ASSOCIATION OF METABOLOC SYNDROME WITH OSTEOPOROSIS

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Abstract

Metabolic syndrome (MetS) and osteoporosis are two major healthcare problems worldwide. Metabolic syndrome is a constellation of medical conditions consisting of central obesity, hyperglycemia, hypertension, and dyslipidemia, in which each acts on bone tissue in different ways. The growing prevalence of MetS and osteoporosis in the population along with the controversial findings on the relationship between both conditions suggest the importance for further investigation and discussion on this topic. This review aims to assess the available evidence on the effects of each component of MetS on bone metabolism from the conventional to the contemporary. Previous studies suggested that the two conditions shared some common underlying pathways, which include regulation of calcium homeostasis, receptor activator of NF-κB ligand (RANKL)/receptor activator of the NF-κB (RANK)/osteoprotegerin (OPG) and Wnt-β-catenin signaling pathways. In conclusion, we suggest that MetS may have a potential role in developing osteoporosis and more studies are necessary to further prove this hypothesis.

Keywords: bone, dyslipidaemia, hyperglycaemia, hypertension, obesity, osteoporosis, metabolic syndrome, vitamin D.

Introduction

The definition of metabolic syndrome (MetS) has evolved with time, but it pivots on central obesity, hypertension (HPT), hyperglycaemia and dyslipidaemia. MetS alters the mechanical loading, hormonal and biochemical profile of the body, thereby producing complex effects on bone health. The proinflammatory and pro-oxidative body environment might be detrimental to bone health (1).

Metabolic syndrome (MetS) and osteoporosis are two seemingly unrelated conditions, yet previous studies have demonstrated the relationship between these two conditions. Approximately a quarter of the adult population, worldwide, has MetS, making it a significant public health challenge (2).

Osteoporosis is characterized by skeletal fragility and susceptibility to fracture attributed to reduction of bone mass and deterioration of bone micro-architecture (3). It is a metabolic bone disease occurring in both men and women, particularly when they grow older. Osteoporosis is a major health problem due to the high morbidity, mortality, and significant health care cost involved. Osteoporosis affects more than 200 million people globally (4). Osteoporosis causes 1.3 million fractures, with 500,000 vertebral, 250,000 hip, and 240,000 wrist fractures costing $10 billion per annum in the USA (5).

The accretion in the prevalence for both diseases prompts the need to understand the relationship between MetS and osteoporosis. The occurrence of both diseases is basically dependent on lifestyle, genetic, metabolic, nutritional, and hormonal factors (6). Abdominal obesity, dyslipidemia, hyperglycemia, and hypertension are factors associated with the occurrence of osteoporosis, which are also components of MetS (7). Each feature might give different impacts on bone health. Abdominal adiposity is associated with osteopenia and osteoporosis (8,9).

In this review, evidence of bone loss in animal models of MetS was presented, followed by evidence from human epidemiological studies. The pathogenesis of bone loss due to MetS as evidenced by in vitro studies was also discussed. We hope this review provides the readers with a clear picture on the relationship between MetS and osteoporosis.

The Association between MetS and Osteoporosis.

In Vivo Studies

Several animal models of diet-induced MetS have been reported using fructose (10, 11, 12), sucrose (11,13), high-fat (14), high-fructose high-fat (15, 16), and high-sucrose high-fat diet (17). The Nile grass rat, Arvicanthis niloticus, was introduced by Noda et al. (18) as a novel model of MetS. Nile grass rats spontaneously developed dyslipidemia, hyperglycemia, abdominal fat accumulation, hypertension, and hyperinsulinemia. An in vivo study performed using an animal model fed with a Westernized diet (containing high sucrose, lipid, fatty acids, cholesterol, sodium and chloride content; but low proportion of polyunsaturated fatty acid, vitamins, and protein) indicated reductions of bone mineral density

(BMD) and bone mineral content (BMC) at the whole body, femoral, and vertebral levels (19). In a more recent study performed by Li et al. (20), MetS was induced using high-fat diet for 16 weeks in C57Bl/6 mice. Findings from this study showed MetS (increased body weight, plasma lipids, insulin, and insulin resistance) in mice induced with alveolar bone loss, osteoclastogenesis, and inflammation. The current available documented evidence on MetS and osteoporosis in animal studies is still inadequate. Therefore, we need to examine the investigation on the relationship between features of MetS and bone loss in animal studies as well.

