

Functional consequences of sarcopenia and dynapenia in the elderly

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Purpose of review

The economic burden due to the sequela of sarcopenia (muscle wasting in the elderly) are staggering and rank similarly to the costs associated with osteoporotic fractures. In this article, we discuss the societal burden and determinants of the loss of physical function with advancing age, the physiologic mechanisms underlying dynapenia (muscle weakness in the elderly), and provide perspectives on related critical issues to be addressed.

Recent findings

Recent epidemiological findings from longitudinal aging studies suggest that dynapenia is highly associated with both mortality and physical disability even when adjusting for sarcopenia indicating that sarcopenia may be secondary to the effects of dynapenia. These findings are consistent with the physiologic underpinnings of muscle strength, as recent evidence demonstrates that alterations in muscle quantity, contractile quality and neural activation all collectively contribute to dynapenia.

Summary

Although muscle mass is essential for regulation of whole body metabolic balance, overall neuromuscular function seems to be a critical factor for maintaining muscle strength and physical independence in the elderly. The relative contribution of physiologic factors contributing to muscle weakness are not fully understood and further research is needed to better elucidate these mechanisms between muscle groups and across populations.

Keywords

aging, atrophy, cachexia, muscle wasting, weakness

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Introduction

Sarcopenia, as originally defined two decades ago, refers to the age-related loss of muscle mass [1]. Since this time there has been a dramatic increase in scientific inquiry to define the functional consequences and biologic mechanisms of sarcopenia. This explosion of research has at times resulted in ‘sarcopenia’ being directly and causally linked to both muscle weakness and physical disability. The concept of sarcopenia is frequently used in research settings today and is only beginning to be introduced in the clinical arena. However, thus far no consensus on its definition has been established, and there are no recognized tests or diagnostic criteria [2]. We recently authored an article highlighting the disassociation between the age-related loss of muscle mass and that of muscle strength. In this article, we illustrate and raise awareness about the numerous mechanisms, beyond the loss of muscle size due to reduced fiber number and myofibrillar proteins that underlie that muscle weakness in the elderly [3^{*}]. For example, impairments in neural

activation could explain a portion of muscle weakness, as well as potential alterations in other muscular properties that may reduce contractile quality defined here as a reduction in involuntary force production per unit muscle size. In this aforementioned paper, we proposed that the term ‘sarcopenia’ should be used in its original context (the age-related loss in muscle mass), and that the term ‘dynapenia’ be applied to describe the age-related loss of muscle strength [3^{*}]. Regardless of semantics, the deterioration of muscle quantity, contractile quality and neural activation ultimately manifests itself with a reduction in physical function, which results in disability development and costly economic consequences [4,5]. In this article, we will first discuss the societal burden and determinants of the loss of physical function with advancing age. Next, we will briefly review the literature on the physiologic mechanisms underlying muscle weakness in the elderly, and lastly provide perspectives on critical issues and research questions that need to be addressed to help advance our understanding and treatment of the deterioration of

neuromuscular function that leads to physical impairment in the elderly.

Societal burden and determinants of the loss of physical function in the elderly

One of the most important consequences of the loss in physical function is the onset of physical disability. Disability is a complex and multifactorial process that is best portrayed by the WHO's International Classification of Functioning (ICF) and has had a major impact on disability research [6]. Sarcopenia manifests as a critical component of the ICF through its effect on body functions and role in limitations of activities (e.g., poor physical performance). The societal burden and consequences of limitations of activities was first established in the mid-90's when it was observed that poor physical performance was a major prognostic indicator for the development of physical disability, nursing home admission, depression, hospitalization, and even mortality [7]. Because physical performance on these tests are closely linked with muscle function [8], age-associated changes in muscle and nerve biology became a topic of interest for gerontologists and geriatricians.

