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Sarcopenic obesity - definition, etiology and consequences

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Abstract

Purpose of the review—Older obese persons with decreased muscle mass or strength are at special risk for adverse outcomes. We discuss potential pathways to muscle impairment in obese individuals and the consequences that joint obesity and muscle impairment may have on health and disability. Tantamount to this discussion is whether low muscle mass or, rather, muscle weakness should be used for the definition.

Recent findings—Excess energy intake, physical inactivity, low-grade inflammation, insulin resistance and changes in hormonal milieu may lead to the development of so called 'sarcopenic obesity'. It was originally believed that the culprit of age-related muscle weakness was a reduction in muscle mass, but it is now clear that changes in muscle composition and quality are predominant. We propose that the risk of adverse outcomes, such as functional limitation and mortality, is better estimated by considering jointly obesity and muscle strength rather than obesity and muscle mass and the term "sarcopenic obesity" should be revisited.

Summary—Recognition of obese patients who have associated muscle problems is an essential goal for clinicians. Further research is needed to identify new target for prevention and cure of this important geriatric syndrome.

Keywords

adipose tissue; body composition; disability; muscle strength; obesity; older people; sarcopenia

Introduction

This review focuses on a specific feature of obesity, which has been termed "sarcopenic obesity" [1,2**]. In any healthy young and older individuals bone and muscle grow in harmony with change in weight. This harmony is maintained by gravity stimulating the mechanoreceptors in bone and muscle that modulate the production of growth factors [3,4]. This adaptive physiological mechanism may be impaired in some older individuals who become frankly obese without a parallel growth of muscle mass and increment of strength. As

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a consequence, obese persons may end up having too low muscle strength relative to their body size.

We begin by exploring the current definition of and discuss why the term 'sarcopenia', examined within the limits of its etymological roots, is a source of confusion in this field. Next, we will examine the hypothetical pathways that can lead to the obesity/muscle impairment syndrome. Finally, we review the literature on the consequences of sarcopenic obesity in terms of functional and health-related outcomes.

Searching for a definition based on pathophysiology and associated risk

The development of a research agenda on the combined effect of muscle impairment and obesity is hampered by the lack of a widely agreed operational definition. The definitions of muscle impairment and obesity in older persons are controversial and their clustering and synergy in a syndromic entity remain hypothetical.

Obesity is defined as abnormal or extensive fat accumulation that negatively affects health [5]. According to the World Health Organization [5], obesity is defined as Body Mass Index (BMI) ≥ 30 kg/m ^{2} and central obesity as a waist circumference greater than 102 cm in men and 88 cm in women. Whether these criteria are appropriate for older individuals has been questioned.

The term *sarcopenia* comes from the Greek words sarx (meaning flesh) and penia (meaning loss) was originally meant to represent age-related loss of muscle mass with aging [6-9]. At the time this concept was coined, scientists believed that the age-associated decline of muscle strength was largely due to a parallel decline of muscle mass [10,11], and therefore the study of muscle mass was in some way equivalent to the study of muscle function. Baumgartner et al. [12] defined sarcopenia as "appendicular skeletal muscle mass divided by body height squared in meters (muscle mass index)" two standard deviations or more below reference values from young, healthy individuals measured with dual X-ray absorptiometry (DXA). In 2002, Janssen et al. proposed to convert absolute skeletal muscle mass (kg) to percentage of weight (muscle mass / body mass × 100) and to define sarcopenia as more than one standard deviation below the reference values from young, healthy individuals measured with bioelectrical impedance. Criteria for the sarcopenia proposed more recently are based on the amount of lean mass lower than expected for a given amount of fat mass using residuals from linear regression models [13] and ratio between appendicular lean mass and appendicular fat (Harris et al. unpublished data).

The idea that decline in muscle function is largely explained by the parallel decline in mass has not been proven true. Both muscle mass and muscle strength decline with aging, but the decline in strength exceeds what is expected based on the decline in mass [14,15*,16]. The progressive mismatch between mass and strength occurs because of a progressive deterioration of muscle "quality", including decrease in fiber size and number, intrinsic reduction of contractility in the intact fibers [17,18], fat micro and macro-infiltration [19,20], increase in collagen, modification of the motor unit, and impaired neurological modulation of contraction [21]. Evidence has also emerged that muscle strength is more important than muscle mass as a determinant of functional limitation and poor health in older age [14,22-24].

