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REVIEW ARTICLE

Osteoporosis and Obesity

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Abstract

Introduction This article concisely overviews the complex relationship between obesity and bone health. Obesity, characterized by excessive fat accumulation, has been traditionally associated with higher bone mineral density. Also, recent data suggest a favorable bone microarchitecture profile in these patients. However, the increase in bone mineral density does not necessarily confer protection against fractures, and the risk of fractures may vary depending on the skeletal sites.

Factors affecting bone health Various factors, including mechanical factors, hormones, cytokines, inflammation, and bone marrow adiposity, contribute to the adverse effect of obesity on bone. The article explores these factors alongside non-invasive techniques and tools like the Fracture Risk Assessment (FRAX) to evaluate fracture risk.

Bone and Adipose tissue This article also highlights the essential roles of hormones such as vitamin D, Parathormone (PTH), FGF-23 (Fibroblast Growth Factor 23), which affect bone health, and some of the hormones secreted from the adipose tissues such as adiponectin and leptin.

Obesity Paradox and Sarcopenic Obesity The article delves into the intriguing obesity paradox, where an increased BMI correlates with higher bone mineral density but not necessarily reduced fracture risk. Sarcopenic obesity, a combination of excessive fat accumulation and reduced muscle mass, further complicates the relationship between obesity and bone health.

Conclusions Physicians should keep a comprehensive approach to treating obese patients with osteoporosis, including lifestyle modifications, weight management, fall prevention strategies, and pharmacological interventions. Further research is needed to better understand the relationship between obesity and bone health.

Keywords Adipose tissue · Bone mineral density · Obesity · Osteoporosis · Fracture

Introduction

Obesity and osteoporosis are two significant health concerns that impact individuals worldwide. Obesity is characterized by excessive accumulation of fat, and osteoporosis is a condition with reduced bone density and strength, both contributing to increased morbidity and mortality. Interestingly, these seemingly distinct conditions are interconnected through complex mechanisms that influence bone health. This article explores the intricate relationship between obesity and osteoporosis, delving into the effects of obesity on bone health, the impact of osteoporosis on individuals with obesity, and the challenges faced in managing these individuals with osteoporosis. Various aspects, including the endocrine functions of bone, assessment of bone health, the effect of obesity and sarcopenic obesity on bone health, and treatment strategies, have been discussed in this article. By shedding light on the intricate connections between obesity and osteoporosis, this article aims to contribute to a deeper understanding of these conditions, ultimately guiding healthcare professionals and individuals toward improved strategies for prevention, early detection, and treatment.

Basics of Bone

Bone is a composite structure comprised of organic and inorganic components. The inorganic component accounts for approximately two-thirds of the bone mass, while the

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organic component constitutes about one-third. The organic portion primarily comprises type I collagen and non-collagenous proteins such as osteopontin and osteocalcin. The cells, including osteocytes, osteoblasts, and osteoclasts, comprise a small percentage (1–2%) of the organic composition. On the other hand, the inorganic component mainly consists of calcium, phosphorus, and magnesium. These minerals contribute to the rigidity and strength of the bone structure. Three key regulators play significant roles in bone mineral metabolism: 1,25(OH)2Vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). 1,25(OH)2Vitamin D enhances the absorption of calcium and phosphorus from the intestine. PTH increases calcium levels while decreasing phosphorus levels through phosphaturia. FGF23 is a major player in phosphorus metabolism, promoting phosphaturia. It also inhibits both PTH and 1-alpha hydroxylase, thereby reducing the levels of active vitamin D (1,25(OH)2Vitamin D). These regulatory factors work in concert to maintain the balance of minerals crucial for bone health.

Bone as an Endocrine Organ and the Relationship of Bone and Obesity

In addition to providing structural support, bone serves as a multifunctional organ with endocrine capabilities. Several factors are secreted by bone cells, acting in both endocrine and paracrine manners. Among these factors, fibroblast growth factor 23 (FGF23) plays a pivotal role as the predominant hormone regulating phosphate homeostasis. FGF23 acts on sodium phosphate co-transporters primarily in the proximal tubules, leading to phosphate excretion. Furthermore, FGF23 modulates calcium homeostasis by inhibiting parathyroid hormone and the 1-alpha hydroxylase enzyme, thereby reducing the conversion of 25(OH) Vitamin D to its active form, calcitriol [1,25 (OH)2]. Osteoprotegerin, sclerostin, and osteocalcin are other important factors produced by bone cells, regulating the functions of osteoblasts and osteoclasts. Bone's involvement in energy metabolism is exemplified by osteocalcin, which is produced by osteoblasts. Osteocalcin, directly and indirectly, influences insulin sensitivity, beta cell function, and fat metabolism by impacting adiponectin production from adipose tissue. Thus, bone exhibits direct and indirect effects on glucose and fat metabolism, while obesity reciprocally influences bone health.

