Body composition assessment in the prediction of osteoporotic fractures

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Purpose of review
To give an overview of recent research findings and insights on the role of body composition assessment in fracture risk prediction.

Recent findings
While there is to date little doubt that bone mineral density (BMD) is a main pathogenic factor of osteoporotic fractures, recent studies have emphasized the independent contribution of body composition components, especially lean mass, to fracture risk. In this article, we address body composition changes with aging, before to focus on recent studies addressing the contribution of lean and fat mass to fracture risk, together with some hypothesized mechanisms and clinical implications.

Summary
Recent compelling evidence suggest that clinicians should recognize the potential role of muscle wasting in determining fracture risk among older adults and that measures of lean mass, especially appendicular lean mass – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. More evidence is needed to support certain fat-related indicators in fracture risk prediction, but regional adiposity measures appear promising. Further studies in the field should help to elucidate whether interventions effective at attenuate, prevent, or ultimately reverse skeletal lean mass loss or fat accumulation, may prevent fractures.

Keywords
body composition, dual-energy X-ray absorptiometry, fat, fracture, skeletal muscle

INTRODUCTION
Osteoporotic fractures are common and remain a major public health challenge [1–8]. Bone mineral density (BMD), as assessed by dual-energy X-ray absorptiometry (DXA), has largely been accepted as the standard measure for the diagnosis of osteoporosis (Fig. 1). Although it is well established that a T-score of −2.5 or less – that is, osteoporosis as defined by the World Health Organization (WHO) criteria – is associated with a substantial increase in fracture risk, BMD measurement alone does not reliably predict the fracture risk, a bulk of fractures occurring in patients with a T-score higher than −2.5 [9,10]. This raised the need to identify and consider other risk factors besides BMD to improve the identification of high fracture risk individuals. In 2008, a WHO task force introduced the Fracture Risk Assessment Tool (FRAX, www.shef.ac.uk/frax/), which incorporates independent clinical risk factors for fracture, including body mass index (BMI), combined with BMD if available, to predict individual 10-year risk of hip or major osteoporotic fracture [11]. Recent studies have begun to emphasize the potential role of body composition components and their regional distribution, including lean and fat tissues, to fracture risk. In this article, we address recent findings and insights on the contribution of lean and fat mass to fracture risk, together with some hypothesized mechanisms and clinical implications.

BODY COMPOSITION CHANGES WITH AGING
A hallmark of the aging musculoskeletal system is the progressive loss of skeletal muscle mass, termed...
‘sarcopenia’ by Rosenberg in 1989 [12]. Sarcopenia subsequently evolved to encompass also the parallel muscle function decline – termed ‘dynapenia’ – that occurs with aging and substantially outpaces muscle mass loss [13–16]. A consensual operational definition of sarcopenia has still not been reached [14–16]. Hence, several clinical definition and diagnosis criteria have been proposed, based on muscle mass alone [17,18], or in combination with muscle function (i.e., muscle strength and/or physical performances) [19–21]. Different thresholds for low muscle mass have been recommended in these definitions – including various derivative indicators of appendicular lean mass (ALM; the sum of lean mass in the arms and legs) (Fig. 1) as assessed by DXA – [22], but data for these candidate criteria for sarcopenia against hard outcomes are still sparse.

A concomitant increase in whole-body and regional fat deposits is also a typical manifestation of aging, even without changes to body weight [23–26]. Fat is redistributed from subcutaneous to visceral depots, with an increase in abdominal fat and fat deposition in ectopic sites (e.g., skeletal muscle or bone marrow) [26–30]. Obesity characterizes the abnormal accumulation of body fat and has been defined by the WHO as a BMI of 30 kg/m² or more [31]. However, it is well known that BMI is an imperfect proxy of body fatness mainly because it does not differentiate between lean from fat tissue. Also, there is compelling evidence that the distribution and type of excess fat may be more relevant to health than the total amount of body fat or the classification of obesity [23,26,32–36]. Especially, visceral adipose tissue (VAT) has been related to the development of numerous negative health outcomes, including mortality [37].

Body composition assessment – or the measurements of amount and distribution of body fat and fat-free tissues – extends beyond BMI [38]. DXA has gained interest and acceptance as a reference method, particularly because of its wide availability, relatively low cost, fast acquisition time, and low radiation exposure, compared to other available techniques including magnetic resonance imaging and computed tomography (CT), the gold-standard technique [9,22,39–41]. In order to discriminate between different types of adipose tissue, new tools have been developed, allowing in particular VAT measurements (Fig. 1) [40,42,43].

RECENT INSIGHTS INTO THE CONTRIBUTION OF LEAN AND FAT MASS TO FRACTURE RISK ASSESSMENT

Studies investigating the association between body composition components and fracture risk have mainly focused on bone health, especially BMD as a surrogate marker for future fracture risk. Both lean and fat mass have been positively correlated with BMD, but their relative contribution has been highly controversial [44]. In a meta-analysis of 44 studies (n = 20,226; 75% women; age 18–92) Ho-Pham et al. [44] reported prominent effect of lean mass on BMD as compared to fat mass, when combined men and women. Beyond bone density, several studies have reported positive association between lean mass and bone geometry, microarchitecture and strength estimates [45–48].

Regarding fat, the relationship with bone health appears more controversial and complex, the different patterns of distribution and types of fat-tissue depots likely influencing this relationship, and requires further elucidation [45,49,50,51–55]. Recent evidence suggests a positive association between fat mass and especially trabecular microarchitecture [45]. Also, some studies are in favor of a protective or neutral effect of subcutaneous depots, but a negative effect of VAT on bone structure, microstructure and strength [52–54].

Studies addressing the independent contribution of lean mass to future fracture risk are scarce. Recently, the predictive value of low lean mass, as defined by several thresholds used in various operational definitions of sarcopenia, against fractures, was examined for the first time, in a large homogeneous cohort of 65-year-old community-dwellers (n = 913; 80% women; mean age 65 ± 1 years) from the GERICO study [56*]. Low lean mass, as defined by Baumgartner thresholds, was found to be associated with higher fracture risk over 3 years, independently of FRAX probability with BMD [odds ratio (OR), 2.32; 95% confidence interval (CI), 1.04–5.18] or low BMD (Fig. 2). It also added significant predictive value beyond FRAX (likelihood ratio test for nested models, 4.28; P < 0.039). In this study, data were likely to be influenced by the sarcopenia
More recently, Sornay-Rendu et al. [57**] showed among postmenopausal women ($n = 595$; mean age $66 \pm 8$ years) enrolled in the OFELY cohort and followed-up over 13 years, that each SD increase of lean mass indices (i.e., total lean mass/height$^2$ and ALM/height$^2$), were associated with significantly decreased fracture risk, independently of BMD and clinical risk factors including falls (adjusted hazard ratios of 0.76 for both of $P \leq 0.02$), and with a predominant role of ALM on fracture risk.

These recent findings contrast with few previous studies having failed to find any independent association between low lean mass and fracture incidence [58–63]. Even, in one recent nested case-cohort study, lower ALM/height$^2$ was paradoxically protective of hip fracture risk in men after accounting for hip BMD, but this remains to be fully investigated [64]. The discrepancies between recent study findings and those of earlier researches are likely to be explained by the focus of hip fractures only or the methodologies employed including failure to take into account ALM [57**].

Recent findings also provided first insight into an additive risk of low lean mass and osteoporosis...
In Hars et al. study, the coexistence of sarcopenia and densitometric osteoporosis was associated with a 3.4-fold increase in low trauma fracture risk. When defining sarcopenia as a combination of low lean mass and function, Chalhoub et al. and Yu et al., also highlighted a potential strong role of sarco-osteoporosis in fracture risk in older men. Scott et al. investigated the associations between sarcopenic obesity (i.e., with sarcopenia and obesity defined as the lowest sex-specific tertiles for ALM and the highest sex-specific tertile for total fat mass, respectively) and its components with incident fractures (n = 1089; 51% women; mean age 62 ± 7 years). Sarcopenic obese older men had over threefold higher rates of nonvertebral fractures over 10 years compared with both nonsarcopenic nonobese or obese alone counterparts, after accounting for total hip BMD. Sarcopenic obese women also had higher fracture rates compared with obese alone, but this was mediated by BMD. In another cohort, Scott et al. also revealed the negative impact of the coexistence of sarcopenia, defined as a combination of low lean mass and function, and obesity on fracture, but data were likely to be influenced by the sarcopenia definition retained.

Relatively few prospective studies have investigated the independent contribution of fat mass to the risk of fracture, and even fewer, the impact of different distribution and type of excess fat. Most studies in the field have focused on BMI despite it represents an imperfect measure of body fatness. Low BMI has been well documented as a risk factor for fracture, especially low BMI being a significant BMD-independent risk factor for hip fracture [68]. Conversely, high BMI has been widely accepted to be protective against fractures, however, some studies have revealed that fractures are frequent in obese individuals and suggested that obesity increases fracture risk at certain location independently of BMD [35,68–74]. Recent data regarding the relationship between high BMI and fracture risk, not all unanimous, have suggested that this relationship differ by anatomic site and gender [68,75,76]. Especially, some evidence point positive association between BMI and the risk of humerus or ankle/lower leg fractures in women [68,77]. In males, data are less available.

The prospective association between fat-related indices (i.e., direct assessment of body composition) and fractures has not been well documented. Some studies, including a large one by Leslie et al. [61,62] (n = 40,050 women and 3600 men, age ≥50 years), have shown that lower fat mass is predictive of hip and osteoporotic fractures, but the associations were lost when considering BMD or FRAX probability. Emerging data suggest that regional adiposity measures might add predictive information over and above BMD, despite data still remain controversial. More importantly, most of the studies fail to adequately consider the role of potential confounding and mediating factors making it difficult to determine the true independent contribution of these regional fat storages. Especially, a growing body of studies has focused on indicators of abdominal obesity as assessed by DXA. Recently, Sornay et al. [57**] showed that increased visceral and...
subcutaneous abdominal fat mass were associated with decreased major osteoporotic fractures risk in postmenopausal women (n = 595; mean age 66 ± 8 years), but the association was weakened after adjustment for BMD and did not persist after accounting for competing risk of death. Conversely, in Machado et al. [78*] study (n = 433 women; men age 73 ± 5 years), higher VAT had a significant association with incident nonspine fractures over 4.3 years but only in nonobese women, even after adjustment for BMD.

In recent years, the fatty degeneration of thigh muscles has also gained attention. Lang et al. [60] reported that decreased thigh muscle Hounsfield unit values obtained by CT-lower values indicating greater fatty infiltration of muscle – was associated with increased risk of hip fracture in men and women, independently of BMD. At thigh level, decreased DXA-derived subcutaneous fat thickness was also recently found to be strong contributors to hip fracture risk in men and women, independently of BMD and other clinical risk factors [64].

**HYPOTHESIZED MECHANISMS**

Low lean mass may act on fracture through increased fall risk. Low muscle mass may lead to reduced muscle strength and physical impairments and in turn increase the risk of falls. In a recent retrospective longitudinal study comparing several operational definitions of sarcopenia as predictor of prospective incidence of falls, falls risk was selectively predicted by the Baumgartner et al. [79] thresholds. Only few studies have investigated the direct contribution of fat mass to falls, while numerous studies have shown that high BMI imparts an increased fall risk [80]. Recently, it was shown in the CHAMP study, that both nonsarcopenic and sarcopenic obese men (with sarcopenia defined using EWGSOP definition) [21] had significantly higher 2-year fall rates compared with with nonobese men [67]. While adiposity may cushion the fall impact at some bone sites, the site-specific association found in certain studies may conceivably be largely explained by a different fall mechanism in obese individuals [71], with greater impact forces during a fall associated with increase weight for humeral fractures, and excessive stresses over time on bones/joints because of higher loads (e.g., increased joint torque) for ankle fractures.

There is emerging research in the connections between muscle, fat, and bone, as evidenced in several recent reviews [35,38,81–90]. Main mechanisms behind the adverse effect of muscle loss on bone status include decreased mechanical stimuli, followed by a deregulation of systemic signals including sex hormones and regulating metabolism hormones, and a modulation of expression of local factors, including proinflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha) [87]. If the protective effect of fat on bone may mainly be attributed to greater mechanical load and hormonal factors (e.g., increased secretion of insulin and amylin from pancreatic β-cells, increased levels of sex-hormones, increased aromatization of androgen to estrogen), certain adipokines such as the leptin and adiponectin have shown both positive and negative effects on bone, whereas fat may exert a negative effect on bone by increased proinflammatory cytokines and imparting insulin resistance, especially for VAT [89]. Of note, recently, it was shown recently that VAT may not have a prominent effect on bone microarchitecture and skeletal strength independently of BMI or weight, suggesting that the increased risk for fractures associated with higher VAT found in certain studies may be attributable to other factors, especially skeletal loading [51]. As opposed to this, Sundh et al. [50**] recently showed that only local adipose tissue (i.e., subcutaneous tibia fat) was inversely associated with cortical density and positively associated with cortical porosity at distal tibia, suggesting a local adverse effect of adipose tissue on bone, rather than systemic (Fig. 3).

