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The impact of obesity on bone health: an overview

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Abstract

Obesity is a major health problem that has multisystemic consequences. One of the addressed topics in the current investigation regards the influence of obesity on bone metabolism. Despite of the broadly accepted notion that obesity is associated with a positive effect on bone health, recent evidence has challenged this idea by suggesting an increased risk of fracture in specific sites.

Therefore, this review intends to review succinctly the intricate connections between obesity and bone metabolism by addressing the roles of the mechanical, inflammatory, and hormonal factors, among others. It will also focus on the overall impact on bone mineral density and bone fracture occurrence. **(Endokrynol Pol 2022; 73 (6): 954–958)**

Key words: *obesity; bone metabolism; bone mineral density; fractures*

Introduction

Obesity is a major health challenge of modern medicine that results from an imbalance between energy intake and expenditure (influenced by several other factors such as hormonal changes and genetic, environmental, and social factors) [1]. Defined as a body mass index (BMI) ≥ 30 kg/m^2 (and characterized by excessive fat accumulation), this condition is associated with more than 200 pathological conditions that range from those with cardiovascular impact such as diabetes mellitus, dyslipidaemia, and hypertension, to others such as sleep apnoea, osteoarthritis, depression, dementia, and even several types of cancer [2, 3]. During the last 50 years, the prevalence of obesity has grown tremendously, reaching pandemic proportions nowadays (globally, it increased from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women) [3]. Taking into account that this disease is associated with an estimated decrease in life expectancy of between 5 and 20 years (depending on the severity of obesity and its associated comorbidities), it is not surprising that it has been the focus of multiple investigation efforts [3, 4]. One of the controversial topics addressed in recent decades regards its relationship with bone metabolism. Increased body weight has been considered a factor that leads to an increase in bone mass and a decrease in the risk of fracture. Despite this, there is increasing evidence that fat mass accumulation may have a negative impact on fracture risk (mainly when adjusting to patient bone mass) [5, 6]. The remaining controversies around the issue can be explained by the multiplicity of players involved (sometimes with antagonistic effects), which includes adipokines (such as leptin or adiponectin), inflammatory factors, or even the distribution of fat mass [7].

Herein, the intricate connections between obesity and bone metabolism will be succinctly reviewed. In the first phase, the authors address the roles of the mechanical, inflammatory, and hormonal factors (among others). Then they focus on the overall impact on bone mineral density and bone fracture occurrence.

Bone-related consequences of obesity

Obesity was traditionally regarded to have a beneficial effect on bone metabolism, leading to an increase in bone strength and a decrease in fracture risk [8, 9]. Most of the published data supports this hypothesis, which can be explained by several mechanisms.

Mechanical factors

One of the reasons for increased bone mineral density (BMD) among patients with obesity is the augmented mechanical load and strain associated with this disease [10]. Research on body composition revealed

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that obesity is related not only to increased fat mass (with the respective passive loading) but also to increased lean mass and higher induced muscle strain. This ultimately appears to have positive effects on bone modelling, density, and architecture [7], by means of decreased apoptosis and increased differentiation of osteoblasts and osteocytes [11]. Despite the large cross-sectional area of the hip of patients with obesity measured by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) [12, 13], the size of the tibias and radius measured by high-resolution peripheral QCT presented no differences between obese and normal-weight subjects [14]. It thus appears that mechanical factors are not sufficient to explain all the effects of adipose tissue on bone.

Obesity is also associated with increased intramyocellular fat content, which can lead to poor muscle function and augmented fracture risk [15]. The hypothesis that a combination of this compromised muscular function and postural instability [16] predisposes individuals to falls and associated injuries is backed by various articles [17, 18]. The importance of impaired muscle function among elder individuals with obesity has raised increased interest to the concept of sarcopenic obesity. In these cases, the increase in weight is associated with a relative decrease in muscle mass. It is thought that this is due to muscle damage caused by changes in skeletal muscle lipid metabolism, insulin resistance, and adipose inflammatory mediators that result in a preferential mobilization of muscle tissue instead of using adipose tissue as an energy source. These changes usually occur in the setting of physical inactivity (common among individuals with obesity), which is associated with decreased energy expenditure and increased fat mass (adding more fuel to this vicious cycle) [5]. So, it is not surprising that a recent systematic review and meta-analysis reported that older adults with sarcopenic obesity had higher nonvertebral fracture rates and increased falls risk compared with those with sarcopenia alone [19].

In addition, it is also believed that although the value of BMD is greater among subjects suffering from obesity, BMD might not be sufficiently increased to face the larger impact forces that occur when such falls happen, or when other types of biomechanical traumas harm the skeleton [7, 20].