Depending on the population studied and definition used, sarcopenia is estimated to occur in 5–45% of older adults [4,9]. Low levels of muscle mass have been linked with poor health outcomes that include functional impairments [10], outright physical disability [11] and mortality [12]. The sequelae that follow sarcopenia are responsible for approximately \$18 billion in direct healthcare costs in the USA annually [5]. To put this in perspective, it has been estimated that the yearly economic cost of osteoporotic fractures in the USA is \$16.3 billion [13]. Considering that the total number of older adults is expected to double over the next 25 years, the absolute costs associated with sarcopenia are expected to rise sharply [14]. The study of sarcopenia is appealing because it is a modifiable risk factor, as increasing muscle mass has the capability of reducing incidence of disability despite the co-occurrence of age-related diseases. Several interventions have demonstrated success at improving muscle mass such as resistance exercise, and it is now clear that resistance-type exercises have the capability of improving physical function in an acute manner [15,16]. Additionally, as there are no medical treatments for sarcopenia, several pharmaceutical agents (e.g. testosterone, angiotensin-converting enzyme and myostatin inhibitors) have the potential of improving muscle quantity and contractile quality [17–19]. Many of these agents are in the early stages of development, and testosterone therapy is undergoing a phase III RCT [20].

The popularity of sarcopenia was brought to the forefront in both European and North American population cross-

sectional studies identifying a strong association between individuals with low muscle mass and the prevalence of disabilities in instrumental activities of daily living (IADLs) and falls during the past year [4]. However, new data with more characteristic information on subclinical diseases have noted a reduced or no association between physical function and skeletal-muscle mass [21,22]. These contradictory studies began a new trajectory for understanding the role of sarcopenia, or lack thereof, in governing losses in physical function. Over the past decade, cross-sectional studies have been largely replaced by longitudinal studies that are better suited to understand the independent association between low-muscle mass and incidence of physical impairments and disability. The most current evidence from longitudinal studies suggests sarcopenia is not associated with health outcomes in the elderly [23^{••},24,25]. The most recent data from the Invecchiare in Chianti (InChianti) Study, a cohort of 1115 participants between 65–102 years, demonstrated that muscle cross-sectional area (CSA) of the calf was not associated with an increased risk of mortality when covariates were considered [23^{••}]. Additional analyses that defined sarcopenia according to sex-specific categories through regression techniques confirmed no association with mortality. In another large cohort of older adults, Newman *et al.* [24] found that whole leg-muscle mass and thigh CSA was not associated with risk of mortality. However, both grip and leg extensor muscle strength was highly associated with mortality, despite accounting for muscle mass, suggesting that sarcopenia may be secondary to the effects of dynapenia [24]. Collectively, these findings indicate that overall neuromuscular function and not simply muscle mass is a critical factor for determining health in the elderly.

Although associations with mortality have predominated the literature, preservation of physical independence is arguably more important for older adults. The first studies on sarcopenia established a strong and consistent association between low muscle mass and impairments in physical function [21,22]. For example, Janssen [26] found that both men and women with a low skeletal muscle index enrolled in the NHANES study were more likely to report needing assistance with personal care or handling routine daily chores [11]. Janssen cross-validated these results with data from the Cardiovascular Health Study and found that women, but not men who had severely low-muscle mass were at elevated risk of disability 8 years later. However, new evidence challenges these findings. Data from the InChianti Study indicates that sarcopenia of the calf muscle had little influence on poor walking speed, a powerful predictor of incident disability and frailty in older adults [23^{••}]. Additionally, Visser *et al.* [25] reported that thigh muscle CSA was not associated with the incidence of mobility

limitation. Interestingly, knee extensor strength was associated with mobility limitation even when adjusting for muscle mass [8,27]. Although initial reports support the importance of muscle mass, new data are beginning to shift the paradigm towards risk factors for muscle weakness [28•].