In the complex choice between muscle mass and muscle strength as valid markers of age-related muscle impairment, it is useful to recapitulate the methodological work that led to the definition of osteoporosis. Initially bone mineral density was proposed as a diagnostic marker of osteoporosis because it reflected morphometric changes in bone that occurred over the lifetime and was accelerated by menopause. Subsequent studies demonstrated that bone mineral density discriminated individuals at high risk of fracture [25]. Later studies have

indicated that not only bone structure, but bone quality, may contribute to fracture risk, along with functional aspects of health such as weight loss and frailty [25,26]. Similarly, age-related changes in muscle tissue are mostly interesting because of their functional consequences. It is now clear that muscle macro-architecture reflects only poorly the amount of actively contracting proteins. Consistently, studies have found that muscle mass is only a poor cross-sectional and longitudinal correlate of physical function [14,23,27].

Sarcopenic obesity

In spite of the limitation discussed above, most of the literature focuses on the obesity/low muscle mass combination (Table 1), appropriately defined as sarcopenic obesity.

Like sarcopenia, sarcopenic obesity was first defined by Baumgartner [1] as a muscle mass index less than 2 SD below the sex-specific reference for a young, healthy population. In 2002, Davison et al. [28] defined sarcopenic obesity using anthropometrics and bioelectrical impedance. Definitions based on strength are more recent and present intrinsic challenges. The usual normalization of strength by body size or by fat mass conceals part of the discrepancy between the “engine” and the “mass to be moved” which is the “raison d’être” for discussing sarcopenic obesity. Thus, operational definitions based on crude rather than “normalized” strength have been proposed (Stenholm et al. unpublished data) [29**,30*]. Although there are no generally accepted criteria for low muscle strength, measuring strength is easier and cheaper than measuring muscle mass. The use of more sophisticated methods such as DXA or computed tomography should also be kept as an option in more thorough clinical examination and especially in establishing the effectiveness of interventions.

In studies using muscle mass as an indicator of sarcopenia, sarcopenic obesity prevalence ranges from 4 to 12 percent [1,28,31] (Table 1.). Based on BMI and hand grip strength measurements in four epidemiological studies, sarcopenic obesity can be roughly estimated between 4 to 9 percent (Table 2.).

Pathways to the obesity/muscle impairment syndrome

Age-related changes in body composition

Longitudinal studies have shown that fat mass increases with age and is higher among later birth cohorts peaking at about age 60-75 years [32-34], whereas muscle mass and strength starts to decline progressively around the age of 30 years with a more accelerated loss after the age of 60 [35-37]. Visceral fat and intramuscular fat tend to increase, while subcutaneous fat in other regions of the body declines [38-41]. Furthermore, fat infiltration into muscle is associated with lower muscle strength and leg performance capacity [20,42*].

The increase in body weight and fatness are probably due to progressive decline in total energy expenditure stemming from decreased physical activity and reduced basal metabolic rate [43] in the presence of increased or stable caloric intake exceeding basal and activity-related needs. Aging is also associated with a decline in a variety of neural, hormonal and environmental trophic signals to muscle. Physical inactivity, hormonal changes, pro-inflammatory state, malnutrition, loss of alpha-motor units in the central nervous system, and altered gene expression accelerate the loss of muscle mass and mass-specific strength [7, 44-46].

Given the age-related changes in body composition, obesity and low muscle mass (or low muscle strength) may coexist in same person simply by chance. However, there is some evidence for a causal link between obesity and low strength.

Physical activity

Sedentary life-style is an important risk factor for weight gain [47]. Obese persons also tend to be less physically active and this may contribute to decreased muscle strength [48]. Finally, muscle atrophy leads to reduction in metabolic rate both at rest and during physical activity and may further aggravate the sedentary state, all of which can cause weight gain. Two recent studies have shown that weight loss intervention combining diet and exercise among older obese people improves muscle strength and muscle quality in addition to fat loss confirming the hypothesis about tight connection between adiposity and impaired muscle function [49, 50*].