Finally, recent studies have also emphasized the role of bone marrow adiposity in skeletal health and metabolism [91–94].

**CLINICAL IMPLICATIONS**

The evidence aforementioned suggest that clinicians should recognize the potential role of muscle...
wasting in determining fracture risk among older patients and that measures of lean mass, especially ALM – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. This is also the case for obese patients who may be at exacerbated risk of fracture. Further studies should help to determine the contribution of lean mass in refinements of FRAX and other fracture prediction models.

The actual available evidence, especially from recent comparisons of sarcopenia definitions against falls and fractures, suggest that Baumgartner definition (i.e., based on ALM/height\(^2\) two standard deviations below the mean of a young reference group, an analogy with osteoporosis; 5.45 kg/m\(^2\) in women and 7.26 kg/m\(^2\) in men) \([17]\) may represent a reasonable approach of sarcopenia, particularly among nonobese older adults, although more validation studies are required \([79,95]\). Of note, the inclusion of functional measures in the definition of sarcopenia did not confer a better predictive value for incident falls \([79]\). Furthermore, without denying or minimizing the importance of functional measures, a sarcopenia definition based on low ALM/height\(^2\) alone is suggested as particularly suitable for early diagnosis and intervention due to the low prevalence found when using a composite definition of sarcopenia combining both low muscle mass and function \([95]\). For example, in two homogeneous cohorts of 68-year and 63-year-old men and women – that is, the GERICO cohort \((n = 767)\) and a nationally representative British birth cohort \((n = 1566)\), respectively – \([96,97]\), low lean mass (i.e., ALM/height\(^2\)) prevalence ranged from 10.7 to 30.7%, whereas the prevalence of low lean mass combined with either weakness or slowness was considerably lower, between 1.3 and 7.3%, with overall higher prevalence found in women. This higher prevalence gives more sensitivity for screening purpose, and thus a better chance to offer preventive interventions. Given the recent establishment of an ICD-10 (M62.84) code for sarcopenia, major steps forward are expected in the near future, especially regarding candidate criteria for sarcopenia, which should help to refine clinical recommendations \([15]\).

More evidence is needed to support certain fat-related indicators in fracture risk prediction, but regional adiposity measures appear promising. Future work, especially using more appropriate imaging techniques as CT and comprehensive sets of risk factors, are needed to shed light on the role of fat accumulation and distribution on future fracture risk.

The lack of association found in certain studies does not imply that body composition assessment may not be useful for a given set of patients and should not contradict the importance of soft tissues in the pathogenesis of osteoporotic fractures.

**CONCLUSION**

Recent studies have begun to emphasize the independent contribution of low lean mass to fracture risk among older adults, suggesting that identification of low lean mass – which can be assessed simultaneously with the BMD measurement – should be considered in fracture risk assessment beyond BMD and clinical risk factors. Further studies in the field should help to elucidate whether interventions effective at attenuate, prevent, or ultimately reverse lean mass loss or fat accumulation, may prevent fractures.

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**Conflicts of interest**

There are no conflicts of interest.

**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


32. In this elegant work investigating in the same study the risk of fracture by lean mass and fat mass (i.e., total body and abdominal, including visceral and subcutaneous fat), among older women followed up over 13 years, only lean mass and above all appendicular muscle mass indexes were found to be associated with fracture risk independently of BMD and clinical risk factors.


35. In a large cohort of 65-year-old men and women, this study investigated for the first time the predictive value of low lean mass, as defined by several thresholds used in various operational definitions of sarcopenia, against fractures. Low lean mass, as defined by the Baumgartner thresholds, predicted 3-year fracture incidence, independently of FRAX probability with BMD.


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Findings from this large study of older men and women suggest that sarcopenic obesity may contribute to exacerbated fracture risk. Sarcopenic obese older men and women had lower BMD and increased risk of fracture over 10 years, compared with obese individuals. Sarcopenic obese older men had an over three-fold increased rate of fractures compared to those who were nonsarcomenic obese, or obese alone, independently of BMD.


In this study investigating the relationship between DXA-derived visceral fat and the incidence of fractures in a population of elderly women, higher visceral fat was associated with increased risk of nonspine fractures over 4 years in nonobese women, independently of BMD.