Mechanisms underlying muscle weakness in the elderly

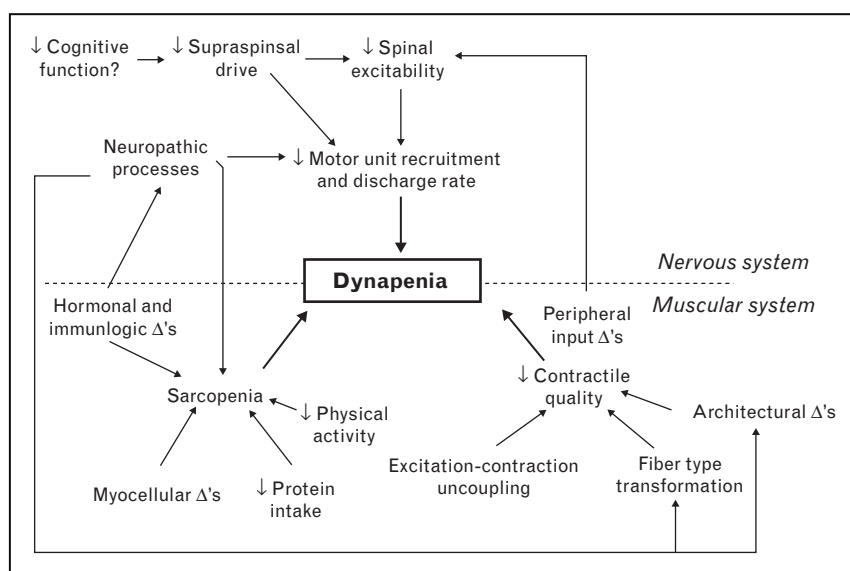
The mechanisms accounting for a decline in muscle strength, defined as the maximal amount of force that can be produced voluntarily can be attributed to a combination of 'neural' and 'muscular' factors. For example, impairments in neural (central) activation, such as that due to a reduction in descending excitatory drive from supraspinal centers, suboptimal motor unit recruitment and rate coding, and/or neuromuscular transmission failure can result in dynapenia. Additionally, an overall reduction in muscle quantity due to muscle fiber apoptosis or atrophy, as well as reduced contractile quality due to excitation-contraction uncoupling, changes in actomyosin structure and function, and infiltration of adipocytes into muscle fibers can result in dynapenia. Figure 1 depicts a theoretical model of the neurologic and muscular factors potentially leading to dynapenia.

There is limited evidence from longitudinal aging studies on the relative contribution of neural activation, muscle quantity and contractile quality on explaining dynapenia. However, the data that does exist suggests

that the loss of muscle mass, whereas it does certainly contribute to some of the loss of strength, is far from the sole or even primary explanatory variable [29••,30]. This assertion is based on data from the health, aging, and body composition study, which indicates that the decline in muscle strength is much more rapid than the concomitant loss of muscle mass, and that maintaining or gaining muscle mass does not prevent aging-related declines in muscle strength [29••,30]. For example, Delmonico *et al.* [29••] followed 1678 older adults over 5-years and observed that on average men lost approximately 16% of their knee extensor muscle strength but only 5% of their thigh-muscle mass. Women lost approximately 13% of their muscle strength but only 3% of their muscle mass. The explanations for these findings either result from a lack of one-to-one association between changes in muscle mass and strength or that other factors are involved. Such factors include impairments of neural activation of the knee extensors and/or reductions in contractile quality.

To our knowledge, there are no longitudinal studies describing age-associated impairments in neural activation of muscle; however, there are cross-sectional studies. The primary way to control exerted muscle force is via recruitment of additional motor units within a given alpha-motoneuron pool and/or increased motor unit discharge rate [31]. When these two physiologic properties are optimized, maximal muscle activation results. The most common way to globally investigate whether neural impairments are responsible for a

Figure 1 Proposed biologic mechanisms contributing to dynapenia (the age-associated loss of strength)



This figure is an updated version of our previously proposed model [3•] and it summarizes the influence of multiple factors that may lead to muscle weakness in the elderly. Adapted with permission [3•].

reduction in strength is to deliver a supramaximal electrical stimulus to a peripheral nerve or muscle during a maximal voluntary contraction and evaluate the 'added force'. Although this technique is not without limitations [32,33], it does provide insight into the degree of voluntary muscle activation. The largest study to date indicates that healthy older adults have impairments in activation of the knee extensors, a muscle group that is highly relevant for physical functioning [34]. Furthermore, frail elderly individuals show an even greater deficit in neural activation [35] and there is evidence suggesting that many age-related clinical conditions, such as total knee arthroplasty also result in deficits in neural activation [36]. Although these data are convincing, there are some cross-sectional studies yielding conflicting results [37]. Over the past couple of years there have been several reports suggesting a link between muscle weakness and cognitive decline [38,39]. One of the more intriguing of these studies observed that poor physical function and muscle strength coexisted with cognitive impairment and that this relationship was independent of muscle mass and physical-activity level [38]. This finding raises the question of the inter-relationship between neural activation and cognitive function, and further work is needed to better understand these associations.