Hormonal and inflammatory factors

Another proposed mechanism is the capacity of adipose cells to convert testosterone into oestradiol through the action of the aromatase. The resultant higher levels of circulating oestrogens can prevent bone loss, mainly amongst post-menopausal women with obesity [21]. A lower serum level of sex hormone binding globulin among individuals with obesity also leads to an increase in the free form of sexual hormones, enhancing oestrogen uptake by bone tissue [10, 22]. Despite their important action, oestrogens are not the only hormonal link between adipose tissue and bone. Other factors include a rise in the production of insulin [23], which directly promotes osteoblast proliferation and differentiation in vitro (with an apparent anabolic effect on bone) [23–25]. Furthermore, adipose tissue can influence bone metabolism by producing various adipokines. One of these is Leptin, an adipokine that is involved in the regulation of appetite and energy homeostasis, which is produced in higher levels among subjects with obesity. This hormone achieves its anabolic effects on bone by acting directly on osteoblasts and chondrocytes [26]. Leptin stimulates the differentiation and proliferation of osteoblasts and inhibits the genesis of osteoclasts in vitro [27]. Knockout of the *leptin receptor* gene leads to decreased bone volume and BMD [28], which is a finding that supports the important role of this hormone in the fat-bone crosstalk. Interestingly, leptin also influences bone indirectly through its action in the hypothalamus and sympathetic nervous system [26].These mechanisms have different outcomes on bone formation/resorption, which makes the interpretation of its true effect in vivo more complicated and sometimes leads to conflicting results [29]. It is even reported that the effect of leptin differs according to the different areas of the skeleton [30]. Despite these facts, it is highly likely that leptin has an overall positive effect on bone, enabling the skeleton to adapt to changes in soft tissue mass [26].

Another adipokine is adiponectin, a hormone whose levels are diminished in obese states. Similar to leptin, it also has a dual action with opposite outcomes on bone metabolism, which makes its global effect uncertain [31]. The mechanisms related with the action of these 2 controversial agents are reviewed in detail in many studies, as are the mechanisms of other less studied agents in this context, such as resistin, visfatin, amilyn, preptin, sclerostin, or glucagon-like peptide-1 and 2 [32, 33].

Despite the initial evidence that obesity is beneficial for bone health, recently-published studies have challenged this notion by showing that excess adiposity can have harmful effects on the skeleton, resulting from an increased risk of fracture (mainly among post-menopausal females)[34]. Interestingly, it is not only the excessive adiposity, but also body composition and location of the adipose tissue that appear to play an important role in this relationship. This occurs because visceral (intraabdominal) fat is associated with detrimental outcomes on bone formation, strength, and structure, whereas subcutaneous fat is related

with more favourable outcomes [35, 36]. One explanation for this observation is the low-grade inflammatory state, which typifies obesity and which leads to the increased production of cytokines such as tumour necrosis factor (TNF-), or interleukin 6 (IL-6) [37]. These inflammatory factors, which are mainly associated with abdominal obesity [38], interfere negatively with the balance between bone formation and resorption, as a result of their role in the promotion of osteoclast differentiation and activity [39]. The significant rise in the prevalence of osteoarthritis among patients with this disease is another supporting argument for this concept [40].

Recent studies have found that bone has not only a structural function but also an endocrine one. By producing substances such as osteocalcin, it can interfere in several physiological mechanisms such as energy balance, glucose metabolism, and insulin secretion [41]. In obesity, known as a state of insulin resistance and a relative decrease in insulin secretion, there seems to be a reduction in osteocalcin production by osteoblasts, according to several studies (and the same was found among patients with diabetes). Considering that insulin has an important effect in the production and differentiation of osteoblasts (being associated with a bone mass increase), this hypothesized relationship between osteocalcin and insulin may be another link between excessive adiposity and bone [5, 41].

Other factors

Another presumed link is related with bone marrow constitution; it is known that osteoblasts and adipocytes originate from the same stem cell and that an adipocyte-enriched yellow bone marrow develops during the state of obesity. This fatty bone marrow impairs bone regeneration [42] and is related with endplate depression and fractures in individuals with evidence of morphological bone weakness [43]. This fact is supported by an inverse correlation between adipose-enriched bone marrow in the vertebral bones and trabecular BMD [44]. Interestingly, older women with higher visceral adipose tissue quantity have increased levels of bone marrow fat, which suggests that visceral fat can exert harmful effects on bone through the accumulation of bone marrow adipose tissue [45].

