$) • A significant impact on health-related quality of life ($P = 0.046$) • No significant differences between the two groups in the other outcomes 	Neelemaat et al. ⁶⁶
Oral growth hormone (capromorelin)	Randomized, double-masked, placebo-controlled, multicentre study	395 (314), men and women aged 65–84 years	2 years of treatment to four dosing groups (10 mg three times/week, 3 mg twice a day, 10 mg each night, and 10 mg twice a day)	Placebo during 2 years	<ul style="list-style-type: none"> • Increase in LBM 1.4 vs. 0.3 kg ($P = 0.001$) • Improved tandem walk by 0.9 s ($P = 0.02$) in the pooled treatment vs. placebo groups • Improved stair climb by 12 months ($P = 0.04$) • Significant dose-dependent increase in LBM ($P < 0.001$, 3 mg vs. placebo) • Significant improvements in physical function ($P = 0.013$, 3 mg vs. placebo) and insulin resistance ($P = 0.013$, 3 mg vs. placebo) • Significantly improved 6-min walking distance ($P = 0.003$) • A significant impact on health-related quality of life ($P = 0.046$) • No significant differences between the two groups in the other outcomes 	White et al. ⁶³
The selective androgen receptor modulator GTX-024 (enobosarm)	Randomized, double-blind, placebo-controlled, multicentre study	120, healthy elderly men (>60 years of age) and post-menopausal women	Four different dose groups (doses of 0.1, 0.3, 1, and 3 mg of GTX-024 daily) for 86 days	Placebo for 86 days	<ul style="list-style-type: none"> • Increase in LBM 1.4 vs. 0.3 kg ($P = 0.001$) • Improved tandem walk by 0.9 s ($P = 0.02$) in the pooled treatment vs. placebo groups • Improved stair climb by 12 months ($P = 0.04$) • Significant dose-dependent increase in LBM ($P < 0.001$, 3 mg vs. placebo) • Significant improvements in physical function ($P = 0.013$, 3 mg vs. placebo) and insulin resistance ($P = 0.013$, 3 mg vs. placebo) • Significantly improved 6-min walking distance ($P = 0.003$) • A significant impact on health-related quality of life ($P = 0.046$) • No significant differences between the two groups in the other outcomes 	Dalton et al. ⁶⁴ and Russ et al. ⁶⁷
Angiotensin-converting enzyme inhibitor (perindopril)	Randomized, double-blind, placebo-controlled study	130 (65), participants aged 65 years with mobility problems or functional impairment	Perindopril for 20 weeks	Placebo for 20 weeks	<ul style="list-style-type: none"> • Increase in LBM 1.4 vs. 0.3 kg ($P = 0.001$) • Improved tandem walk by 0.9 s ($P = 0.02$) in the pooled treatment vs. placebo groups • Improved stair climb by 12 months ($P = 0.04$) • Significant dose-dependent increase in LBM ($P < 0.001$, 3 mg vs. placebo) • Significant improvements in physical function ($P = 0.013$, 3 mg vs. placebo) and insulin resistance ($P = 0.013$, 3 mg vs. placebo) • Significantly improved 6-min walking distance ($P = 0.003$) • A significant impact on health-related quality of life ($P = 0.046$) • No significant differences between the two groups in the other outcomes 	Sumukadas et al. ⁶⁸