With regards to contractile quality, the one longitudinal study that we are aware of did not observe a change in single fiber force/unit area when individuals in their early 70's were followed up approximately 9 years later [40]. However, the majority of both human and animal cross-sectional studies do observe a reduction in single fiber and whole muscle contractile quality [41–44]. For example, it was recently reported that the age-related decline in knee extensor muscle strength was accompanied by a 20–28% decline in single fiber contractile quality in muscle fibres expressing the type I myosin heavy chain isoforms [44]. Accordingly, there is evidence that alterations in muscle quantity, contractile quality and neural activation collectively contribute to dynapenia. The relative contribution of these factors is not fully understood, and it is likely to vary between muscle groups and across populations.

Conclusion

The literature has evolved over the past two decades with new evidence that has improved identification of modifiable risk factors for loss in physical function among the elderly [45]. The data first led the research community toward sarcopenia as a major modifiable risk factor for health outcomes. These data provided the rationale to propose appropriately designed longitudinal studies to unequivocally evaluate sarcopenia in the etiology of

disability. The results from this new research stunned many scientists by suggesting that muscle mass is not associated with the same outcomes that once popularized sarcopenia. These recent findings provide new avenues and ideas on how to rehabilitate the loss in physical function among the elderly.

The research community is now challenged with determining how to develop a consensus definition of sarcopenia and/or dynapenia [46]. Such a definition would catapult efforts to diagnose and treat losses in physical function. This task is complicated by determining what single measure or combination of measures to assess for developing a clinical tool. The first efforts used similar strategies as those seen in defining osteoporosis where individuals with a two SD lower muscle mass than a young reference group were considered sarcopenic. The strategy works well for osteoporosis because the density of bone is directly related to fracturability [47] and has the clinical significance needed to set appropriate thresholds for diagnosis and treatment [48]. However, these approaches cannot apply to sarcopenia because it overestimates the prevalence of sarcopenia [49] and muscle size is not the sole contributor to losses in physical function [3^{*},22,24,29^{**}]. Additionally, the simple use of muscle size even after adjustments for body anthropometry cannot account for obese individuals having greater muscle mass despite higher levels of physical disability [50]. Another approach is to measure muscle strength, but this measure can be influenced by psychosocial aspects (e.g., depression, cognitive function) that need to be studied in further depth. Other ideas include using a ratio of muscle strength per unit mass [21], or stratifying by BMI [23^{**}]. Each method is complicated by errors in predictability and stability across varying anthropometrics.

The current opinions stated in this article are not meant to minimize the global significance of muscle size and the biological study of muscle regulation. Muscle size and the mechanisms that govern it are critical for maintaining a protein reservoir needed to withstand resistance to disease conditions [51]. Muscle tissue provides a rich source of protein necessary to construct immune defenses and is associated with survival of several conditions including cancer [52]. Additionally, there is evidence from clinical trials on anabolic hormones demonstrating favorable changes in muscle size with a concomitant increase in muscle strength [53]. Therefore, further study of the mechanisms of muscle regulation will provide the knowledge to develop new pharmaceutical agents to attenuate muscle loss seen with many diseases. Minimizing atrophy during the disease process will provide patients with the means to recover. Such circumstances continue to make the study of muscle size management an important endeavor.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 347).

- 1 Rosenberg IH. Summary comments. *Am J Clin Nutr* 1989; 50:1231–1233.
- 2 Visser M. Towards a definition of sarcopenia: results from epidemiologic studies. *J Nutr Health Aging* 2009; 13:713–716.
- 3 Clark BC, Manini TM. Sarcopenia \neq dynapenia. *J Gerontol A Biol Sci Med Sci* 2008; 63:829–834.
- Article highlighting the neural and muscular contributors to loss in muscle strength with aging and where the terminology of dynapenia was created.
- 4 Baumgartner RN, Koehler KM, Gallagher D, *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; 147:755–763.
- 5 Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004; 52:80–85.
- 6 Jelsma J. Use of the International Classification of Functioning, Disability and Health: a literature survey. *J Rehabil Med* 2009; 41:1–12.
- 7 Guralnik JM, Ferrucci L, Pieper CF, *et al.* Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* 2000; 55:M221–M231.
- 8 Manini TM, Visser M, Won-Park S, *et al.* Knee extension strength cutpoints for maintaining mobility. *J Am Geriatr Soc* 2007; 55:451–457.
- 9 Abellan van Kan G. Epidemiology and consequences of sarcopenia. *J Nutr Health Aging* 2009; 13:708–712.
- 10 Reid KF, Naumova EN, Carabello RJ, *et al.* Lower extremity muscle mass predicts functional performance in mobility-limited elders. *J Nutr Health Aging* 2008; 12:493–498.
- 11 Janssen I, Baumgartner RN, Ross R, *et al.* Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol* 2004; 159:413–421.
- 12 Kimyagarov SR, Klid S, Levenkrohn, *et al.* Body mass index (BMI), body composition and mortality of nursing home elderly residents. *Arch Gerontol Geriatr* 2009. [Epub ahead of print]
- 13 Ray NF, Chan JK, Thamer M, Melton LJ 3rd. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997; 12:24–35.
- 14 2008 Older Americans Well Being, Federal Interagency Forum on Aging-Related Statistics. Available at www.agingstats.gov/agingstatsdotnet/main_site/default.aspx [Accessed December 2009].
- 15 Pahor M, Blair SN, Espeland M, *et al.* Effects of a physical activity intervention on measures of physical performance: results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci* 2006; 61:1157–1165.
- 16 Snijders T, Verdijk LB, van Loon LJ. The impact of sarcopenia and exercise training on skeletal muscle satellite cells. *Ageing Res Rev* 2009; 8:328–338.
- 17 Abellan van Kan G, Andre E, Bischoff Ferrari HA, *et al.* Carla Task Force on Sarcopenia: propositions for clinical trials. *J Nutr Health Aging* 2009; 13:700–707.
- 18 Bellofatto V. Pyrimidine transport activities in trypanosomes. *Trends Parasitol* 2007; 23:187–189; discussion 190.
- 19 Sumukadas D, Witham MD, Struthers AD, McMurdo ME. ACE inhibitors as a therapy for sarcopenia: evidence and possible mechanisms. *J Nutr Health Aging* 2008; 12:480–485.
- 20 The Testosterone Trial, ClinicalTrials.gov, Editor. 2009, A service of the U.S. National Institutes of Health.
- 21 Lauretani F, Russo CR, Bandinelli S, *et al.* Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* 2003; 95:1851–1860.
- 22 Visser M, Newman AB, Nevitt MC, *et al.* Reexamining the sarcopenia hypothesis. Muscle mass versus muscle strength. Health, Aging, and Body Composition Study Research Group. *Ann N Y Acad Sci* 2000; 904:456–461.
- 23 Cesari M, Pahor M, Lauretani F, *et al.* Skeletal muscle and mortality results from the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci* 2009; 64:377–384.
- Data from this article suggested that muscle size is not associated with mortality or physical function in the elderly.
- 24 Newman AB, Kupelian V, Visser M, *et al.* Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci* 2006; 61:72–77.
- 25 Visser M, Goodpaster BH, Kritchevsky SB, *et al.* Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well functioning older persons. *J Gerontol A Biol Sci Med Sci* 2005; 60:324–333.
- 26 Janssen I. Influence of sarcopenia on the development of physical disability: the Cardiovascular Health Study. *J Am Geriatr Soc* 2006; 54:56–62.
- 27 Visser M, Simonsick EM, Colbert LH, *et al.* Type and intensity of activity and risk of mobility limitation: the mediating role of muscle parameters. *J Am Geriatr Soc* 2005; 53:762–770.
- 28 Bouchard DR, Janssen I. Dynapenic-obesity and physical function in older adults. *J Gerontol A Biol Sci Med Sci* 2010; 65:71–77; Epub 2009 Nov 3.
- Article illustrating the importance of dynapenia and obesity in the context of a nationally representative sample of older adults.
- 29 Delmonico MJ, Harris TB, Visser M, *et al.* Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *Am J Clin Nutr* 2009; 90:1579–1585.
- Investigators found a clear dissociation between the loss in muscle mass and strength. This provided the framework to propose that other factors are contributing to the loss in muscle strength among older adults.
- 30 Goodpaster BH, Park SW, Harris TB, *et al.* The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006; 61:1059–1064.
- 31 Monster AW, Chan H. Isometric force production by motor units of extensor digitorum communis muscle in man. *J Neurophysiol* 1977; 40:1432–1443.
- 32 de Haan A, Gerrits KH, de Ruiter CJ. Counterpoint: the interpolated twitch does not provide a valid measure of the voluntary activation of muscle. *J Appl Physiol* 2009; 107:355–357; discussion 357–358.
- 33 Taylor JL. Point: the interpolated twitch does/does not provide a valid measure of the voluntary activation of muscle. *J Appl Physiol* 2009; 107:354–355.
- 34 Stevens JE, Stackhouse SK, Binder-Macleod SA, Snyder-Mackler L. Are voluntary muscle activation deficits in older adults meaningful? *Muscle Nerve* 2003; 27:99–101.
- 35 Harridge SD, Kryger A, Stensgaard A. Knee extensor strength, activation, and size in very elderly people following strength training. *Muscle Nerve* 1999; 22:831–839.
- 36 Mizner RL, Stevens JE, Snyder-Mackler L. Voluntary activation and decreased force production of the quadriceps femoris muscle after total knee arthroplasty. *Phys Ther* 2003; 83:359–365.
- 37 Klass M, Baudry S, Duchateau J. Voluntary activation during maximal contraction with advancing age: a brief review. *Eur J Appl Physiol* 2007; 100:543–551.
- 38 Auyeung TW, Kwok T, Lee J, *et al.* Functional decline in cognitive impairment: the relationship between physical and cognitive function. *Neuroepidemiol* 2008; 31:167–173.
- 39 Boyle PA, Buchman AS, Wilson RS, *et al.* Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Arch Neurol* 2009; 66:1339–1344.
- 40 Frontera WR, Reid KF, Phillips EM, *et al.* Muscle fiber size and function in elderly humans: a longitudinal study. *J Appl Physiol* 2008; 105:637–642.
- 41 D'Antona G, Pellegrino MA, Carlizzi CN, Bottinelli R. Deterioration of contractile properties of muscle fibres in elderly subjects is modulated by the level of physical activity. *Eur J Appl Physiol* 2007; 100:603–611.
- 42 Ochala J, Frontera WR, Dorer DJ, *et al.* Single skeletal muscle fiber elastic and contractile characteristics in young and older men. *J Gerontol A Biol Sci Med Sci* 2007; 62:375–381.
- 43 Russ DW, Grandy JS, Ward CW. Muscle quality and sarcoplasmic reticulum function are reduced in hindlimb muscles of old rats. *Med Sci Sports Exercise* 2009; 41: Abstract.
- 44 Yu F, Hedstrom M, Cristea A, *et al.* Effects of ageing and gender on contractile properties in human skeletal muscle and single fibres. *Acta Physiol (Oxf)* 2007; 190:229–241.
- 45 Brown M. Too many weak days: diagnosis: physical frailty. *Mo Med* 2009; 106:121–125; quiz 125–126.
- 46 Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. *J Nutr Health Aging* 2009; 13:724–728.
- 47 Silva MJ. Biomechanics of osteoporotic fractures. *Injury* 2007; 38 (Suppl 3): S69–S76.

- 48 Szulc P, Duboeuf F, Schott AM, *et al.* Structural determinants of hip fracture in elderly women: re-analysis of the data from the EPIDOS study. *Osteoporos Int* 2006; 17:231–236.
- 49 Newman AB, Kupelian V, Visser M, *et al.* Sarcopenia: alternative definitions and associations with lower extremity function. *J Am Geriatr Soc* 2003; 51:1602–1609.
- 50 Alley DE, Chang VW. The changing relationship of obesity and disability, 1988–2004. *JAMA* 2007; 298:2020–2027.
- 51 Tisdale MJ. Cancer cachexia. *Curr Opin Gastroenterol* 2010; 26:146–151.
- 52 Mantovani G, Maccio A, Massa E, Madeddu C. Managing cancer-related anorexia/cachexia. *Drugs* 2001; 61:499–514.
- 53 Bhasin S, Woodhouse L, Casaburi R, *et al.* Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J Clin Endocrinol Metab* 2005; 90:678–688.