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REVIEW ARTICLE

POSTMENOPAUSAL OSTEOPOROSIS IN OBESE WOMEN

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ABSTRACT

Obesity and osteoporosis are two common diseases with an increasing prevalence and a high impact on morbidity and mortality. Obese women have always been considered protected against osteoporosis. Fat and bone are linked by many pathways, which ultimately serve the function of providing a skeleton appropriate to the mass of adipose tissue it is carrying. Leptin, adiponectin, adipocytic estrogens and insulin/amylin are involved in this connection. However, excessive body fat, and particularly abdominal fat, produces inflammatory cytokines which may stimulate bone resorption and reduce bone strength. Even more recent studies have shown conflicting results. There is growing evidence that obesity, and particularly severe obesity, may be related to an increased risk of fracture at different skeletal sites which is partially independent from bone mineral density (BMD). This review aimed to examine the literature data on the relationships of body mass index (BMI) and fat mass with osteoporosis in postmenopausal women.

Key words: BMI, obesity, menopause, osteoporosis.

INTRODUCTION:

Obesity (body mass index, BMI: 25-39.9 Kg/m^2) decreases sex hormone binding globulin (SHBG) which in turn increases free sex steroids and protects the bone (1, 2). Besides, hyperinsulinemia inhibits the transcription of insulin-like growth factor-binding protein (IGFBP-1) in the liver and decreases its serum levels increasing IGF-1 that stimulate the proliferation of osteoblasts. Therefore, IGFBP-1 is considered as simple marker of insulin resistance (3, 4, 5). However, an inverse relationship between body weight or BMI and the risk of fractures has also been shown. Excessive body fat, and particularly abdominal fat, produces inflammatory cytokines which may stimulate bone resorption and reduce bone strength (6-9).

Adipocyte, leptin and osteogenesis

Leptin, a hormone secreted by white adipose tissue, acts via obese receptor b (OB-Rb receptors) in the hypothalamus to decrease food intake and increase energy expenditure by activating sympathetic system. The sympathetic system has a tonic inhibitory action on leptin synthesis. Thus, adrenergic blockade often increases circulating leptin and its gene expression which are increased in obesity along with decreased sympathetic sensitivity of adipose tissue. Obesity due to dysregulation of energy balance may partly involve in decrease leptin sensitivity (10). In obesity, modification of adipocyte sensitivity to insulin inhibits lipid accumulation suppressing lipogenesis, increases triglyceride hydrolysis, increases fatty acid and glucose oxidation, and reduces the size of white fat depots suppressing adipocyte proliferation (11).

Leptin has a dual effect on bone, acting by two independent mechanisms. Centrally, it stimulates sympathetic neurons acting in the hypothalamus that indirectly inhibits bone formation. Leptin deficiency results in low sympathetic tone, ablation of adrenergic signaling leading to a leptin-resistant high bone mass. Beta-adrenergic receptors on osteoblasts regulate their proliferation and production of more receptor activator of nuclear factor KB ligand that activates osteoclast resulting in decrease of bone mass (12, 13). Peripherally, leptin act as a signal molecule with growth factor characteristics, and is able to stimulate osteoblasts and inhibit formation and activity of osteoclast which promotes osteogenesis (14).

Neuroendocrine regulation of bone remodeling

Recent genetic studies have shown that there is a central control of bone formation, mediated by a neuro-endocrine mechanism; this involves leptin that controls

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body weight, reproduction and bone remodeling (15). Leptin inhibits bone formation by the osteoblasts, thus its deficiency results in a high bone mass phenotype despite hypogonadism. Peripherally, bone remodeling is regulated by calcitropic hormones (parathyroid hormone, thyroid hormone, sex steroids, etc.). Bone remodeling occurs in a specialized vascular structure known as bone remodeling compartment (BRC), made up of flattened cells which display all the characteristics of lining cells in bone including expression of osteoprotegrin (OPG) and receptor activator of nuclear factor KB ligand (RANKL). The reduced bone turnover leads to a decrease in the number of BRCs, while increased turnover causes an increase in number of BRC. The dominant pathway regulating osteoclast recruitment is the RANKL/OPG system, while other factors runt related transcription factor (RUNX), Osterix are involved in osteoblast differentiation, modulated by calcitropic hormones (16, 17).