Exogenous testosterone (T) alone or with finasteride (T + F)	Randomized, blinded, placebo-controlled study	70 (46), men age 65 years and older with low testosterone serum (<350 ng/dL)	(1) Enanthate, 200 mg every 2 weeks, with placebo pills daily (T-only); (2) enanthate, 200 mg every 2 weeks, with 5 mg F daily (T + F) over 36 months	(3) Placebo injections and pills (placebo) over 36 months	<ul style="list-style-type: none"> • Significantly improved performance in a timed functional test ($P < 0.002$ for both T and T + F vs. placebo) • Increased handgrip strength compared with placebo ($P < 0.05$) • Increase in lean body mass [3.77 ± 0.55 kg (T-only) and 3.64 ± 0.56 kg (T + F) vs. -0.21 ± 0.55 kg for placebo ($P < 0.0001$)] • Decrease in fat mass and significant decrease in total cholesterol, low-density lipoprotein, and leptin, without affecting high-density lipoprotein, adiponectin, or fasting insulin levels • Combined physical training and nutrition intervention significantly improves health-related quality of life and handgrip strength • The exercise-only group showed a significantly increased handgrip strength 	Page <i>et al.</i> ⁶⁹
Exercise training	Randomized, controlled study	Exercise and nutrition group ($n = 30$), exercise-only group ($n = 28$), and control group ($n = 31$)	(1) Exercise and nutrition, (2) exercise only	Control group over 12 weeks	<ul style="list-style-type: none"> • Combined physical training and nutrition intervention significantly improves health-related quality of life and handgrip strength • The exercise-only group showed a significantly increased handgrip strength 	Kwon <i>et al.</i> ⁷⁰

LBM, lean body mass.

Table 2. Potential treatment of muscle wasting in patients with heart failure

Treatment	Study design	Study population: n in total (in treatment group)	Outcomes				Reference
			Body weight (kg)	Exercise capacity: peak VO ₂ (mL/kg/min)	6-min walk test (m)	Body composition, other	
Essential amino acid supplement	Randomized, placebo controlled, double blind	38 (21)	Increase in body weight by > 1 kg in 80% of supplemented patients (mean 2.96 kg) and in 30% of controls (mean 2.3 kg) ($P < 0.05$) Unchanged	BL: 13.5 ± 1.7 ; EoS: 14.9 ± 1.9 ($P < 0.05$)	BL: 331 ± 124 ; EoS: 405 ± 130 ($P < 0.001$)	• Increase in maximum work output ($P < 0.05$)	Ebner et al. ⁴ and Aquilani et al. ⁷¹
Recombinant human growth hormone	Randomized, placebo controlled, double blind	50 (25)	Unchanged	Not performed	Unchanged	• Increased left ventricular mass and septal wall thickness ($P = 0.0001$, $P = 0.03$) • No significant change in posterior wall thickness • Increased serum level of insulin-like growth factor 1 ($P < 0.0001$) • Increase in maximum work output ($P < 0.05$)	Ebner et al. ⁴ and Osterziel et al. ⁷²
Testosterone	Randomized, placebo controlled, double blind	70 (35)	BL: 64 ± 14 ; EoS: 67 ± 11	BL: 13.4 ± 4.4 ; EoS: 16.3 ± 1.7 ($P < 0.05$)	BL: 387 ± 121 ; EoS: 437 ± 138 ($P < 0.05$)		Ebner et al. ⁴ and Caminiti et al. ⁷³
Exercise training (bicycle ergometer)	Randomized, controlled, open label	24 (12)	Not changed	BL: 15.1 ± 3 ; EoS: increase of 17.5 ± 17 ($P < 0.01$)	Not performed	• Reduction of myostatin mRNA ($P = 0.02$) • Reduction of myostatin protein ($P = 0.02$)	Ebner et al. ⁴ and Lenk et al. ⁷⁴
Administration of salbutamol (per os)	Randomized, placebo controlled, double blind	12 (6)	No significant changes	BL: 18.9 ± 1.9 ; EoS: 17.9 ± 1.4 ($P = 0.41$)	Not performed	• No significant change in right quadriceps strength	Ebner et al. ⁴ and Harrington et al. ⁷⁵

BL, baseline; EoS, end of study.

of clinical trials using potential treatments of muscle wasting or including measurement of body composition in ageing (Table 1) and in patients with CHF (Table 2), which are often similar.

