Current Geriatrics Reports (2018) 7:147–153
https://doi.org/10.1007/s13670-018-0245-1

PULMONOLOGY AND RESPIRATORY CARE (D BREEN, SECTION EDITOR)

Muscle Wasting in the Hospitalised COPD Patients—How Can it Be Prevented and Treated?

Tara Cahill[1] · Mohammed Ahmed[2]

Published online: 13 July 2018

Abstract

Purpose of Review COPD exacerbations are widely recognised as a significant cause of mortality and morbidity through their impact on respiratory function but their effect on skeletal muscle function and mass receives less attention. In this article, we review the association of this entity with COPD, the potential contributing factors, and the evidence behind the interventions available to manage this condition with a focus on the elderly population.

Recent Findings In patients with COPD, there has been a paradigm shift from the focus on body weight and mass index to a more detailed assessment of the loss of muscle mass and function defined as sarcopaenia. Factors that can potentially lead to sarcopaenia has been the subject of multiple basic science and translational research studies. Interventions that have been proven to be associated with clinically significant outcomes in COPD patients include early mobilisation, inpatient exercise programmes, early pulmonary rehabilitation, and nutritional interventions. Prolonged courses of steroids following an acute exacerbation are non-beneficial and can lead to loss of muscle function.

Summary Multiple factors can potentially contribute to sarcopaenia among patients admitted with COPD exacerbations and should be identified early and treated in a multidisciplinary setting. Nutritional interventions, early mobilisation, and limitation of systemic steroid prescribing are simple and effective interventions that should be utilised.

Keywords Sarcopaenia · Chronic obstructive pulmonary disease · Exacerbation

Introduction

One of the hallmarks of modern medicine is the significant advances in the management of chronic conditions including pulmonary diseases. While these advances have improved overall survival in many diseases, they have had less impact on associated morbidity and quality of life. Indeed, in many cases the prolongation of life associated with better medical care may have a detrimental effect on quality of life. This phenomenon is often best seen in chronic pulmonary diseases including chronic obstructive pulmonary disease (COPD), where metabolic abnormalities and alterations in body composition (i.e. muscle loss with changes in adipose tissue mass) can affect disease outcome and increase healthcare burden and cost [1•]. Increased age and severity of disease are independently associated with deterioration in health-related quality of life (HRQOL) [2]. COPD is common in older people; in the USA, 10% of those older than 75 years have COPD [3]. The prevalence increases with age for both men and women through all decades and is highest among women aged 65–74 (10.4%) compared to 11.2% among men aged 75–84 [3].

This article is part of the Topical Collection on *Pulmonology and Respiratory Care*

✉ Tara Cahill
tara.hannon@hse.ie

Mohammed Ahmed
Jamaleldeen@gmail.com

[1] Galway University Hospital, Newcastle Road, Galway H91 YR71, Ireland

[2] Department of Respiratory Medicine, Galway University Hospital, Galway, Ireland

Disease Burden

High healthcare costs are widely associated with COPD especially as the disease progresses. In Canada, the mean annual total COPD-related cost per patient is estimated to be $4147 ($6255). Both the costs for maintenance therapy and

acute treatment increase with more severe disease [4]. In 2010, the estimated total cost of COPD in the USA was $36 billion with $32.1 billion related to healthcare costs directly [5]. The economic burden from COPD is expected to continue to increase secondary to the ageing population, tobacco use, and air pollution [6]. It is currently the fourth leading cause of death worldwide, and the World Health Organization (WHO) predicts that it will become the third leading cause by 2030. The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016 and it was estimated to be the cause of 3.17 million deaths globally in the year 2015 [7].

COPD Acute Exacerbations

COPD exacerbations, whether infective or non-infective, lead to impaired quality of life, reduced survival, and associated high healthcare costs [8]. Globally, COPD is an important cause of emergency department ED visits. The significant role of exacerbations to the overall economic burden of COPD is widely recognised [9]. The cost of exacerbations can range from US$11966 per episode in the USA to the lowest estimate of US$479, which has been reported from Spain [10, 11]. Putting these costs in the broader context of the COPD burden, a retrospective study in Canada demonstrated that 40% of the total costs of COPD patients were attributable to the treatment of acute exacerbations and the main driver of the exacerbation cost is hospitalisation [4].

In addition, as the disease progresses, patients develop increasing frequency of exacerbations, they become increasingly short of breath and frequently develop increasing physical weakness. This in turn can have a significant impact on quality of life with many patients displaying both physical and psychological effects directly related to their chronic disease. Shortness of breath on exertion is one of the dominant complaints of this patient population. This symptom can result from multiple causes, including impaired pulmonary function and altered lung mechanics. However, in addition, it has been shown that exercise performance remains substantially reduced even with bilateral lung transplant, which suggests that the lungs alone cannot explain exertional dyspnoea [12]. The effects of acute exacerbations on muscle strength and physical activity may have important long-term consequences.

Sarcopaenia in COPD

Muscle is the largest organ in the body and has functions other than just locomotion and respiration. It also contributes to metabolism; facilitating energy homeostasis, heat regulation, insulin sensitivity, and amino acid metabolism. It contributes to the endocrine function through cytokine production. Muscle accounts for nearly 60% of the bodies overall protein stores; pathological changes to this important metabolically active tissue can have profound consequences. The consequences are often severe in older adults, as the strength and functional declines can in turn contribute to a number of adverse health outcomes, including loss of function, disability, and frailty with loss of strength, increased likelihood of falls, and ultimately risks loss of independence [13, 14].

Sarcopaenia is a condition characterised by loss of muscle mass and muscle strength [15]. It is a multifactorial disorder where specific mechanisms related to ageing, chronic disease, or inactivity are difficult to distinguish. It includes both muscle loss and muscle dysfunction; the latter involves contractile impairment and because of this metabolic and endocrine abnormalities affecting whole-body metabolism, systemic inflammation, and immune system regulation. It is a major determinant of disease outcome and longevity [1].Cost-effective control of chronic disease and optimal ageing require sarcopaenia prevention, diagnosis, and treatment. Previous research has found that walking time in daily life does not spontaneously recover at 1 month following hospital admission, with minimal improvements seen in those who have the largest decline in quadriceps strength [16]. Following an exacerbation, low levels of physical activity are associated with a 50% increase in the risk of hospital readmission [17].

Pathophysiology of Sarcopaenia in COPD

In a study, reported by Costa et al. in 2015, which examined the associated between sarcopaenia and COPD, the authors reported a prevalence rate of 39.6%. Other studies have shown rates from 20 to 40% [18, 19•]. However, to develop effective interventions in this patient population, a better understanding of the underlying pathophysiology is needed. Several factors are associated with the development of sarcopaenia; many of these individual factors are readily seen during COPD exacerbations. Each of these factors must be assessed individually and in doing so we can potentially develop individualised programmes to counteract their effects and in turn reduce the morbidity associated with sarcopaenia in the COPD population, see Fig. 1.

Inactivity

This factor is probably the easiest to understand in that the most straightforward explanation for muscle loss during an exacerbation is secondary to physical inactivity. Patients who are admitted to hospital with COPD exacerbation can have prolonged periods of bed rest and inactivity. Pitta et al., in 2006, demonstrated that COPD patients tend to be severely inactive during and after an exacerbation [16]. Patients with frequent exacerbations show a more rapid decline in their

Fig. 1 Factors contributing to sarcopaenia among patients hospitalised with acute chronic obstructive pulmonary disease exacerbations. Factors marked with an asterisk can be targeted with interventions that are evidence based

physical activity levels compared to more stable patients. This study demonstrated that after only 5 days of hospital admission, 7% of the baseline value of quadriceps strength was lost. The reason for this loss of muscle strength could be attributed to the low activity levels during admission. At the beginning of the hospitalisation period (day 2), patients spend minimal time on weight-bearing activities (median, 7% of the time during the day). More surprisingly, this remained almost unchanged close to discharge (median, 9%). In addition, the short time spent by patients walking is characterised by low movement intensity (slow walking speed). These results raise concerns about how we manage acute exacerbations.

A Cochrane review examined the impact of interventions including exercise programmes to improve the strength and function of acute medical patients 65 years and older [20]. They looked at nine trials, in which seven had a substantial proportion of respiratory patients included in the analysis. The exact respiratory diagnoses were not recorded but documentation of conditions ranged from dyspnoea, pneumonia, and infection to general respiratory. The review showed a small but significant reduction in hospital length of stay in participants who received the intervention (mean difference 1.08 days shorter in the intervention group, 95% CI − 1.93 to − 0.22). It also showed a small but significant rise in the proportion of those discharged to home versus residential care (Relative Risk 1.08, 95% CI 1.03 to 1.14). Exercise was defined as any physical intervention programme designed to maintain or improve patient strength or function. The interventions varied from walking programmes to patients mobilising at ward level to more patient specific exercise programmes.

Another Cochrane review looked at pulmonary rehabilitation and exacerbations in COPD and showed a reduction in the odds of future readmission (pooled OR 0.44, 95% confidence interval (CI) 0.21 to 0.91) but no significant reduction in mortality. Pulmonary rehabilitation after acute exacerbations has been shown to be associated with clinically and statistically significant improvement in HRQoL [21]. A study carried out by Rodriguez, 2016 looked at using a step exercise protocol from the third day of hospital admission until **1** month after discharge [22]. Their results showed that the median length of hospital stay was similar in both groups (6 days). One month after discharge, the time spent sitting per day was only significantly reduced in the IG (13 to 7 h/day, $p = 0.007$). In addition, the percentage of patients doing moderate to vigorous activity (> 3 MET) more than 150 min/week was significantly higher in the IG compared with the usual care group (56 vs. 12%, $p = 0.04$). Moreover, the number of steps per day showed a trend to also be higher in the former group (4282 vs. 2835, respectively). Unfortunately, this study did not look at readmission rates but results are positive from a functional perspective. So, to combat inactivity contributing to muscle loss and weakness**,** research would endorse getting patients active as soon as possible. A full early pulmonary rehabilitation programme may not be necessary to gain adequate results; simple exercise programmes may also have beneficial effects.

Inflammation

Systemic inflammation is associated with an accelerated decline in lung function and is heightened during episodes of exacerbation. It is now a recognised risk factor for other complications in patients with COPD. High levels of airway and systemic inflammatory markers are associated with a faster subsequent decline in FEV1 and chronic bacterial colonisation [23]. It has been shown to be present not only in acute exacerbations but also in stable COPD [24]. Systemic or local inflammation has been demonstrated both in skeletal muscle and in the blood of COPD patients [24]. Byun et al. carried out a study looking at inflammatory biomarkers in COPD [25]. In this cohort of 80 COPD patients, the authors correlated sarcopaenia with systemic inflammatory biomarkers interleukin-6 (IL-6) and high sensitivity tumour necrosis factor α (hsTNFα). They also assessed hand grip strength and skeletal muscle mass as a measure of overall muscle strength and demonstrated significant correlations with levels of IL-6 and hsTNFα. In multivariate analysis, higher hsTNFα was a significant determinant for the presence of sarcopaenia in this COPD population.

It is now generally accepted that the chronic systemic inflammation associated with COPD contributes significantly to muscle degradation. Evidence indicates that inactivity amplifies the catabolic response of skeletal muscle to inflammatory mediators. In healthy volunteers, the muscle catabolic effects of experimental hypercortisolaemia, at concentrations that mimic severe injury, were threefold greater during experimental bed rest than in ambulatory conditions [26]. However, it remains unclear if potential interventions directly aimed at reducing systemic inflammation in COPD have a direct impact on sarcopaenia among patients admitted with acute exacerbations and this is an area where further research is required.

Glucocorticosteroids

Corticosteroids, whether inhaled or oral, remain central to the treatment of COPD exacerbations and aim to limit inflammation following an acute episode. Proximal myopathy is a well-known consequence of this pharmacological therapy [27]. Decramer et al. demonstrated that the average daily steroid dose independently explained and up to 51% of the variance in quadriceps strength in patients admitted with COPD [28]. Steroid-induced myopathy was associated with severe peripheral muscle weakness; quadriceps force being 23 ± 14 versus $71 \pm 23\%$ in control patients with COPD without exacerbation ($p < 0.001$). They also established that even at low doses, steroids can cause a chronic form of muscle weakness. On follow-up, the survival of patients with steroid-induced myopathy was reduced in comparison with control patients with COPD with similar degree of airflow obstruction ($p < 0.025$). The REDUCE study tested the hypothesis that in patients presenting to the emergency department with acute exacerbation of COPD, a 5-day course of systemic glucocorticoid treatment would not result in an inferior clinical outcome compared with conventional 14-day treatment, but would significantly decrease glucocorticoid exposure and reduce unwanted side effects associated with prolonged and cumulative steroid use [29]. The primary end point of this trial was time to next COPD exacerbation during a follow-up of 6 months. The results showed that a 5-day course of glucocorticosteroids during an exacerbation was noninferior to a 14-day course. In conclusion, clinicians should be aiming to limit not only the dosage of these drugs but also the overall duration.

Nutrition

Weight loss and the associated decrease in body mass index (BMI) are a common feature of a COPD exacerbation. This is due to reduced oral intake, impaired substrate utilisation, and increased requirements during the acute stage of an exacerbation. Changes in body composition are frequently observed in patients with COPD. Evidence indicates that 20–30% of COPD patients with normal BMI show reduced muscle mass according to dual energy X-ray absorptiometry (DXA) or bio-electrical impedance analysis (BIA) [30]. BMI is currently the most commonly used nutritional threshold variable, since it is clearly related to quality of life [31]. However, more recent data demonstrate that specific unfavourable changes in body composition, especially a decrease in lean mass, can be more reliable predictors of mortality than low BMI alone [32]. When examined, it has been demonstrated that more than 80% of COPD patients have a normal or increased body weight, yet the evidence would demonstrate that 20–30% of COPD patients with normal BMI show reduced muscle mass when examined using dual energy x-ray absorptiometry (DXA) or bio-electrical impedance (BIA) [30].

Muscle loss and dysfunction has also been associated with the pathological deposition of adipose tissue. This has been defined as sarcopenic obesity [33]. The clinical outcomes seen in sarcopenic obese patients with chronic diseases or cancer are worse than that of obese patients with normal muscle mass [34]. There may be two causative processes involved in the development of sarcopenic obesity. Firstly, long-term physical inactivity combined with a positive energy balance (high calorific intake with poor energy expenditure) can lead to obesity with disuse muscle atrophy. Secondly, in obese patients bearing a chronic comorbidity, the activation of systemic inflammation may rapidly lead to muscle loss and dysfunction and the development of sarcopenic obesity as frequently seen in COPD [1•]. It has been suggested that looking at BMI alone as a nutritional marker is no longer appropriate and focus should move to lean muscle mass [35]. By using BIA instead of weight alone, clinicians may be better equipped to monitor lean body mass. The use of screening tools to determine risk of developing sarcopaenia in this patient population should be encouraged. [36] An example of this is the SARC-F Tool (Table 1) [37].

Ageing

Evidence suggests that skeletal muscle mass and skeletal muscle strength decline in a linear fashion with age, with up to 50% of mass being lost by the 8th decade of life [38]. As previously mentioned, COPD is common in the older population. Depending on the definition that is used for sarcopaenia, the prevalence in 60–70-year-olds is reported as 5–13%, while the prevalence ranges from 11 to 50% in people > 80 years [39]. Worldwide, the number of people aged ≥ 60 years was estimated at 600 million in the year 2000, a figure that is expected to rise to 1.2 billion by 2025 and 2 billion by 2050 [7]. Even with a conservative

Table 1 SARC-F Tool used for the functional assessment of sarcopaenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 lb (4.5 kg)?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have in walking across a room?	None = 0 Some = 1 A lot, use of aids or unable = 2
Rise from chair	How much difficulty do you have in transferring from chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have in climbing a flight of 10 steps?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 times = 1 4 or more = 2

estimate of prevalence, sarcopaenia currently affects more than 50 million people today and this will increase to greater than 200 million in the next 40 years [36].

Neurodegeneration

The maintenance of muscle mass requires normal innervation and regular activation; malfunction of any of these elements can lead to muscle function deterioration and ultimately muscle loss. The exact causes underlying the age-related changes in the neuromuscular system are still unknown but there is evidence that mitochondria, a critical element involved in energy production and cellular signalling, may be either a primary trigger or at least an important player in this process [40].

Experimentally, mitochondrial abnormalities have been identified in both neurons and muscle fibres in elderly and sedentary subjects, and known mechanisms exist whereby abnormal mitochondrial functions can promote neuromuscular disorders [41]. However, it is still unclear whether mitochondrial dysfunction, at a level reported for these two tissues in normal human ageing, is a primary cause of the phenotypic and functional changes seen in sarcopaenia. Together with other dysregulated processes, mitochondrial abnormalities are likely to contribute to loss of skeletal muscle mass and function with age [42].

Conclusion

Sarcopaenia, which includes muscle loss and dysfunction, is a common feature of COPD and its cause is multifactorial. A number of these causes are more prevalent during an exacerbation. Early identification of sarcopaenia would allow for timely preventative and therapeutic interventions for this clinical entity. For the time being, currently available tools for assessment of muscle mass and strength should be implemented as much as possible in clinical practice.

Once aware of the contributing factors to this condition, clinicians should strive to minimise their impact during the acute exacerbation by addressing each element described above, where possible. In the COPD patient, the focus should be shifted from weight and BMI to the assessment of lean muscle mass and muscle strength. Interventions should be implemented to maintain such variables. These include early mobilisation, maintenance of physical function, and provision of adequate nutrition to maintain optimum lean muscle. This is better achieved through a multidisciplinary approach involving clinicians, physiotherapists, clinical nutritionists, and nurse specialists. In addition, frequent exacerbators should be identified and a greater emphasis should be placed on early recognition of exacerbations and intervention through patient education, thus allowing early initiation of an appropriate treatment plan. This may result in limiting the levels of inflammation and thus minimising its effect on skeletal muscle. Sarcopaenia in COPD patients, especially the elderly, can have far reaching consequences and further research on early identification and novel therapies is required and should be encouraged.

Compliance with Ethical Standards

Conflict of Interest Tara Cahill and Mohammed Ahmed declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1.• Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr Edinb Scotl. 2014;33(5):737–48. **Provides a very detailed yet succinct description of sarcopaenia and its causative factors.**