Inflammation

It is now evident that adipose tissue is an active metabolic tissue that secretes hormones and proteins. For example, in adipose tissue, either adipocytes directly or infiltrating macrophages produces pro-inflammatory cytokines, such as interleukin(IL)-6 and tumor necrosis factor (TNF)-α [51] and adipokines, such as leptin and adiponectin, that up-regulate the inflammatory response [51,52*,53], which, again, may contribute to muscle mass and strength decline [54-58]. Cesari et al. [55*] reported that pro-inflammatory cytokines were positively associated with fat mass and negatively with muscle mass. In the InCHIANTI study, Schrager et al. [29] found that obese community-dwelling older persons with low muscle strength had elevated levels of CRP and IL-6 compared to those with normal strength. Thus, a pro-inflammatory state may be one of the key factors in creating a vicious cycle of decreased muscle strength among obese persons.

Insulin resistance

Studies in animals and humans have found that inflammatory molecules mediate obesity-related insulin resistance through a cross-talk between cytokine receptors and insulin receptor signaling pathways [59,60]. It has been hypothesized that muscle fat infiltration causes insulin resistance in obese individuals [61,62] and this hypothesis has been partially confirmed in humans [63-65].

Since insulin is a powerful anabolic signal on proteins [66,67], insulin resistance in obese individuals may promote muscle catabolism. Studies have shown that insulin resistance is an independent correlate of poor muscle strength [68-70] and older diabetic patients show accelerated loss of leg muscle strength and quality [71*]. Furthermore, resistance training improves insulin sensitivity and glycemic control [61,72].

Growth hormone and testosterone

Increased adiposity is often associated with high circulating free fatty acids [73,74], which inhibit growth hormone production and decrease plasma insulin-like growth factor I (IGF-I) [75,76]. Recent study showed that sarcopenic obese persons had depressed growth hormone secretion compared to obese persons [77]. Similarly, obese individuals tend to have lower testosterone [78]. Noteworthy, low levels of these anabolic hormones have been reported positively associated with low muscle strength [7,79-81] and may therefore contribute to muscle impairment in obese individuals [82].

Malnutrition and weight loss

Weight gain results from the misbalance between energy intake and expenditure. Older persons tend to obtain too little proteins in their diet [83] which may impair protein muscle turnover, especially during periods of weight loss [84-86] which is often coincident with accelerated sarcopenia.

Association between obesity and muscle impairment

Clearly, our discussion on the possible origins of sarcopenic obesity is in no way exhaustive and several other mechanisms could be hypothesized. Based on the research summarized above, it is reasonable to hypothesize that low muscle strength and obesity may be pathophysiologically connected which makes them more likely to be associated than expected by chance alone.

We examined the hypothesis that obesity (BMI $\geq$ 30 kg/m^2) and low muscle strength (lowest sex-specific hand grip strength tertile) are connected in four epidemiological studies that included persons aged 65 years and older. The reason why we choose muscle strength and not muscle mass in this analysis has been addressed above. Consistently across the four studies, participants with poor muscle strength were approximately two times more likely to be obese compared to those with normal strength when adjusted for age, gender and body weight (Table 2.). It is also evident that obesity and poor strength are not necessarily coexistent and can occur in isolation.

Consequences of obesity/muscle impairment syndrome

Obesity is a strong risk factor for poor health, reduced functional capacity and quality of life in older persons [5,87,88*,89]. Analogously, low muscle strength has proven to be strong predictor of functional capacity, institutionalization and mortality [23,90]. Initial evidence indicates that when obesity and muscle impairment co-exist they act synergistically on the risk of developing multiple health related outcomes [91**,92]. Noteworthy, most of what we know currently is based on a definition of sarcopenic obesity that uses low muscle mass as a criterion.

It is intuitive that individuals with disproportionally poor muscle strength compared to their large body are more at risk of being disabled and of developing disability in the future. Ongoing studies within Baltimore Longitudinal Study on Aging are exploring the effect of obesity and poor muscle strength on the biomechanics and energetic expenditure of gait. Given the same task (workload) the energy expenditure, oxygen consumption and muscle force required for an obese person are higher than those required by a normal weight persons, potentially limiting their physical performance [93,94].