This basic physiologic unit is strategically close to stromal elements of the marrow as well as the microvascular supply (18). Osteoclasts originate from hematopoietic precursors in the circulation and bone marrow, while osteoblasts are derived from bone-marrow mesenchymal stem cells (MSCs) (19-21). The differentiation of these two cell lines within this milieu is coordinated during active bone remodeling, in part because MSCs are the source of a variety of cytokines that influence osteoclast differentiation. Macrophage and their monocytic precursors become osteoclasts under the influence of two stromal-derived cytokines, macrophage colony-stimulating factor and receptor activator of nuclear factor KB ligand (also known as tumor necrosis factor, ligand superfamily member- 11)(20).

Osteoporosis and obesity, two disorders of body composition, have several common features including a genetic predisposition and a common progenitor cell. With aging, the composition of bone marrow shifts in favor of increased number of adipocytes, increased osteoclast activity and declined function of osteoblast those results osteoporosis. Secondary causes of osteoporosis, including diabetes mellitus, glucocorticoids and immobility, are associated with bone-marrow adiposity. (22)

Fat and bone mass

Elevated body weight or body mass index that induces greater mechanical loading on bone are positively correlated with increased bone mineral density and with reduced risk of fragility fractures (6, 23). Abundant adipose tissue is considered an important source of estrogen production and may contribute to increased BMD; however, this finding has been confirmed in women but not in men (24).

Zhao et al. (25) found that there is a positive correlation between fat mass and bone mass in both sexes, when results are not corrected for the mechanical loading effect of body weight. However, when the mechanical loading effect caused by total body weight is statistically removed, both fat mass and percentage of fat are negatively correlated with bone mass (26). Consistent with this finding two more recent studies, carried out on large cohorts of Chinese and Korean subjects found that subjects with a higher percentage of body fat presented lower bone mineral density and a higher prevalence of osteoporosis, production of pro- inflammatory cytokines (IL-6 and TNF-α). IL-6 and TNF-α is higher in abdominal fat than in subcutaneous fat, whereas, aromatase activity and adiponectin secretion is lower in visceral fat (27, 28).

An increased fat mass imposes a greater mechanical stress on bones, and in response bone mass increases to accommodate the greater load. Moreover, many hormones may link fat mass to bone tissue. An excess in fat mass is associated with an increased aromatization of androgens to estrogens in adipose tissue, an increased secretion of insulin and amylin from pancreatic β-cells, decreased sex hormone binding globulin serum levels with increased levels of free sex steroids and changes in the production of adipokines (leptin and adiponectin). Leptin is considered to play a crucial role in the protective effect of fat on bone. However, *in vitro* studies have recently confirmed that the effect of leptin on bone is complex and not completely understood (29). Moreover, some cross sectional studies to assess the role of leptin on BMD have reported both negative and positive effects (30, 31). Adiponectin that correlates negatively with obesity in general and central adiposity in particular, has been reported to stimulate both bone formation and bone resorption but its effect on BMD remains controversial (32–34).

Obesity is now known as a systemic inflammatory condition and obese tissue secretes various inflammatory cytokines; interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) which may up- regulate the receptor activator of nuclear factor k -ligands, stimulating osteoclastogenesis leading to bone resorption. The risk of incident ankle and upper leg fractures was significantly higher in obese than non-obese women, while the risk of wrist fracture was significantly lower (26). A study carried out in Italian postmenopausal women with fracture reported that increased BMI was associated with a significantly higher risk of humerus fracture and a lower risk of hip fracture, but no relationship was seen between BMI and either wrist or ankle fractures (27). Fracture in postmenopausal

women is site-dependent, obesity being protective against hip and pelvis fractures but associated with an almost 20% increase in risk for proximal humerus fracture compared with normal/underweight women (35). Though the reasons for site specific differences in fracture site in obese compared with non-obese individuals have not been established, it is consistently found that obesity is associated with reduced levels of 25-hydroxyvitamin D. In addition, the consequent higher serum parathyroid hormone levels reported in obese individuals could have an adverse effect on cortical bone (36, 37).