2. Ståhl E, Lindberg A, Jansson S-A, Rönmark E, Svensson K, Andersson F, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3:56.
3. Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998–2009. NCHS Data Brief. 2011;63:1–8.
4. Maleki-Yazdi MR, Kelly SM, Lam SY, Marin M, Barbeau M, Walker V. The burden of illness in patients with moderate to severe chronic obstructive pulmonary disease in Canada. Can Respir J. 2012;19(5):319–24.
5. Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific medical and absenteeism costs of COPD among adults aged ≥ 18 years in the United States for 2010 and projections through 2020. Chest. 2015;147(1):31–45.
6. Bustacchini S, Chiatti C, Furneri G, Lattanzio F, Mantovani LG. The economic burden of chronic obstructive pulmonary disease in the elderly: results from a systematic review of the literature. Curr Opin Pulm Med. 2011;17(Suppl 1):S35–41.
7. World Health Organization. Chronic Obstructive Pulmonary Disease (COPD). 2018. Available from: http://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
8. Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, Verea H, Murio C, Ros F, Vidal R, IMPAC Study Group. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004;59(5):387–395.
9. Donaldson GC, Wedzicha JA. COPD exacerbations .1: epidemiology. Thorax 2006;61(2):164–168.
10. Perera PN, Armstrong EP, Sherrill DL, Skrepnek GH. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. COPD. 2012;9(2):131–41.
11. Miravitlles M, García-Polo C, Domenech A, Villegas G, Conget F, de la Roza C. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. Lung. 2013;191(5):523–30.
12. Singer JP, Peterson ER, Snyder ME, Katz PP, Golden JA, D'Ovidio F, et al. Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med. 2014;190(9):1012–21.
13. Xue Q-L, Walston JD, Fried LP, Beamer BA. Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: the women's health and aging study. Arch Intern Med. 2011;171(12):1119–21.
14. Dufour AB, Hannan MT, Murabito JM, Kiel DP, McLean RR. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: the Framingham Study. J Gerontol A Biol Sci Med Sci. 2013;68(2):168–74.
15. Janssen I. Evolution of sarcopenia research. Appl Physiol Nutr Metab Physiol Appl Nutr Metab. 2010;35(5):707–12.
16. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. Chest. 2006;129(3):536–44.
17. Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM, Estudi del Factors de Risc d'Agudització de la MPOC investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax 2003;58(2):100–105.
18. Cesari M, Pedone C, Chiurco D, Cortese L, Conte ME, Scarlata S, et al. Physical performance, sarcopenia and respiratory function in older patients with chronic obstructive pulmonary disease. Age Ageing. 2012;41(2):237–41.
19.• da Rocha Lemos Costa TM, Costa FM, Moreira CA, Rabelo LM, Boguszewski CL, Borba VZC. Sarcopenia in COPD: relationship with COPD severity and prognosis. J Bras Pneumol Publicacao Of Soc Bras Pneumol E Tisilogia. 2015;41(5):415–21. **This paper evaluates the prevalence of sarcopaenia in COPD patients and also confirms that sarcopaenia correlates with a worse prognosis in COPD.**
20. de Morton NA, Keating JL, Jeffs K. Exercise for acutely hospitalised older medical patients. Cochrane Database Syst Rev. 2007;1:CD005955.
21. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2018 May 12]. Available from: https://doi.org/10.1002/14651858.CD005305.pub4/full
22. Rodriguez DA, Rodo-Pin A, Guerrero M, Coll R, Huerta A, Soler N, et al. Impact of step exercises as an early intervention during COPD exacerbation. Eur Respir J. 2016;48(suppl 60):PA2061.
23. Donaldson GC, Seemungal TAR, Patel IS, Bhowmik A, Wilkinson TMA, Hurst JR, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995–2004.
24. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994;150(5 Pt 1):1453–5.
25. Byun MK, Cho EN, Chang J, Ahn CM, Kim HJ. Sarcopenia correlates with systemic inflammation in COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:669–75.
26. Ferrando AA, Stuart CA, Sheffield-Moore M, Wolfe RR. Inactivity amplifies the catabolic response of skeletal muscle to cortisol. J Clin Endocrinol Metab. 1999;84(10):3515–21.
27. Bowyer SL, LaMothe MP, Hollister JR. Steroid myopathy: incidence and detection in a population with asthma. J Allergy Clin Immunol. 1985;76(2 Pt 1):234–42.
28. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am J Respir Crit Care Med. 1994;150(1):11–6.
29. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309(21):2223–31.
30. Vermeeren M a P, Creutzberg EC, Schols AMWJ, Postma DS, Pieters WR, Roldaan AC, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med. 2006;100(8):1349–55.
31. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1791–7.
32. Schols AMWJ, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 2005;82(1):53–9.
33. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629–35.
34. Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist. 2012;17(10):1240–5.
35. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr Edinb Scotl. 2010;29(2):154–9.
36. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M, European Working Group on Sarcopenia in Older People. Sarcopenia: European

consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412–423.
37. Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community screening tool for sarcopenia? J Am Med Dir Assoc. 2014;15(9):630–4.
38. Metter EJ, Conwit R, Tobin J, Fozard JL. Age-associated loss of power and strength in the upper extremities in women and men. J Gerontol A Biol Sci Med Sci. 1997;52(5):B267–76.
39. Morley JE. Sarcopenia: diagnosis and treatment. J Nutr Health Aging. 2008;12(7):452–6.
40. Joseph A-M, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM-D, et al. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell. 2012;11(5):801–9.
41. Bua EA, McKiernan SH, Wanagat J, McKenzie D, Aiken JM. Mitochondrial abnormalities are more frequent in muscles undergoing sarcopenia. J Appl Physiol Bethesda Md 1985. 2002;92(6):2617–24.
42. Hepple RT. Mitochondrial involvement and impact in aging skeletal muscle. Front Aging Neurosci. 2014;6:211.