To date, exercise training is the treatment of choice. There is discussion about the best way of muscle training.^{50,51} Endurance exercise has been shown to decrease systemic inflammatory markers⁵² and improve endothelial function in elderly individuals.⁵³ These effects could potentially counteract the anabolic resistance in elderly individuals, as discussed earlier. In line with this, endurance training combined with immediate protein ingestion leads to improved muscle oxidative capacity, indicating that protein feeding improves the qualitative muscle adaptations to endurance training such as mitochondrial biogenesis.⁵⁴ Endurance exercise seems to improve muscle quality more than muscle quantity. Contrastingly, light-load resistance training is known to exert better hypertrophic effects on the musculature compared with endurance exercise.^{51,55} A combination of both along with each of the exercise regimens alone should be tested in future clinical trials.

It is important to keep in mind that not only the limb musculature but also a reduced inspiratory muscle capacity might account for lower exercise capacity in the elderly. In patients with CHF, for example, among whom 5% and 15% are affected by cachexia, exercise intolerance and dyspnoea have been attributed partially to the dysfunction of the skeletal and the respiratory musculature.⁵⁶ This is underlined by the study by Laoutaris *et al.* who investigated the work capacity of inspiratory muscle by assessing the inspiratory strength and the sustained maximal inspiratory pressure in patients with heart failure.⁵⁷ Among 60 patients and 30 control subjects, they found both parameters to be reduced by 46% and 23%, respectively. Reduced inspiratory muscle performance correlated with lower peak oxygen consumption and lower 6-min walk distance, indicating an association of inspiratory muscle dysfunction with reduced exercise capacity. A pilot study on 27 patients with CHF showed that combined aerobic training with resistance training and inspiratory muscle training resulted in incremental benefits in both peripheral and respiratory muscle weakness, cardiopulmonary function, and quality of life compared with that of aerobic training alone.⁵⁷ The mechanisms involved in exercise-induced improvement of functional capacity await to be completely elucidated. However, there is evidence that physical exercise may target myostatin regulation, thereby increasing muscle growth and mass.^{57,58} Furthermore, exercise training has long been shown to induce favourable skeletal muscle angiogenesis.^{51–54}

In daily clinical practice, in addition to exercise training, patients' nutrition should be optimized to prevent nutritional lack of protein and micronutrients. All factors that are important for muscle function should be identified and addressed including therapy of iron deficiency and lack of vitamin D.⁵⁹

The latter is underestimated but very common, for example, in European patients with heart failure and reduced kidney function, and may lead to additional muscle symptoms, such as weakness and cramps.⁶⁰

Effects of specific nutritional therapy alone on the underlying catabolic process of muscle wasting, if existing, remain to be established. Meanwhile, the provision of nutritional supplements incorporating essential amino acids combined with exercise training has been suggested to be the best method of attenuating muscle wasting.^{50,61}

According to this, potential synergistic effects that could accrue from nutritional therapy in conjunction with new drugs are conceivable and should be searched for in future clinical trials. Candidate drugs to treat muscle wasting disease that are available or in development include myostatin antagonists, ghrelin agonists, selective androgen receptor molecules, megestrol acetate, activin receptor antagonists, espidolol, formoterol, and fast skeletal muscle troponin inhibitors.^{62–64} Recently, the first promising results of a phase III trial 'Prevention and treatment of muscle wasting in patients with cancer' were demonstrated where the selective androgen receptor modulator enobosarm had consistently demonstrated increases in lean body mass and better physical function across several populations without the toxic effects associated with androgens along with a lower hazard ratio for survival in cancer patients.⁶⁵ Therefore, the selective androgen receptor enobosarm may become one of the first available drug against muscle wasting in man.

Conclusion

Maintaining muscle mass and strength is a key challenge in order to confer good quality of life in patients with chronic illness and in the elderly. Although effective treatments beyond exercise training currently remain to be established, the pathophysiological findings may pave the way for therapeutic approaches to muscle wasting disease. Optimizing skeletal muscle mass and function in ageing and in chronic illness is one of the chapters that are far from finished and gains future potential for new therapeutic targets to come.

Acknowledgement

We acknowledge the support of the German Research Foundation and the Open Access Publication Funds of Göttingen University.

Conflict of interest

None declared

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