Methods of Assessment of Bone Health

Fractures are a significant concern due to their association with increased mortality risk, particularly in the elderly. Detecting individuals predisposed to fractures is crucial for effective fracture prevention. Bone health assessment evaluates three key parameters: quantity, quality, and strength. Various methods, categorized as invasive or non-invasive, have been developed for assessing these parameters.

Bone biopsy with tetracycline labeling has been considered the gold standard for evaluating bone health, but its invasive nature limits its widespread use. Advancements in radiology have enabled non-invasive assessment techniques. Dual-energy X-ray absorptiometry (DXA) is the most widely available method for measuring bone quantity. Quantitative ultrasound is another technique, albeit less commonly used. In terms of bone quality, bone biopsy was previously the sole method, but high-resolution peripheral quantitative CT (HR-pQCT) now allows non-invasive measurement of bone quality parameters at the distal ends of long bones, such as the radius and tibia.

To assess fracture risk, the Fracture Risk Assessment Tool (FRAX) questionnaire was developed in 2008. It incorporates factors such as parental history of hip fracture, previous fracture history, smoking status, rheumatoid arthritis, and secondary osteoporosis. The FRAX score predicts the risk of hip fracture and major osteoporotic fracture. A calculated FRAX score of 20% or higher for major osteoporotic fracture or 3% or higher for hip fracture indicates the need for pharmacological treatment.

By utilizing these assessment tools and identifying individuals at high risk of fractures, healthcare professionals can implement appropriate preventive measures and interventions to reduce the burden of fractures and improve bone health.

Obesity

Obesity is the term used to denote the excessive accumulation of fat, which leads to an increased risk of health predisposition to various ailments. Various parameters can be used for quantifying obesity, and one of the critical parameters is BMI; however, it is not a perfect parameter to measure obesity. BMI is derived by dividing the person's body weight in kilograms by the square of the person's height in meters. BMI is expressed in Kg/m^2. According to WHO, a BMI of more than 25 is defined as overweight, and a BMI of more than 30 is defined as obesity [1]. However, the cut for Asians is different; overweight is defined as a BMI of more than 23, and obesity as a BMI of more than 25 (Table 1). However, this definition does not give us information regarding the relative muscle or fat mass percentage. Two people can have the same BMI, but body composition might differ because of different body fat and muscle mass percentages. People with obesity and decreased muscle mass, termed sarcopenic obesity, are more at risk of various health ailments. Sarcopenic obesity is found to have adverse effects on bone

Table 1 BMI cutoff for classification of obesity in general population and Asians

Classification	General population (BMI)	Asians (BMI)
Underweight	< 18.5	< 18.5
Normal	18.5–24.9	18.5–22.9
Overweight	25–29.9	23–24.9
Obese	≥ 30	≥ 25

BMI body mass index, kg/m^2

and predispose to poor bone microarchitecture, compared to obese people with the same BMI without sarcopenia.

Sarcopenia and Obesity

Sarcopenia is a condition characterized by the progressive loss of muscle mass, which leads to impaired muscle function and strength. It poses a significant health risk as it increases the likelihood of falls, fractures, and mortality. Sarcopenic obesity, a condition marked by the coexistence of obesity and sarcopenia, compounds the health consequences. The combination of excess fat accumulation and muscle mass loss creates a detrimental synergy that amplifies morbidity and mortality in affected individuals, creating a vicious cycle.

Sarcopenia initiates a decline in physical activity, which contributes to fat accumulation and subsequent obesity. Obesity, in turn, exacerbates the adverse effects of sarcopenia, leading to various comorbidities such as insulin resistance, metabolic dysfunction, and type 2 diabetes mellitus. These conditions, coupled with chronic inflammation, further accelerate muscle mass loss, perpetuating the vicious cycle.