Few studies have examined the combined effect of obesity and muscle mass or strength in older persons on physical functioning or disability. Studies based on muscle mass and obesity provides conflicting data. In the New Mexico Elder Health Survey sarcopenic obese participants were more likely to be disabled than participants who were just obese or sarcopenic [1]. In the 8-year follow-up of the New Mexico Aging Process Study, Baumgartner et al. [95] demonstrated that older participants with sarcopenic obesity at baseline had over 2-fold higher risk of developing IADL disability than those who were not sarcopenic obese at baseline. However, two other cross-sectional studies based on NHANES III [28] and a sample of older women in Verona [31] did not find an association between sarcopenic obesity and poor physical functioning. In fact, they only observed an association between obesity and functional decline, not with low muscle mass. In their studies Davison et al. and Zoico et al. both used same categorization to define sarcopenic obesity based on the estimated fat and muscle mass quintiles. The use of muscle mass, rather than a functional measure such as strength, as an indicator of sarcopenia may possibly explain why they did not find association with physical functioning, although the Baumgartner definition was based on muscle mass and obesity.

There are only few studies about the combined effect of obesity and muscle impairment where muscle impairment was defined by poor muscle strength. In the cross-sectional Finnish Health 2000 Survey persons with combination of increased fat percentage and decreased muscle strength had higher prevalence of walking limitation compared to those with only high fat

percentage or low muscle strength [30]. In the InCHIANTI study we showed recently that older persons with high BMI and low strength experience a steeper decline in walking speed and have higher probability of mobility disability than those with either poor muscle strength or obesity alone (Stenholm et al. unpublished data).

The mortality risk associated with obesity coupled with poor strength was studies by Rantanen et al. [90] who examined hand grip strength and body mass index as predictors of 30-year all-cause mortality in initially healthy men. These authors found that overweight persons in the lowest grip strength tertile had 1.39 times higher mortality risk compared to normal weight persons in the highest grip strength tertile. Increased mortality related to sarcopenic obesity is an important finding and sheds light over the dilemma related to body composition and mortality. Previous studies have shown that muscle strength is a strong predictor of mortality [24,90,96,97], whereas the relationship between obesity and mortality remains controversial [98,99*,100]. In old age, obesity may protect against mortality, but if combined with low muscle strength, the risk of mortality may exceed the protective effect. Future studies should examine this topic with large samples including also oldest old people and sample sizes that allow analyzing cause-specific mortality.

Many open questions remain on the genesis and the consequences of the obesity/muscle impairment syndrome in older persons that should be addressed in future research. For example, it will be important to examine gender differences in the development and consequences of this condition. Women are known to have more fat mass as well as lower absolute and relative muscle strength than men [42,101], and may therefore be more prone to develop obesity and poor strength. Based on our descriptive analysis in four different data sets, the association seems to be more common in women than in men. This is in line with recent obesity-studies showing that the consequences of obesity may be more severe in women than in men [89,102,103]. In obese women even small decline in muscle strength may cause difficulties in bearing their excess weight and in moving efficiently.

We have excluded from this review the potential association between sarcopenic obesity and specific obesity-related illnesses, because Dominguez et al. [91] have reviewed the cardiometabolic consequences of sarcopenic obesity, especially in reference to diabetes and cardiovascular diseases. Future studies are needed to understand the effect of disproportionate amount of fat and muscle strength, on cardiovascular, metabolic and musculoskeletal diseases.

In this review we have tried to avoid as much as possible the use of the term “sarcopenic obesity” to describe the combination of obesity and low muscle strength. However, some misuse of this term is almost unavoidable and reflects the true confusion in the literature. A central issue in future discussion about the obesity/muscle impairment geriatric syndrome is a search for new, more comprehensive terminology that takes into account the findings of research conducted in the last decade.

Conclusions

The imbalance between obesity and muscle impairment, either defined by low muscle mass or poor muscle strength is associated with important, negative health outcomes in older individuals. Recent epidemiological studies suggest that this syndrome is related to accelerated functional decline and high risk of diseases and mortality and, therefore, the identification of affected older patients should be an essential goal for clinicians. Expanding our understanding of the complex etiology of the obesity/muscle impairment syndrome and identifying therapeutic targets may offer a tremendous opportunity to limit the expansion of disability that the joined effects of the demographic transformation and the ongoing obesity epidemic will

certainly determine. More collaboration between researchers in different fields is needed to fulfill these goals.

