The bone-muscle-adipose tissue axis: mechanisms and clinical implications

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ABSTRACT

The prevalence of obesity, osteoporosis, and sarcopenia has increased dramatically over recent decades, contributing to frailty, disability, and reduced quality of life, particularly in aging populations. While excess body weight was traditionally considered protective for skeletal health due to increased mechanical loading, accumulating evidence indicates that adiposity, especially when centrally distributed and associated with metabolic dysfunction, may adversely affect bone quality and increase fracture risk despite normal or elevated bone mineral density.

Bone, skeletal muscle, and adipose tissue are now recognized as components of an integrated biological system that communicates through endocrine, paracrine, and inflammatory pathways and shares common progenitor cells. Adipokines, myokines, and osteokines regulate tissue remodeling, energy metabolism, and insulin sensitivity, linking alterations in body composition to musculoskeletal and metabolic disorders. Aging amplifies these interactions through progressive muscle loss, visceral fat accumulation, hormonal changes, and chronic low-grade inflammation, giving rise to emerging clinical phenotypes like osteosarcopenic obesity.

This review summarizes current clinical and biological evidence on the interactions among obesity, skeletal muscle, and bone, and discusses the implications of these relationships for integrated lifestyle-based interventions aimed at preserving musculoskeletal integrity and metabolic health across the lifespan.

KEYWORDS

Excess adiposity, body composition, body mass index, bone mineral density, skeletal muscle, sarcopenia, osteosarcopenic obesity.

Introduction

The global prevalence of obesity and osteoporosis has increased dramatically over recent decades, placing a growing burden on healthcare systems worldwide. Obesity is one of the major risk factors for cardiometabolic diseases, while osteoporosis is a leading cause of fragility fractures, disability, and loss of independence in older adults [1]. In parallel, the progressive decline of skeletal muscle mass and strength with aging, defined as sarcopenia, further contributes to frailty, mobility limitations, and increased mortality [2].

Initially, obesity and osteoporosis were viewed as unrelated conditions. Excess body weight was traditionally considered beneficial for skeletal health, based on the assumption that greater mechanical loading would stimulate bone formation and result in higher bone mass [3]. However, accumulating clinical and experimental evidence has challenged this interpretation, showing that adiposity may exert complex and potentially detrimental effects on bone, particularly when fat accumulation is predominantly visceral and associated with metabolic disturbances [4,5].

Aging is accompanied by profound changes in body composition. The progressive loss of muscle mass and strength in aging occurs in parallel with an increase in fat mass and a redistribution of adipose tissue toward visceral depots [3,6,7]. These changes occur alongside hormonal alterations, chronic low-grade inflammation, and reduced physical activity, all of which contribute to musculoskeletal deterioration and metabolic dysfunction [8].

In recent years, bone, skeletal muscle, and adipose tissue have come to be recognized as components of a tightly integrated biological system (Figure 1). Since they communicate through endocrine and paracrine signaling and originate from shared progenitor cells, these tissues operate via highly interdependent regulatory mechanisms. Within this context, the concept of osteosarcopenic obesity has emerged, describing the concurrent impairment of muscle, adipose, and bone compartments [9-12].

This review provides an integrated overview of the interactions among obesity, bone tissue, and skeletal muscle.

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Obesity and skeletal health: beyond the mechanical paradigm

Obesity is characterized by excessive fat accumulation and is strongly associated with cardiovascular diseases and other metabolic complications [13]. Osteoporosis is a metabolic bone disorder defined by reduced bone strength due to alterations in bone mass and microarchitecture, leading to an increased risk of fragility fractures [14]. Previously, higher body weight was considered protective against osteoporosis, as individuals with elevated body mass index (BMI) generally exhibit higher bone mineral density (BMD) values [15]. However, BMD alone does not fully capture bone strength or fracture risk. A more refined understanding of the relationship between adiposity and bone emerges when body composition is considered. When obesity is defined according to fat mass rather than BMI, its apparent protective role largely disappears. Indeed, high fat mass has been inversely associated with bone mass in premenopausal women [16], and trunk fat has been shown to correlate negatively with BMD in both sexes [17]. Moreover, vertebral fractures have been reported even in young women with severe obesity [18]. Beyond total fat mass, visceral adiposity has emerged as a major determinant of skeletal fragility. Excess central fat accumulation is associated with reduced bone strength and increased fracture risk [7,19]. The relationship appears particularly pronounced in severe obesity, where metabolic, inflammatory, and endocrine alterations may further compromise bone quality [3].

Endocrine and inflammatory mechanisms linking adipose tissue and bone

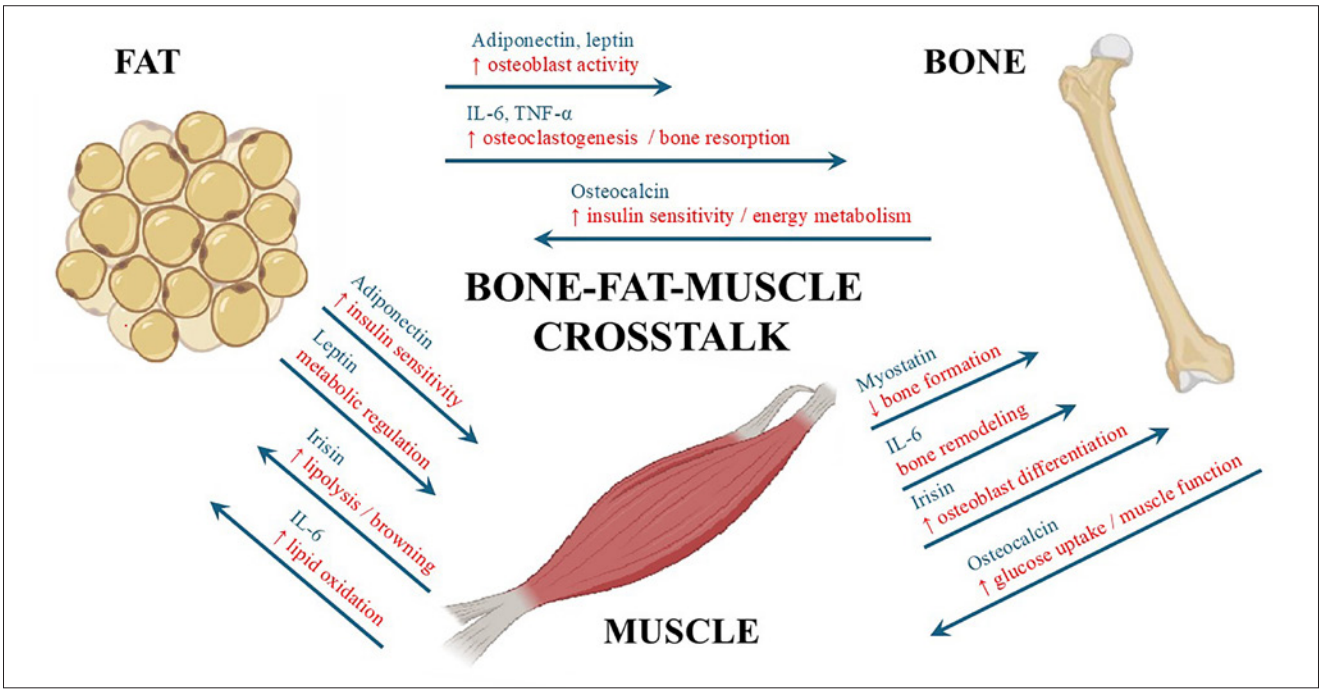
Adipose tissue, as an active endocrine organ, secretes adipokines, cytokines, and growth factors that influence metabolism, inflammation, and tissue remodeling [20]. Leptin has been extensively studied for its effects on bone, which appear to depend on central and peripheral signaling pathways. Peripheral leptin may promote osteoblast activity, whereas central leptin signaling suppresses bone formation [20]. Circulating leptin levels are often positively associated with BMD in postmenopausal women [20]. Adiponectin, typically reduced in obesity, promotes osteoblast differentiation and inhibits osteoclast activity [20]. Pro-inflammatory cytokines including IL-6 and TNF-α promote osteoclast differentiation and activity while inhibiting osteoblast function, thereby shifting bone remodeling toward resorption and impairing bone quality [21]. Overall, these alterations contribute to reduced bone strength and increased fracture risk.

At the cellular level, adipocytes and osteoblasts derive from a common mesenchymal stem cell population. The balance between adipogenic and osteogenic differentiation is regulated by molecular pathways. Disruption of this balance, driven by inflammation, hormonal changes, or metabolic dysfunction, may favor marrow adiposity at the expense of bone formation [22]. Moreover, bone itself is recognized as an endocrine organ that releases factors such as osteocalcin and osteopontin, which influence glucose metabolism, insulin sensitivity, and energy homeostasis [23].

Skeletal muscle as a central regulator of metabolic and skeletal homeostasis

Skeletal muscle is the largest organ of the human body and plays a fundamental role in whole-body metabolism. In addition to its mechanical function, muscle acts as an endocrine organ by secreting myokines that influence adipose tissue function [24]. Irisin, IL-6 and myostatin regulate lipolysis, adipogenesis, and insulin sensitivity.

Figure 1 The bone-muscle-fat crosstalk.



Among muscle-derived factors, IL-6 represents a paradigmatic example of a molecule with dual and context-dependent effects. While transient increases during exercise exert beneficial metabolic effects (including enhanced glucose uptake, increased lipid oxidation, and improved insulin sensitivity), chronic elevation of IL-6 under conditions of low-grade inflammation (e.g., obesity and aging) promotes catabolic processes in skeletal muscle [25]. In this context, IL-6 is associated with increased muscle protein degradation, impaired muscle regeneration, and the development of muscle atrophy. Moreover, chronic IL-6 exposure contributes to insulin resistance and may exacerbate the decline in muscle mass and function, thereby linking systemic inflammation to sarcopenia and metabolic dysfunction [25]. Adipose tissue, in turn, secretes adipokines that modulate muscle glucose uptake, lipid oxidation, and inflammatory status. Adiponectin enhances muscle insulin sensitivity, whereas excess leptin and inflammatory mediators promote insulin resistance and muscle protein breakdown [24]. Physical activity and nutritional strategies are key modulators of this reciprocal endocrine communication.

Beyond the specific role of IL-6, chronic low-grade inflammation associated with visceral obesity also significantly impacts skeletal muscle metabolism. Persistent exposure to pro-inflammatory cytokines promotes anabolic resistance, impairs muscle protein synthesis, and enhances proteolytic pathways, thereby contributing to muscle wasting. These effects are mediated, at least in part, by the activation of catabolic pathways such as the ubiquitin-proteasome and autophagy-lysosome systems, along with the inhibition of anabolic signaling pathways including the IGF-1/Akt/mTOR axis [26]. Moreover, inflammation-induced insulin resistance further exacerbates metabolic dysfunction across tissues, reducing glucose uptake and impairing energy utilization in skeletal muscle [8]. Chronic inflammation is also associated with mitochondrial dysfunction and increased oxidative stress, which further contribute to muscle deterioration [26]. Skeletal muscle and bone are anatomically and functionally interconnected. Mechanical forces generated by muscle contraction stimulate bone formation, but endocrine signaling also plays a critical role. Muscle-derived factors such as irisin promote osteoblast differentiation, whereas myostatin inhibits osteogenic pathways [27]. IL-6 also participates in the regulation of bone remodeling by modulating osteoclast and osteoblast activity [28]. Bone-derived molecules such as osteocalcin and sclerostin influence muscle metabolism and function. Osteocalcin enhances muscle glucose uptake and insulin sensitivity, while elevated sclerostin levels have been associated with muscle atrophy [27]. Alterations in muscle-bone communication contribute to age-related conditions such as osteoporosis and sarcopenia. Integrated interventions combining resistance exercise and adequate nutritional intake are therefore essential for preserving musculoskeletal health [29].

Aging, body composition, and metabolic health

Aging is accompanied by a progressive and interrelated remodeling of muscle, adipose, and bone tissues. From midlife onward, a steady decline in skeletal muscle mass and strength leads to sarcopenia [2], a condition consistently associated with reduced mobility, increased risk of falls and fractures, loss of independence, and higher mortality [2].

At the same time, body composition shifts toward a preferential accumulation of visceral adipose tissue and increased fat infiltration within skeletal muscle (myosteatosis) [13]. These alterations are associated with adipocyte hypertrophy, altered stem cell differentiation, chronic low-grade inflammation, and broader metabolic dysfunctions [30].

In parallel, bone undergoes age-related deterioration, a process markedly accelerated in postmenopausal women due to estrogen deficiency. The consequent development of osteoporosis substantially increases the risk of fragility fractures and contributes to adverse health outcomes [31].

Taken together, the convergence of these alterations underpins osteosarcopenic obesity, a clinical condition characterized by the concurrent presence of reduced bone mass, impaired muscle mass and function, and excess adiposity [9]. The coexistence of these alterations, compared with each condition alone, results in compounded adverse outcomes, including worsening physical performance, increased risk of falls and fractures, and reduced quality of life, particularly in older adults. The pathophysiology of osteosarcopenic obesity reflects the integrated effects of chronic low-grade inflammation, endocrine dysregulation, and altered stem cell differentiation, as discussed above, which collectively promote muscle loss, bone fragility, and adipose tissue dysfunction. Importantly, this condition also poses diagnostic challenges, as traditional indices such as BMI or BMD alone may underestimate the underlying alterations in body composition and tissue function [9-12].

Lifestyle interventions

The growing recognition of the interdependence between adipose tissue, skeletal muscle, and bone has important clinical implications. Therapeutic strategies should move beyond isolated, disease-specific approaches and adopt integrated lifestyle interventions targeting body composition, metabolic health, and functional capacity.

Weight loss remains central to the management of obesity, but energy restriction and bariatric surgery have been associated with bone loss and reductions in lean mass, particularly in older adults and postmenopausal women [32]. Nutritional strategies should therefore aim to counteract anabolic resistance while avoiding excessive energy restriction that may compromise bone and muscle health [29]. Adequate protein intake is essential, particularly in older individuals [9,29,33]. Diets providing adequate protein intakes, with an appropriate distribution across meals and an emphasis on high-quality protein sources rich in essential amino acids, support muscle protein synthesis and may contribute to the preservation of lean mass during weight loss [33].

Micronutrient adequacy, including calcium and vitamin D, is essential for preserving BMD and neuromuscular function, while other nutrients such as magnesium, vitamin K, potassium, iron, and zinc contribute to bone remodeling, muscle per-

formance, and oxidative balance [29].

Dietary patterns rich in antioxidant compounds may further support the muscle-bone-adipose tissue axis. Diets rich in fruit, vegetables, whole grains, and omega-3 fatty acids are associated with reduced inflammation and improved metabolic profiles [29].

Physical exercise represents a fundamental intervention for preserving musculoskeletal and metabolic health across the lifespan. Resistance and impact-loading exercise are particularly effective in stimulating osteogenesis, preserving bone mass, and promoting muscle hypertrophy and strength [29,34]. Aerobic exercise contributes to the reduction of fat mass and visceral adiposity, while improving cardiovascular fitness and insulin sensitivity. In addition, balance and functional training reduce fall risk and improve neuromuscular coordination, which are critical outcomes in individuals with osteoporosis, sarcopenia, and obesity [29,34].

In individuals with frailty, mobility limitations, or multiple comorbidities, alternative or adjunctive strategies such as low-impact exercise modalities and supervised rehabilitation programs may be required to ensure safety and adherence [29].

Conclusions

Obesity, osteoporosis, and sarcopenia are increasingly recognized as interconnected conditions that share biological pathways involving endocrine regulation, inflammation, and alterations in stem cell differentiation. Excess adiposity, particularly visceral fat, may compromise bone quality despite elevated BMD, while age-related muscle loss contributes to functional decline and metabolic dysregulation. Within this integrated framework, osteosarcopenic obesity emerges as a comprehensive phenotype reflecting the cumulative burden of concurrent alterations in muscle, bone, and adipose tissue, and emphasizing the need for multidimensional prevention and treatment strategies.

Future research should further clarify the molecular mechanisms governing bone-muscle-adipose tissue crosstalk and support the development of targeted strategies aimed at preserving musculoskeletal integrity and metabolic health across the lifespan.

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