Preventing sarcopenic obesity requires a multifaceted approach. Adequate protein intake is essential to maintain muscle mass, while regular physical activity, including resistance training exercises, helps preserve muscle function. Adopting healthier lifestyle habits encompassing a balanced diet and increased physical activity is crucial for preventing sarcopenic obesity and its associated complications.

Effect of Adipose Tissue on Bone

Adipose tissue (AT) consists of fat cells distributed all over the body in the subcutaneous or visceral adipose tissues around the internal organs. The function of adipose tissue varies from organs as energy storage regions to endocrine organs secreting various factors that regulate energy metabolism and affect various organ systems. AT also has various other functions, such as insulin sensitivity, blood pressure regulation, endothelial function, coagulation, and inflammatory response. There are two types of adipose tissue, namely white and brown adipose tissue, which are energy-storing tissue and site of non-shivering thermogenesis. Hence, brown adipose tissue helps in fighting obesity.

Numerous hormones are secreted from adipose tissue, and these hormones exert complex effects on bone cells, ultimately influencing bone health. Leptin and adiponectin are the two major hormones secreted by brown adipose tissue. They directly affect bone cells, including stem cells, osteoblasts, and osteoclasts [2, 3]. Leptin promotes the bone marrow stromal cells to develop into osteoblasts and prevent them from getting differentiated into adipocytes, increasing ALP, osteocalcin, and type I collagen [3, 4]. Leptin has a negative influence on osteoclasts [5]. Similarly, studies have shown that adiponectin, directly and indirectly, affects bone cells [6, 7]. Various cytokines secreted from the adipose tissue, IL-6, and TNF-alpha, also affect bone metabolism negatively. Brown adipose tissue, mainly expressed in newborns, is also expressed in adults in a minimal amount and decreases with age. Evidence suggests that brown adipose tissue also positively affects bone metabolism.

The Obesity Paradox

It has been shown in the medical literature that an increase in BMI is associated with increased bone mineral density. Even though the BMD is higher, the risk of fracture is not decreased; rather, the risk of fracture is increased at the ankle, legs, and humerus. This phenomenon is known as the obesity paradox.

Historically, it is believed that obesity positively affects bone, both in terms of bone mineral density and fracture risk [8]. Many older studies have shown a positive correlation between obesity and BMD [8, 9]. In addition, the risk of hip fracture was lower in obese individuals [10]. On the contrary, studies in the recent past have shown contradictory results, documenting an increased prevalence of fragility fractures in postmenopausal obese individuals presenting with fragility fractures [11].

Osteoporosis—Definition and Pathogenesis

Osteoporosis is a skeletal disorder that is characterized by decreased bone mass, leading to fragile bone with an increased risk of fragility fractures. Areal BMD measured by DXA scans are widely used to diagnose osteoporosis. However, DXA scans are not a foolproof method to diagnose osteoporosis. Bone biopsy is required to demonstrate the pathology and diagnosed osteoporosis accurately. The skeletal microarchitecture also deteriorates in osteoporosis,

predisposing the individual to fracture. Previously, bone biopsies were required to study the alterations in the microarchitecture; however, nowadays, High-resolution peripheral quantitative computed tomography (HR-pQCT) can be used to assess the microarchitecture non-invasively. Fuller Albright gave a simple definition of osteoporosis as "too little bone in bone" as early as 1940, which still stands true [12].

Bone Mineral Density and Osteoporosis in Obesity

Traditionally, obesity is thought to be protective for BMD, and studies have shown higher BMD in obese individuals. Many factors were thought to be responsible for the higher BMD in these patients. Both mechanical and metabolic factors have been postulated to be the reason for this observation.

Mechanical Factors

Obese individuals have increased mechanical loading, which is proven to have a positive effect on the bone [13]. Except for the subset of individuals with sarcopenic obesity, obese individuals have higher fat and muscle mass. This results in a favorable effect on bone density by increasing the passive loading and muscle strain on the bone, leading to a positive effect on bone geometry.