Obesity

Previous studies by Halade et al. (21) introduced a simple and convenient method in the establishment of novel model for age-associated postmenopausal osteoporosis with obesity induced by high-fat (HF) diet containing 10% corn oil using 12-month old female C57Bl/6J mice. The high-fat diet was given to the mice for six months raised body weight, visceral fat mass, abdominal fat mass, fasting serum glucose, fasting serum insulin, while BMD was reduced. Continuous oral administration of HF corn oil diet for half a year induced an accumulation of adipocytes in mice. Another study utilizing HF diet to induce obesity in male C57Bl/6J mice found reduced BMD, trabecular and cortical bone densities at the tibia of obese mice. Apart from that, bone histomorphometric analysis showed infiltration of adipocytes in the bone marrow of obese mice (22). The most recent study demonstrated that obese mice fed with a high-fat diet had decreased trabecular bone volume and cortical bone growth shown by micro-computed tomography analysis (23).

Dyslipidemia

Obesity and dyslipidemia often co-exist due to accumulation of visceral fat. Graham et al.(24) reported that HF diet was able to cause hypercholesterolemia in mice, evidenced by high total cholesterol, LDL, and unesterified cholesterol. These abnormalities further affected bone quality as the BMC and trabecular structural parameters in femur and tibia were reduced. In a subsequent experiment done by Pirih et al. (25), high-fat diet-induced hyperlipidemia mice demonstrated elevated total serum cholesterol, increased glucose levels, and reduced HDL. Micro-computed tomographic analysis indicated reduction in bone surface and bone volume, suggesting the occurrence of impaired bone remodeling in hyperlipidemia mice. Biochemical analysis of mice serum in hyperlipidemia mice displayed augmented levels of parathyroid hormone (PTH), tumor necrosis factor-α (TNF-α), C-terminal telopeptide of type-1 collagen (CTX; a bone resorption marker), calcium, and phosphorus. At the same time, lower levels of amino-terminal propeptide of type-1 collagen (PINP; a bone formation marker) was found. Another experiment was done to access BMD and bone mechanical strength in hypercholesterolemia mice model induced by high-fat high-cholesterol (HFHC) and sodium cholate diet. Hypercholesterolemic mice showed cortical and trabecular bone loss in the femur and vertebrae, whereby the mechanical strength of the bones decreased significantly (26).

Hyperglycemia

Hyperglycemia is a characteristic of diabetes mellitus, a metabolic disease due to impaired insulin secretion (type I diabetes), insulin action (type II diabetes), or both. Previous studies demonstrated greater glomerular filtration rate, increased urinary calcium, reduced fractional calcium reabsorption, and a 53% reduction in the level of osteocalcin (a marker for bone formation) in streptozotocin (STZ)-induced diabetic rats compared to normal rats (27). In another investigation done by Amir et al. (28), BMD of distal femur and vertebra was significantly reduced in diabetic Cohen rats (non-obese rats of type II diabetes) compared to normal rats.

Hypertension

The significance of calcium metabolism in hypertension and osteoporosis has been reported. In an in vivo experiment using spontaneous hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY), SHR had lower BMD and bone magnesium content. Administration of a calcium diet augmented BMD and bone calcium content, while bone magnesium content was reduced in both SHR and WKY. Furthermore, the presence of a low percentage of trabecular bone area and newly-formed bone area in SHR compared to WKY were evaluated by Bastos et al. (29). These findings implied a significant relationship between high blood pressure and bone loss.

Human Studies

In contrast to animal studies, human epidemiological studies yield inconclusive results on the relationship between bone health and MetS, whereby positive, negative, and not significant relationships between the two conditions have been reported. In the Rancho Bernardo Study on 420 men (mean age = 74.2 ± 9.7) and 676 women (mean age = 74.4 ± 10.9), 23.5% of men and 18.2% of women had MetS. The incidence for osteoporotic non-vertebral fractures was significantly higher in women with MetS (OR = 3.76, 95% CI 1.27–11.13), but not in men. Men and women with MetS had lower BMD at total hip relative to those without MetS, implying that MetS may be another risk factor for osteoporotic fracture. A later cohort study displayed a negative relationship between MetS and type II diabetes and BMD in 3458 non-diabetic and 735 diabetic male veterans aged 50 to 76 years. Diabetic subjects had lower hip BMD compared to non-diabetic subjects. The BMD level of diabetic subjects and MetS subjects was similar. The findings suggested both MetS and diabetes are associated independently with lower BMD and higher osteoporosis prevalence in men (30). Cross-sectional studies have been performed in the Korean population by Kim et al. (31) and Hwang and Choi (32). Study by Kim et al.(31) involved a total of 2888 Koreans (1780 elderly men aged 40 years and 1108 postmenopausal women) and MetS subjects were found to have lower BMD at the femoral neck compared to normal subjects. Waist circumference was reported as the most significant negative predictor of BMD among all the MetS components. The study by Hwang and Choi (32)

recruited 2548 women subjects aged 18 years and above. They found that women with MetS had a lower vertebral BMD. An increase in the components of MetS presented in the subjects was associated with a lower vertebral BMD. In a recent study conducted by Wang et al. (33) involving 9930 Chinese adults aged 40 years or older in China, it was observed that the occurrence of osteoporotic fracture was higher among women with MetS (OR = 1.22; 95% CI 1.12–1.54), but not among men.

A few studies also reported a positive relationship between MetS and bone health. In a retrospective study in the USA involving 8197 subjects aged 20 and above, 22% of the subjects were found to have MetS. Subjects with MetS (0.86 g/cm2) were found to have higher femoral neck BMD compared to those without MetS (0.80 g/cm2) (34). There was a significant relationship between muscle mass and MetS and prevalence of osteoporosis among Koreans (1654 men and 1979 women, aged 50–93 years). Body composition and BMD were determined using dual-energy X-ray absorptiometry (DEXA) and findings showed that higher muscle mass and MetS were associated with a lower prevalence of osteoporosis in men and women (OR 0.65, 95% CI 0.46–0.91) (35).

The Effects of Individual MetS Components on Bone

Each component of MetS affects bone metabolism. The role of adiposity on bone health is complex. Adiposity increases body mass and exerts mechanical loading on the bone, thereby stimulating bone accrual(36). Aromatase enzymes in the abdominal subcutaneous and visceral adipose tissue synthesize oestrogens which are protective of bone health(37,38). On the other hand, adipose tissue is also a major source of proinflammatory enzymes, such as interleukin (IL)-1 (IL-1), IL-6 and tumour necrosis factor-alpha (TNF-α).87 In particular, visceral fat was shown to be a significant source of IL-1β, IL-6 and IL-15 in obese men (39). These cytokines encourage the formation of osteoclasts and bone resorption activities while decreasing the formation of osteoblasts and bone formation (40). Adipose tissue also sequesters lipid-soluble hormones, such as testosterone and vitamin D essential in maintaining bone health, making them unavailable to bone tissue (41,42). A study in the Chinese population demonstrated that visceral fat area, an index of visceral adiposity, correlated negatively with serum 25-hydroxyvitamin D3 level (43). Apart from that, visceral adipose tissue also secretes adipokines, such as leptin and adiponectin (44). Leptin regulates energy metabolism by controlling satiety (44). Leptin has both anabolic and catabolic effects on the skeleton. Leptin exerts anabolic effects on osteoblasts, and it inhibits osteoclast formation by acting through RANKL/OPG pathway. At the same time, leptin exerts catabolic actions on the bone by acting on the sympathetic nervous system and increasing catecholamine and neuropeptide Y (NPY) secretion (45). Overall, a higher leptin level is associated with higher BMD and bone mineral content according to a meta-analysis, especially post-menopausal women (46). Adiponectin improves the insulin sensitivity of liver and muscle, but its level is inversely associated with BMD in humans, although preclinical studies reveal an anabolic effect, through inhibition of SOST and modulation of RANKL/OPG pathway (47).