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Table 1

Comparison of different sarcopenic obesity definitions and prevalences

	Definition of sarcopenic obesity	N	Mean age (SD)	Prevalence*
New Mexico Aging Process Study [1]	- Sarcopenia: skeletal muscle mass -2 SD below mean of young population or < 7.26 kg/m^2 in men and < 5.45 kg/m^2 in women. - Obesity: percentage body fat greater than median or > 27% in men and 38% in women.	831	60 and over	M: 4.4% F: 3.0%
NHANES III [28]	- Sarcopenia: two lower quintiles of muscle mass (<9.12 kg/m^2 in men and <6.53 kg/m^2 in women) - Obesity: two highest quintiles of fat mass (>37.16% in men and > 40.01% in women).	M: 1391 F: 1591	M: 76.3 (1.7†) F: 77.3 (2.2†)	M: 9.6% F: 7.4%
[31]	- Sarcopenia: two lower quintiles of muscle mass (<5.7 kg/m^2) - Obesity: two highest quintiles of fat mass (>42.9%)	F: 167	71.7 (2.4)	F: 12.4%

*Age and gender adjusted prevalence.

†Standard error

Table 2

Prevalence of obesity and impaired muscle strength and odds-ratios for obesity associated with impaired muscle strength in four epidemiological studies of persons aged 65 years and older[†].

		Impaired strength		Not impaired muscle strength		Impaired vs. not impaired strength
	Mean age (SD)	Obese	Not obese	Obese	Not obese	OR (95 % CI) [*]
BLSA (N = 1026)	75.8 (7.1)					
N (%)		45 (4.4)	296 (28.9)	114 (11.1)	571 (55.7)	1.95 (1.01-3.79)
Age-adjusted prevalence (%) male / female		M: 3.5 F: 6.6	M: 30.5 F: 28.2	M: 15.2 F: 9.4	M: 47.7 F: 59.0	
Health 2000 Survey (N = 1413)	76.4 (7.6)					
N (%)		129 (9.1)	335 (23.7)	267 (18.9)	682 (48.3)	2.62 (1.69-4.06)
Age-adjusted prevalence (%) male / female		M: 6.1 F: 11.0	M: 29.6 F: 20.0	M: 15.3 F: 21.2	M: 49.0 F: 47.8	
InCHIANTI (N = 856)	74.3 (6.9)					
N (%)		74 (8.6)	218 (25.5)	139 (16.2)	425 (49.7)	1.96 (1.17-3.30)
Age-adjusted prevalence (%) male / female		M: 6.3 F: 8.7	M: 30.5 F: 21.6	M: 13.6 F: 18.3	M: 50.6 F: 48.9	
LASA (N = 1189)	75.8 (7.2)					
N (%)		85 (7.2)	281 (23.6)	219 (18.4)	604 (50.8)	1.20 (0.74-1.95)
Age-adjusted prevalence (%) male / female		M: 5.1 F: 8.9	M: 26.2 F: 21.4	M: 11.3 F: 24.4	M: 57.4 F: 45.2	

BLSA (Baltimore Longitudinal Study on Aging), USA (1959-2007) [104]:

Impaired strength: lower gender-specific tertile of hand grip strength (<33 kg in men and <20 kg in women); Obese: BMI ≥ 30 kg/m^2

Health 2000 Survey, Finland (2000-01) [105]:

Impaired strength: lower gender-specific tertile of hand grip strength (<322 N in men and <176 N in women); Obese: BMI ≥ 30 kg/m^2

InCHIANTI, Italy (1998-2000) [106]:

Impaired strength: lower gender-specific tertile of hand grip strength (<32 kg in men and <18 kg in women); Obese: BMI ≥ 30 kg/m^2

LASA (Longitudinal Aging Study Amsterdam), Netherlands (2001-02) [107,108]:

Impaired strength: lower gender-specific tertile of hand grip strength (< 33 kg in men and < 20 kg in women); Obese: BMI ≥ 30 kg/m^2

[*] Adjusted for age, gender, body weight.

[†] Details of the studies: