Obesity and osteoporosis

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ABSTRACT

Osteoporosis is the most common skeletal disease and a major public health problem. It affects around 1/3 of postmenopausal women, an incidence that is expected to double in the next thirty years due to the increase in life expectancy. Besides a significant increase in morbidity and mortality, osteoporosis and its complication i.e. the low energy fracture, also result in a considerable and continuously growing economic burden for healthcare systems. Understanding the factors involved in the manifestation of the disease and its complications is crucial for the development of disease prevention and treatment programs. On the other hand, obesity has become a global epidemic and obesity related medical conditions also infer a tremendous economic cost. The relationship between obesity and bone metabolism is complex and not fully understood. Several mechanical, biochemical and hormonal mechanisms have been suggested to explain the association between the adipose tissue and bone diseases. Most studies indicate a positive correlation between Body Mass Index (BMI) and bone density. However, the effect of obesity on the bone is probably not favourable in terms of skeletal micro-architecture, whereas low-grade systemic inflammation and specific peptides and adipokines seem to play a crucial role. The study of these factors and the interpretation of the events arising from the interaction between adipose tissue and bone metabolism seem to constitute an emerging field of research in the area of bone metabolism.

KEYWORDS: Adipose Tissue, Bone Mineral Density, Obesity, Overweight, Skeletal Microarchitecture

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and progressive deterioration of the bone microarchitecture. Its main consequence is fragility of the bones and increased risk of low energy fractures [1,2]. Osteoporosis affects at least 200 million people globally, with high health cost involved [3]. In the US alone, osteoporosis is responsible for 1.3 million fractures, with 500,000 vertebral, 250,000 hip and 240,000 wrist fractures, costing $10 billion per annum with increasing prevalence and cost [4]. Its prevalence is expected to increase and by 2040 the relevant cost is expected to rise by 100–200% [5].

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Obesity represents the most common metabolic disease. It is characterised by increased body weight and especially an excess of adipose tissue. BMI is an imperfect, but a widely used measure of obesity as it provides a crude but easily estimated evaluation of the severity of this condition. It is defined as a person's height in kilograms divided by the square of his/her height in meters (kg/m^2). The World Health Organisation (WHO) defines obesity as a BMI of 30 kg/m^2 or higher, while a person with a BMI of 25-30 kg/m^2 is considered as overweight. Obesity has become a major health issue and a global epidemic. Its worldwide prevalence has been doubled in the last three decades [6]. It represents a serious public health issue alongside a major health risk factor for the individual. It is estimated that around 13% of adults are obese [7], whereas the combined overweight and obese individuals account for the majority of the adult population in some Western countries. Furthermore, alarming rates of obesity and overweight are observed in children [8]. Presence of obesity is strongly associated with several metabolic diseases including diabetes mellitus type 2 (T2DM), hyperlipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), and furthermore with cardiovascular events and certain types of cancer.

The skeleton is tasked with ensuring two main functions. Firstly, to support, protect and facilitate soft tissue function (structural role) and secondly, to be a reservoir of calcium salts, from which the body draws calcium when it is in poverty due to reduced intake or increased losses (metabolic role). From the structural point of view, the size and strength of the skeleton must be proportional to the mass of soft tissues to serve its purpose. Regarding its function as a reservoir, there is a mechanism that releases calcium during periods of reduced intake or losses and moves calcium to the skeleton during periods of abundance. In order to exert both these functions, the skeleton utilizes a number of hormones and peptides. Both roles of the skeleton, i.e. supporting and storage, are based on the control of skeletal homeostasis, while it appears that body weight, and in particular adipose tissue, plays a leading role.

Adipose tissue is nowadays considered an endocrine gland, secreting numerous peptides collectively characterized as lipokines, rather than a simple fat store. Lipokines are currently a field of intensive research. The common evolutionary path of adipocytes and osteoblasts themselves, which originate from the same parenchymal stem cell, is of great interest because many of the mechanisms that determine the evolution of these cells in one direction or the other are common and could be common therapeutic goals for the treatment not only of metabolic bone diseases but also of the other obesity-related metabolic diseases that were mentioned above.

The interrelation between the skeletal and adipose tissues is complex, dynamic and not fully clarified yet. Various molecular pathways have been explored by which adipose tissue communicates and interacts with the skeleton. These pathways include several factors such as leptin, adiponectin, resistin, myokines, pro-inflammatory cytokines, and vitamin D. Additionally, the bone tissue affects metabolic parameters, including body weight control, through bone-derived factors, such as osteocalcin and osteopontin. In any case, the interplay between the adipose tissue and the skeleton is both mechanical and metabolic.

A. METABOLIC ASSOCIATION

Vitamin D

The impact of suboptimal vitamin D concentrations on the musculoskeletal system is well-documented and vitamin D deficiency is associated with osteoporosis. Vitamin D deficiency is quite common among obese adults. In particular, serum 25-hydroxy-vitamin D (25OHD) concentrations are about 20% lower in obese people compared with individuals of normal weight. Furthermore, serum 25OHD is inversely associated with body weight, BMI and fat mass [9, 10, 11, 12].

An important parameter with clinical implications is that restoration of vitamin D levels is much more difficult in obese compared to normal weight individuals [13, 14]. This is likely due to i) sequestration of vitamin D in the fat stores and ii) co-existent secondary hyperparathyroidism in obese adults. The clinical implication of this issue is that often considerably higher cumulative doses of vitamin D are required to achieve optimal levels in these indi-

viduals.

Interestingly, although vitamin D levels have been shown to be persistently lower in obese adults, which theoretically would lead to lower BMD predominantly through reduced calcium absorption, studies have demonstrated that adults with obesity seem to have lower bone turnover compared with normal weight, and higher BMD with thicker and denser cortices [15]. This paradoxical phenomenon is not fully understood yet. Some theories support that obese individuals develop compensatory mechanisms whereas other studies hypothesize that fat may serve as reservoir for vitamin D, however, none of these theories has not been proven.

Oestrogens

Oestrogens are steroid hormones that have a key role in the maintenance of skeletal homeostasis exerting a protective effect by promoting bone formation and reducing bone resorption. Adipose tissue is one of the major sources of aromatase, an enzyme which synthesises oestrogens from androgen precursors. Obese post-menopausal women have been shown to have higher serum concentrations of oestrogens compared with non-obese controls [16]. Even though oestrogens are not the sole regulator of skeletal homeostasis, this difference can possibly explain, at least in part, the increased BMD observed in obese women (alongside the increased mechanical loading, which is discussed below).

High fat diet

One persistent finding in animal models of obesity is the reduced quality (increased porosity – poor microarchitecture) despite the increased bone mass. Especially high fat diet induced obesity is associated with increased bone quantity (larger bone size and mineral content) but decreased bone quality (lower size-independent mechanical properties) [17] as well as increased bone marrow adiposity [18]. It seems likely that bone microarchitecture is adversely affected leading to reduced bone quality.

Bone marrow adiposity and osteoporosis

A common progenitor, a pluripotential, bone marrow-derived mesenchymal stem cell (BMSC) gives rise to both adipocytes and osteocytes [19]. In fact, this stem cell has an equal propensity for differentiation into osteocytes or adipocytes or a number of other cell types (including endothelial, fibroblasts, chondrocytes). This differentiation is a complex process controlled by several transcription factors. The process, although characterised by plasticity, is irreversible once it has been completed [20]. A plausible mechanism that could lead to osteoporosis is that of switching of the differentiating process to adipocytes rather than osteocytes. This phenomenon is naturally observed with advancing age, but it has been described in generalised obesity and post-menopausal osteoporosis [21].

The factors involved in this process are not yet fully understood, with oestrogens [22] and peroxisome proliferator activated receptor-γ (PPARγ) [23] described in some studies as the possible parameters affecting the differentiation process.

In conclusion, emerging data over the last years have given rise to the hypothesis that fat infiltration of the bone marrow has been associated with osteoporosis [24].

Leptin

Leptin is a cytokine-like hormone, produced primarily by the adipocytes. It plays a key role in maintaining long-term energy and appetite control. Its effects on energy and appetite are exerted primarily on hypothalamus. Leptin concentrations are typically elevated in obesity, which represents a leptin-resistant condition. The impact of leptin on bone metabolism is complex, likely both direct and indirect and yet poorly understood with conflicting results. Studies in human have reported both positive roles of leptin [25, 26, 27, 28] and profoundly negative ones [29, 30] on bone health. The heterogeneity of the results of leptin on the skeleton likely reflect the different designs of the various studies and is an area where further, well-designed studies are required.

Inflammatory cytokines (TNF-a and IL-6)

Emerging evidence suggests that inflammation significantly affects bone homeostasis, inducing osteoporosis. Numerous pro-inflammatory cytokines have been implicated in the regulation of osteoblasts and osteoclasts. It is clearly documented that obesity represents a chronic low-grade inflammation state with elevated concentrations of cytokines, in particular TNF-α and IL-6.

TNF-α, which is raised in obesity, induces bone loss through stimulation of osteoclastogenesis via a number of different mechanisms [24]: 1) activates NFκB leading to increased expression of activator of nuclear factor kappa-B ligand (RANK) and RANK ligand (RANKL), which promote bone resorption [31]. 2) reduces the production of osteoprotogerin (OPG), which is the natural inhibitor of RANKL, leading to higher RANKL concentrations and further osteoclastic activity [32]. 3) directly modulates the RANKL-induced signalling pathways, leading to a synergistic activity with RANKL, which promotes further osteoclastic resorption [33].

The strong inflammatory response in obese individuals, as demonstrated by the high levels of mainly TNF-α and to a degree of IL-6, may be, at least partly, responsible for the complicated relationship between obesity and osteoporosis.

Adiponectin

Low adiponectin concentrations are a feature of obesity [34]. Studies, both *in vitro* and *in vivo*, indicate that adiponectin has a positive role on bone mass by stimulating osteoblastogenesis and suppressing osteoclastogenesis [35].

Indirect effects through other metabolic diseases associated with obesity

Metabolic diseases, especially T2DM [36] but also NAFLD [37] and others have adverse effects on bone metabolism, and their increased prevalence in obese individuals may indirectly affect the skeleton. Furthermore, medications used to treat these conditions may positively or negatively affect the bone [38].

B. MECHANICAL ASSOCIATION

The mechanical interplay between the bone and adipose tissues includes two important aspects; the effect of the mechanical loading and the risk of falls.