Metabolic Factors

The metabolic factors include

1. Hormonal factors
2. Cytokines

Hormones

Estrogens are proven to positively affect BMD, increasing bone formation and decreasing bone resorption, providing a protective effect on the bone. Estrogens are synthesized from androgen precursors by an enzyme called aromatase, which is present in adipose tissues. Estrogen levels have been proven to be higher in obese individuals than in non-obese individuals [14]. Apart from estrogens, other hormonal factors and cytokines play a significant role in determining bone health. However, the evidence to prove the role of these factors still needs to be robust and future studies are warranted to clarify the role. They are leptin, adiponectin, resistin, and cytokines such as IL-6 and TNF-α. The effect of leptin on the bone is still controversial as in vitro studies show a positive impact of leptin on bone formation and inhibit bone resorption [15]; however, in vivo, studies have shown conflicting results both in animal models and in human beings [15–18]. Adiponectin is a hormone produced by the adipose tissue, and it positively affects cardiovascular health and glucose metabolism [19]. Adiponectin is found to have a positive effect on BMD, proven by both in vitro and in vivo studies [8].

Cytokines

Obese patients have higher levels of CRP, TNF-α, and IL-6 levels, and it has been postulated that obesity is a state of chronic inflammation. TNF- α and IL-6 promote osteoclast function leading to increased resorption [20]. In addition, these cytokines reduce the levels of adiponectin, resulting in further detrimental effects on bone. Resistin is secreted from adipose tissue and has a role in promoting insulin resistance. It has been found that the hormone increases cytokines and increases both osteoclastogenesis and osteoblastogenesis; however, the final effect on the BMD is not precisely apparent [21].

Other Factors

1. *High-fat diet* It has been shown that a high-fat diet itself has a negative effect on the bone microenvironment and increases systemic inflammation [21, 22]. High-fat diet induces deterioration of bone quality, predominantly affecting the trabecular bone, and also it increases bone marrow adiposity, which in turn affects the bone negatively [23].
2. *Bone marrow fat* Bone marrow fat content is recently associated with an increased risk of osteoporosis. As age advances, bone marrow fat also increases, and this is found to be associated with the risk of osteoporosis in postmenopausal women [24]. Adipocytes and osteoblasts are derived from a standard mesenchymal progenitor stem cell [25]. Estrogens and possibly PPARγ are postulated to be associated with an increased risk of the stem cells being differentiated into adipocyte lineage rather than osteoblast lineage. Estrogens are found to suppress adipocyte differentiation and induce differentiation into osteoblasts [26]. Hence, estrogen-deficient states, especially postmenopausal women, are associated with increased bone marrow fat deposition. In addition, PPARγ promotes bone marrow stem cell differentiation towards adipocyte lineage rather than osteoblast lineage. Enhanced expression of PPARγ in obese mice is associated with increased adipogenesis and decreased osteoblastogenesis, and reduced expression of the same results and vice versa [27, 28]. Many other factors might also contribute to bone marrow adiposity, and the exact interaction between bone marrow fat deposition and its

role in predisposition to osteoporosis has to be studied in the future.

3. *Vitamin D deficiency and secondary hyperparathyroidism* Obese individuals are thought to have lower vitamin D levels than normal controls [29, 30]. These individuals also have a higher prevalence of secondary hyperparathyroidism, which affects the bone negatively and results in deteriorated bone health [31, 32]. However, it is still controversial whether these individuals are truly vitamin D deficient or only the serum levels are lower as there might be a higher reservoir of vitamin D in the fat tissue.
4. *11-Beta-hydroxysteroid dehydrogenase type 1* This enzyme converts cortisone to cortisol; the latter is the active form that acts on the glucocorticoid receptor to exert its effect. We know that glucocorticoids hurt bone health. This enzyme is present in both adipocytes and osteoblasts [33]. Cytokines such as TNFα and IL-6 upregulate the expression of this enzyme [34]
5. *Visceral versus subcutaneous adiposity* It has been postulated that the visceral adipocytes are more metabolically active and they have higher expression of 11-beta HSD, which in turn results in increased conversion of cortisone to cortisol resulting in a negative impact on bone health. However, future studies are required to prove this hypothesis.

Risk of Falls in Obesity

It has been clearly shown that obesity increases the risk of falls, especially in older individuals. This can be because of direct effects on obesity in performing day-to-day tasks or due to the associated comorbidities in these patients, such as diabetes mellitus, cardiovascular disease, arthritis, and hypertension, which in turn may lead to peripheral neuropathy, autonomic neuropathy, orthostatic hypotension, etc. [35]. Obesity has adverse effects on joints resulting in osteoarthritis, increasing the risk of falls. Reduced physical activity in obese patients results in decreased muscle strength which also contributes to risk of falls. In addition, some of the patients with obesity have predominantly fat mass increased with reduced muscle mass, termed sarcopenic obesity. These patients are at an increased risk of falls as sarcopenia is associated directly with falls [36].