It has also been found that low vitamin D levels and hyperparathyroidism are frequent among patients with obesity. Vitamin D deficiency in this context seems to be related with impaired bone formation, with altered bone microarchitecture [5]. This deficiency can be the result of the insufficient ingestion of vitamin D-containing food, limited exposure to sunlight, or the sequestration of this hormone in excess adipose tissue [7]. Supplementation of obese subjects with vitamin D (cholecalciferol) leads to a decrease in levels of PTH and bone turnover and an increase in forearm BMD [46]. Excessive dietary phosphorus intake (mainly when associated with low calcium intake), is also associated with secondary hyperparathyroidism, presenting a negative impact on bone metabolism (although further research is needed to confirm these connections)[5, 47].

Impact of obesity on bone mineral density

The relationship between body mass index (BMI) and bone mineral density (BMD) has been the focus of several studies in recent decades. Despite most studies suggesting a beneficial effect of BMI on BMD [48], there is also evidence that obesity could be related with low BMD and increased risk of osteoporosis [49]. A large study including 13,000 individuals concluded that body fat percentage was positively correlated with osteopaenia and non-vertebral fractures, also implying that states of excessive adiposity (such as obesity) may be related with low BMD [50].

To clarify these conflicting results, a mendelian randomization study including more than 300,000 individuals was conducted. The authors found that BMI may causally increase lumbar and heel calcaneus BMD, with no statistically significant causal effect of BMI on forearm and femoral neck BMD [48]. A recent systematic review and meta-analysis addressing the association of obesity with bone mineral density and osteoporosis concluded that adults with obesity had significantly higher BMD than healthy-weight adults in both evaluated sites (lumbar spine and femoral neck). Obesity was also positively associated with BMD and negatively correlated with osteoporosis [51].

Therefore, the most robust evidence available to date suggests a positive impact of BMI and obesity on BMD. But does it translate to fewer bone fractures?

Obesity and the occurrence of fractures

All the previously presented factors have divergent influences, which indicates that the relationship between fat and bone is a complex one. The interplay of all these agents (with different relevance in different patients) can explain the lack of consensus and conflicting evidence about this issue. This is even more marked when we focus on fracture risk among obese individuals [52]. A state-of-the-art analysis revealed that, until recently, there has been almost no discussion about the relationship between the obese state and the occurrence of fractures. This lack of discussion is a result of the prevailing assumption that the increased BMD among obese patients would logically lead to fewer fractures [53]. However, since the 1980s, an increasing number of studies have brought controversy to the topic. For instance,

a review from 2014 showed that, amongst male patients, most of the evidence points towards an increased incidence of upper forearm and ankle fractures, and a lower incidence of hip, spine, wrist, forearm, and pelvic bone fractures. The pattern for female patients was similar, although a higher incidence of vertebral and humeral fractures was also reported [54]. The lower incidence of hip fractures [55] could be explained by the accumulation of fat pads because these act as a buffer when a patient suffers a fall or is subject to another sort of trauma. Additional evidence has found that the risk factors that predispose to fractures appear to be similar between individuals with or without obesity. Despite this, the pattern of falling among those with obesity was different, with more falls occurring backwards and sidewards [56]. Recent data suggest that BMI does not influence the prevalence of fragility fractures, which indicates that female patients with BMI ≥ 30 kg/m^2 are still prone to develop low-impact fractures, regardless of BMD [16]. Another study revealed that obesity is not a major factor for the occurrence of fractures in these patients [53]. A recent systematic review and meta-analysis about the issue concluded that the risks of hip and wrist fracture were reduced by 25% and 15%, respectively, while the risk of an ankle fracture was increased by 60% in postmenopausal women (in comparison with those with no obesity). This study also added that hip fractures were reduced by 41% among men with obesity and that there were not enough studies to draw any conclusions about premenopausal women (the authors mentioned that overall quality of evidence was very low to low for all evaluated outcomes) [57].

In balance, bearing in mind the relative lack of data in this area, further research is required to fully evaluate the impact of obesity on bone and bone fractures, especially among young and middle-aged individuals.

Conclusion

Obesity and bone metabolism seem to be linked by several mechanisms that may ultimately influence bone mineral density and fracture risk. The players involved include several substances produced by the adipose tissue (such as adiponectin, leptin, and inflammatory factors), mechanical factors, and vitamin D status, among others [5]. Despite the historical notion that obesity may increase bone strength and decrease fracture risk, it is now known that this is not always true (with recent investigations pointing towards an increase in ankle fractures among postmenopausal women with obesity). Despite these recent findings, more observational and interventional studies are needed to strengthen the quality of evidence in this area [57].

Conflict of interest

All authors have read the journal's policy on disclosure of potential conflicts of interest. The authors declare that they do not have any conflict of interest related to this work.

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