Type 2 diabetes mellitus (T2DM) is associated with increased BMD and increased fracture risk. Individuals with MetS suffer from impaired glucose tolerance and are predisposed to T2DM. Chronic hyperglycaemia will trigger the formation of advanced glycation end products (AGEs) when carbonyl group of a reducing sugar reacts with the amino group of macromolecules. The resultant Amadori products are unstable and will undergo subsequent reactions to form AGEs. Intracellular AGEs induce apoptosis of osteoblasts through endoplasmic reticulum stress. AGEs possess a biphasic effect on osteoclasts, whereby early exposure to AGEs inhibit osteoclasts differentiation and bone resorption, whereas late-stage exposure increases osteoclast fusion, podosome number and bone resorption. High glucose and AGEs increase SOST level production by osteocytes, thereby inhibiting bone formation. RANKL production by osteocytes is suppressed by AGEs, thereby inhibiting bone resorption. In combination, the effects caused low bone turnover and affect bone material properties. Human studies showed that skin AGEs were negatively correlated with bone material strength index regardless of diabetic status. In the Baltimore Longitudinal Study of Aging, both impaired glucose tolerance and diabetes status were negatively associated with hip geometry parameters and hip bending strength in women. This highlights a progressive bone impairment which starts even in prediabetic state. Besides, diabetes is also associated with bone marrow adiposity. Since adipocyte and osteoblast share the same mesenchymal progenitor, increased adipocyte differentiation decreases osteoblast differentiation, thereby limiting the osteoblast available for bone turnover. Insulin resistance is linked to high circulating insulin level, which exerts anabolic effects on the skeleton through direct and indirect actions on osteoblasts. All these effects precipitate altered bone geometry, such as increased intracortical porosity but increased trabecular bone density due to ineffective load distribution, as well as reduced bone strength observed in T2DM patients. Impaired glucose tolerance, when progresses to T2DM, has other indirect effects on fracture risk. Patients with diabetes have a higher risk of sarcopenia, which could increase their risk of falls and fractures.

HPT due to high circulating level of sodium ion prevents the reabsorption of calcium, thereby increasing calcium excretion. Subsequently, parathyroid hormone (PTH) production will increase and lead to bone resorption. Mutations in thiazide-sensitive sodium-chloride co-transporter (NCCT) responsible in sodium resorption at the distal convoluted tubule have also been postulated as a genetic link between HPT and bone health. Inactivating mutation of this transporter, as in the case of Gitelman's syndrome, leads to excessive sodium excretion but high BMD phenotype. Heterozygote of mutated NCCT may

also confer protection to the bone but the prevalence of this genotype is not clear.

A diet rich in fat will increase the free fatty acid (FA) in the blood. Oxidized FA can activate PPAR-γ, which subsequently induces the differentiation of adipocytes in the bone marrow and suppresses differentiation of osteoblasts. Oxidized LDL impairs osteoblast differentiation and mineralization process.116 Accumulation of oxidized LDL can induce apoptosis of osteoblasts by lysosomal membrane damage. Oxidized LDL can increase the production of RANKL of osteoblasts without corresponding changes in OPG level and stimulate the differentiation of osteoclasts. On the other hand, oxidized LDL can directly suppress the formation of osteoclasts and the fusion of lysosomes to the ruffled border, thereby affecting their bone resorption activity, via scavenger receptor-A. Mevalonate pathway responsible for the synthesis of cholesterol and isoprenoids is the drug target for dyslipidaemia treatment. Isoprenoids generated from the mevalonate pathway are involved in the prenylation of GTPases, such as Rho, Ras and Rac. Suppression of GTPase prenylation though mevalonate is known to suppress osteoclast differentiation, function and survival.

HDL can prevent oxidized LDL-induced apoptosis of osteoblast by preserving lysosome integrity. Paraoxonase 1 associated with HDL has been shown to prevent oxidation of LDL and lipid peroxidation products, thereby contributing to the protection of HDL on the bone. Apart from cholesterol transport, HDL also suppresses proinflammatory cytokine synthesis from macrophages, which would otherwise promote the formation of osteoclasts over osteoblasts, leading to bone loss.

Conclusion

The relationship between MetS and BMD is complex. After adjusting for the effects of mechanical loading exerted by BMI, the association seems to be negligible or negative. In addition, the relationship may be mediated by sex. The proinflammatory, pro-oxidative and pro-calciuric body environment may contribute to the negative effects of MetS on bone. Improving the metabolic profile of the patients though medications could potentially alleviate the negative effects on BMD. However, excessive weight loss due to MetS management could be detrimental to the bone, and exercises can balance it. In particular, the combination of calorie restriction and exercise can promote a reduction in fat mass while retaining lean and bone mass. Thus, proper management of MetS can benefit not only the cardiovascular system but also the skeletal system.

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