Fracture Risk

Traditionally, obesity is thought to decrease the risk of fractures, predominantly because of its effect on the BMD [37]. However, recent evidence suggests this is partially true, and various studies have contradicting results. One important point to note is that the risk of fractures in obese individuals depends upon the skeletal sites [38–40]. The fracture risk is increased in some of the skeletal sites and decreased in a few. Fracture risk increases at the upper leg, ankles, and proximal humerus but decreases in the vertebra and proximal femur [38, 39]. Even though the fracture risk is increased in some of the skeletal sites, it has been seen that the BMD in these patients is usually preserved or sometimes higher than the age-matched controls.

Sites of Fracture in Obese Individuals

It has already been discussed that obesity increases the risk of fracture at different sites compared to the usual sites of osteoporotic fractures. The ankle, legs, and humerus are the sites where obesity-related fracture risk is higher. Various hypotheses have been put forward for this. One is the hip padding effect because of the excessive fat accumulation. Another factor is the dynamics of falls. In obese individuals, it has been seen that they fall backward or sidewards more commonly compared to non-obese individuals, who fall most commonly to the front. In addition, introversion and extroversion of the ankle might be one of the factors contributing to the increased risk of fractures in the ankle and the legs.

Treatment of Osteoporosis in Obesity

Although there are no specific guidelines addressing the treatment of obesity and osteoporosis as distinct conditions, it is crucial to consider important considerations when managing patients with both conditions. Encouraging lifestyle modifications, such as adopting a healthy diet, implementing weight reduction strategies, and promoting fall prevention measures, should be prioritized for individuals with obesity and osteoporosis. In addition, in all these patients, adequate calcium and vitamin D intake should be ensured. In the realm of pharmacological interventions for osteoporosis, two main categories of drugs are utilized: anti-resorptive agents and anabolic agents. Additional options include selective estrogen receptor modulators (SERMs), hormone replacement therapy (HRT) with estrogen or combined estrogen and progesterone, and calcitonin. Among the anti-resorptive agents, bisphosphonates and denosumab are particularly important. Bisphosphonates can be administered orally or intravenously, with zoledronate being a commonly used intravenous medication. Patients need to be educated about potential adverse effects, such as flu-like symptoms, requiring antipyretics, as well as more serious events such as atrial fibrillation, osteonecrosis of the jaw, and atypical femoral fractures. Before initiating bisphosphonate treatment,

baseline electrocardiogram (ECG) evaluation and assessment by a dental surgeon are recommended. Alternatively, orally administered options include alendronate, risedronate, and ibandronate, which are taken in the morning on an empty stomach, at least 60 min prior to the first meal, with a full glass of water. Remaining upright for the subsequent 60 min after ingestion helps prevent esophagitis associated with the drug. Zoledronate is not advisable for individuals with an estimated glomerular filtration rate (eGFR) below 30 ml/min; in such cases, denosumab can be considered. Denosumab, a fully human monoclonal antibody, acts against the receptor activator of nuclear factor kappa-B ligand (RANKL), impeding its interaction with the RANK receptor. Administered subcutaneously every 6 months, denosumab is prescribed at a dose of 60 μg. Anabolic agents encompass teriparatide, a recombinant form of human parathyroid hormone containing the first 34 amino acids identical to PTH. Another option is an analog of human parathyroid hormone-related peptide (PTHrP), which also consists of 34 amino acids. Both teriparatide and PTHrP analogs are administered via subcutaneous injections. Romosozumab is a monoclonal antibody that inhibits the function of sclerostin. Sclerostin has a negative effect on bone formation by inhibiting Wnt/Beta-catenin signaling pathway.

Conclusion

The relationship between obesity and bone health is complex. Obesity is associated with increased BMD but does not translate into bone quality and strength. Both mechanical and hormonal factors play a role in the detrimental effect of obesity on bone health. Healthcare professionals should understand the impact of obesity on bone health, and obese patients with osteoporosis should be approached holistically with lifestyle modification, weight management, regular exercise, fall prevention strategies, and pharmacological interventions. Further research is required to unravel the underlying mechanisms of the effect of obesity on bone health to identify novel therapeutic targets in this subset of patients.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

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