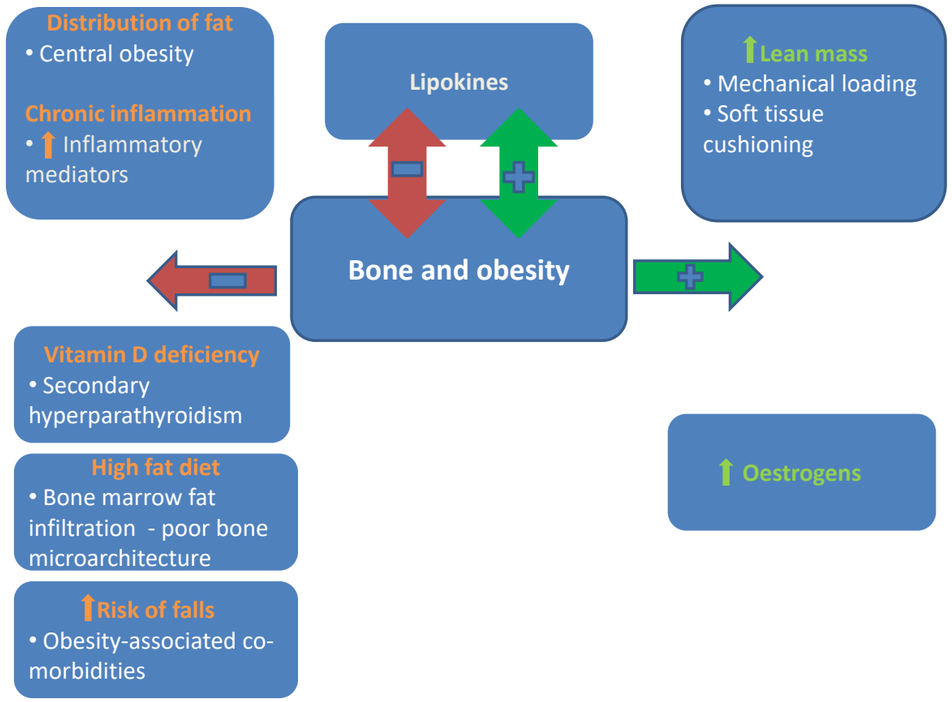
Mechanical loading

The mechanostat theory, developed by Harold M. Frost [39], describes the mechanisms by which mechanical loading influences bone structure by changing the mass and architecture to provide a the necessary adaption. It is universally demonstrated, in practically all the relevant studies, that obese individuals have higher BMD than lean subjects. Furthermore, biochemical markers of bone turnover are lower in obese compared with normal weight individuals [40]. Excessive adipose accumulation imposes a greater static mechanical stress on bone, and it provides an important positive loading effect [41]. It is plausible that is not solely the effect of the passive loading, but also the fact that, in general, obese individuals have increased lean mass (along with fat mass) leading to the favourable effects on the bone of the increased muscle strain [42]. An important exception here is osteosarcopenia, i.e. coexistence of obesity with sarcopenia.

Bony tissue can detect the mechanical forces induced by external loading and produces a compensatory response resulting to formation of new bone. An important parameter, and area of research over the last few years, is the role of sclerostin in bone's adaptive response to mechanical loading. In non-loading states osteocytes secrete inhibitors of the Wnt pathway, predominantly sclerostin, thus favoring osteoclastogenesis [43]. Under loading, instead, the expression of sclerostin by the osteocytes is inhibited. As a result, the Wnt ligands are able to activate this pathway, which, leads to a direct stimulation of osteoblastogenesis and osteoblast migration [44, 45].

However, the overall relationship seems to be complex and possibly site-specific. For example, a study showed that bone size at the radius and the tibia estimated by high-resolution peripheral quantitative computed tomography (hr-pCT) does not differ between obese and normal-weight controls [15].

In summary, the loading factor is an important aspect of the bone-fat interplay exerting a favourable impact. However, it is not sufficient to fully explain the interaction.



Obesity and risk of falls

Falls represent an important and independent risk factor for fractures. High incidence of falls has significant medical implications and results in high economic costs [46]. Several studies have showed that obese and overweight adults carry a higher risk of falls, the aetiology of which is multifactorial [24]:

i) Obesity causes or exacerbates important chronic conditions such as T2DM, cardiovascular disease, arthritis, autonomic dysfunction, orthostatic hypotension, sleep apnoea and hypertension. These metabolic conditions are independent risk factors for falls [47].

ii) Central adiposity compromises core stability and plays an independent role as a fall-related predictor in older women [48].

iii) Obesity is associated with loss of functional independence and reduced ability in performing daily tasks, such as standing up, walking unaided or climbing up stairs, which in turn increases the risks of falls [49].

iv) Finally, obesity adds pressure on the heels, which compromises postural stability and balance ability [50].

In the elderly population, obese individuals are more likely so sustain one or multiple falls compared to normal weight ones [51] leading to higher rates of hospitalisation [52] and reduced quality of life [53]. It is interesting, however, that the same meta-analysis [51] of 31 observational studies showed no evidence of an association between obesity and fall-related injuries in total. The most likely explanation is that the effect of falls in obese in fracture risk is site-dependent: Obesity seems to be protective against hip fracture in women but carries a high risk of fractures at other sites. Obese women sustain more fractures in the ankle [54], leg [55], humerus [56], and vertebral column [57] and fewer in the wrist [58], hip [56] and pelvis [56].

There have been two mechanisms proposed to explain this site-specific discrepancy. First, the fact that the extra fat acts as a cushion protecting from hip and pelvic fractures [59]. Secondly, the pattern of falling appears to be different in obese individuals: they are more prone to sideward and backward falling, whereas normal weight individuals tend to fall forwards [60].

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Conclusions

Bone and adipose tissues are both highly active metabolically and probably interact and affect each other but their association is highly complex and still not fully elucidated. They interplay through adipokines, oestrogens, inflammatory markers and bone derived metabolic factors.

Increased mechanical loading observed in obese individuals compared to their normal weight counterparts exerts a positive effect on bone. However, this probably is not the only effect. Increasing amount of evidence suggests that obesity may have a negative effect on fracture risk and that this effect is likely to be skeletal site-specific and age-dependent. Potential mechanisms contributing to that is the increased risk of falling among obese adults, the low-grade inflammation that accompanies obesity and the fat infiltration of bone marrow observed in such individuals.

A better understanding of the complex interplay between bone and fat may lead to the development of more specific molecular treatment targets and fracture prevention strategies.

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