Obesity and postmenopausal osteoporosis

Obesity has been considered a protection factor against the development of bone loss and osteoporosis, likely for increased androgen aromatization to estrogens in postmenopausal obese women (38, 39). Additionally, mechanical loading appears to stimulate bone formation by decreasing apoptosis and increasing proliferation and differentiation of both osteoblasts and osteocytes by an activation of the intracellular signaling Wnt/β-catenin (40-42). Therefore, the mechanical loading conferred by body weight justified the assumption of a protective role of obesity in the prevention of osteoporosis (38).

More recently, however, the belief that obesity is protective against osteoporosis has been questioned. In fact, epidemiologic and clinical studies have suggested that high level of fat mass might be a risk factor for osteoporosis and fragility fractures (7-9). Indeed, adipose tissue not only stores excess triacylglycerols, but functions as an endocrine organ by releasing several adipokines, which appear to modulate glucose and lipid metabolism, inflammation, appetite and insulin resistance (43, 44). Additionally, the physiological relevance of adipose tissue for skeletal health likely resides in the role that some of these adipokines, such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), might play by interfering with bone cells homeostasis (45-47). Moreover, bone has started to be considered an endocrine organ itself affecting both body weight control and glucose homeostasis through the action of bone-derived factors such as osteocalcin and osteopontin (48, 49). This cross-talk between fat and bone seems to play an important role as homeostatic feedback system in which adipokines and molecules secreted by bone cells might represent the link of an active and functional bone-adipose-glucose axis (50-52), by mechanism(s) not fully clarified yet.

Recent evidences suggest that obesity is also associated with a chronic low-grade inflammation as depicted by increased plasma levels of C-reactive protein (CRP), pro-inflammatory cytokines such as TNF-α, IL-6, and osteopontin (53-56). Few reports also depict an association between obesity and circulating low levels of vitamin D (57-59). Nevertheless to date, few and conflicting data exist about possible correlation among vitamin D, total intact osteocalcin (OSCA), inflammatory markers (60-62) and bone mineral density in obese women.

As low body mass index is a recognized risk factor for fragility fracture, whereas obesity is believed to be protective, because of beneficial effect of mechanical loading, exerted by high body mass, on bone formation. However, contrasting studies have achieved a clear consensus, instead, suggesting that excessive fat mass derived from obesity condition may not protect against osteoporosis or, even worse, could be rather detrimental to bone. Since adipocytes and osteoblasts are derived from a common mesenchymal stem cell precursor, molecules that lead to osteoblastogenesis inhibit adipogenesis and vice versa. The prevalence of obesity (BMI 30 to 34.9 kg/m^2) and morbid obesity (BMI > or = 35 kg/ m^2) demonstrate a normal BMD, as measured by dual-energy X-ray absorptiometry (DXA) (63). Moreover, molecules such as peroxisome proliferators activated receptor-γ and Wnts, regulates both adipocyte and osteoblast differentiation through Wnt signaling, involved in mesenchymal cell fate regulation. However, at present there is no experimental data that relate any influence of the Wnt inhibitor Sclerostin to adipogenesis. In addition, menopause is the condition in which there is a simultaneous increase of adiposity and decrease of bone mass, postmenopausal women have high Sclerostin level inversely associated with circulating estradiol level and since the sex hormone replacement therapy has proved to be effective in attenuating bone loss and reversing menopause-related obesity. Thus Sclerostin contributing in adipogenesis could be an active cause of osteoporosis in postmenopausal state (64).

CONCLUSION:

The evidence for a significant yet complex interaction between fat and bone is summarized in this article. Research has clearly established that there is central regulation of bone remodeling through the hypothalamus and sympathetic nervous system, a pathway that also regulates the metabolic fate and distribution of adipose tissue. Moreover, adipocytes and osteoblasts arise from a common precursor cell, and their destinies, although not mutually exclusive, are intertwined and share a variety of genetic, hormonal and environmental factors. On the other hand, reports suggest that there is a protective role for fat in the skeleton, particularly with respect to fracture risk and bone loss during and immediately after menopause. However, there is mounting evidence that at the extremes of life and old age, fat infiltration in the

bone marrow might not be good for skeletal strength, nor for the optimal function of the bone remodeling unit. The incidence and the pathogenesis of fracture in obese individuals have not yet been clearly defined. To answer those questions, new model systems and more extensive studies at the genetic, molecular and cellular level are needed. Moreover, the growing evidence that obesity may be related to an increased risk of fracture has important public health implications and emphasizes the need to develop effective strategies to reduce fracture risk in obese menopausal women.

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