Obesity and Bone Health

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Abstract

Obesity adversely affects bone health by multiple mechanisms such as increased inflammatory cytokines, dysregulation of hormones affecting bone metabolism as well as direct and indirect effects of adipocyte on bone cell metabolism. Latest research has shown that a high fat mass maybe a risk factor for osteoporosis and fragility fractures.

Keywords: Fragility fractures, bone health, obesity, osteoporosis fat

Introduction

Obesity is a global epidemic. In 2021, an estimated 1·00 billion adult males and 1·11 billion adult females were overweight or obese, with prediction forecast that by 2050, almost 2 in 3 adults over the age of 25 years will suffer from the same[1]. Obesity has been historically believed to have a protective effect on bone mass, however this understanding has recently been challenged[2]. Studies have shown an increased risk of fractures in obese women as compared to normal weight or underweight women (RR: 1.28, 95% CI: 1.04-1.58)[3]. Higher body mass index (BMI) has been observed to increase risk of fracture at specific sites especially distal lower limbs[4].

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Link Between Obesity and Bone Metabolism

The obesity and bone metabolism interplay is complex. Several mechanical, metabolic and hormonal mechanisms have been proposed to explain the connection between the adipose tissue and bone. Adipose tissue is an endocrine organ, releasing adipokines as well as proinflammatory cytokines which interact with the bone microenvironment. Other mechanisms hypothesized for the bone-fat connection are replacement of osteoblasts by fat cells in bone marrow, fat mass and obesity-associated (FTO) gene mutation leading to weight gain and bone fragility and accelerated senescence in stromal stem cells[5].

Adipocytes and osteogenic precursors

Osteoblasts and adipocytes have a common origin from pluripotent mesenchymal stem cells. Osteo-adipogenic transdifferentiation has been observed in conditions causing a low-grade inflammation such as ageing, menopause, osteoporosis as well as obesity[4].

The signals initiating transdifferentiation include the transcriptional activator peroxisome proliferator-activated receptor gamma (PPARγ), leptin and the Wingless-related integration site (Wnt) signalling glycoproteins[5]. Activation of Wnt stimulates osteoblast formation and inhibits adipocyte differentiation. In mild obesity, secreted frizzled-related protein 1 (sFRP-1), is increased in adipocyte stem cells and inhibits Wnt signalling promoting adipocyte differentiation[6].

Inflammatory cytokines and bone

Obesity induces a proinflammatory state elevating circulating levels of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP) and leptin[7]. Inflammatory cytokines enhance osteoclast activity thereby stimulating bone resorption.

Leptin, which is increased in obesity, has been found to be proinflammatory. Leptin has a dual effect on bone metabolism. Directly, leptin stimulates osteoblast progenitors. In obesity, leptin resistance increases bone resorption via serotonergic activity[8].

Overall, the negative effect of leptin on bone predominates in obesity. Adiponectin acts as an anti-inflammatory cytokine and stimulates osteoblastic activity and increases synthesis of type 1 collagen and osteocalcin, which are markers of osteoblasts differentiation and maturation[9]. Adiponectin levels are reportedly low in obese individuals. Proinflammatory cytokines stimulate osteoclast activity via modulation of the RANKL/RANK/OPG pathway and act as mediators of osteopenia and osteoporosis.

Hormonal milieu and bone

Adipose tissue as an endocrine organ causes hormonal dysregulation in obesity and influences the fat-bone interaction. Increased aromatization of androstenedione by aromatase in adipose tissue results in higher circulating estrogen[10]. This high estrogen state may partially combat bone loss in obese postmenopausal women. Obesity has been associated with vitamin D deficiency, causal association of which is not fully understood. Possible explanations for low vitamin D in obesity are larger volume of distribution, bound vitamin D in adipose tissue, diets poor in vitamin D and decreased absorption.

Severe vitamin D deficiency subsequently results in secondary hyperparathyroidism. Parathyroid hormone (PTH) has been directly associated with fat mass[11]. PTH influences calcium metabolism as well as proinflammatory cytokine secretion with resorption effects on cortical bone.

Obesity increases the secretion of pancreatic hormones such as insulin, amylin, and preptin that are shown to have anabolic effect on bone health. However, in the obese with hyperinsulinemia and insulin resistance, the anabolic effect of the pancreatic hormones may be counteracted by paradoxically altered bone microarchitecture which partially explains the higher rates of fracture in obese patients with diabetes.

Obesity and Bone Mineral Density

Several studies have shown a positive relationship between BMI and BMD. Higher BMD in higher BMI individuals is believed to be due to mechanical loading of bone[9]. Weight bearing signals osteocytes to respond to shear stress and stimulates osteoblast differentiation. Lean mass has been shown to determine the effect of mechanical loading more than the fat mass[9]. The increase in BMD in obesity is also partially explained by higher estrogen synthesis from adipose tissue. A higher serum concentration of estrogens was found in obese postmenopausal than in non-obese women[12]. Favorable role of obesity in bone metabolism has been challenged by recent studies which have reported high prevalence of obesity in postmenopausal women presenting with fragility fractures[13]. In obese individuals, BMD may be overestimated due to the overlying subcutaneous tissue. Precise quantitative measurements by high-resolution peripheral quantitative computed tomography and ultrasound have confirmed these observations. These methods are not affected by the overlying soft tissue, thus reliably assessing bone density in obese individuals. The relationship between BMI and fracture is observed to be site-specific with higher risk for non-vertebral fractures as compared to vertebral sites and proximal femur in obese adults[13]. Interestingly, recent research has shown differential impact of obesity on the BMD, with bone mineral density at the femoral neck is significantly lower in the morbidly obese postmenopausal women compared to obese postmenopausal women[14]. Postulated mechanisms are higher proinflammatory cytokines, associated comorbidities and severe vitamin D deficiency with secondary hyperparathyroidism, however further research is a requisite to validate these findings.

Effect of obesity on bone microarchitecture is not well understood. Trabecular bone score has been found to be negatively associated with BMI in obese and morbidly obese postmenopausal women[14].

Obesity, Osteoporosis and the "Obesity Paradox"

It has been widely accepted that obesity is protective against fractures. This unusual association was believed to be one of the many aspects of the "obesity paradox" which is a term to explain the survival advantage that obese individuals have for few chronic diseases as compared to normal weight individuals. Research has shown that the "obesity paradox" is site specific for fractures and holds true for hip, wrist and pelvis fractures[13]. Distribution of adipose tissue may be the explanation for site specific fracture protection conferred by obesity. Visceral fat related increased inflammatory factors as well as mechanical loading have been speculated to be the mechanism behind the obesity paradox[15].

Conclusion

There is a multifaceted, multidirectional relationship between bone and adipose tissue. Understanding the crosstalk between fat and bone will further elucidate the cause of bone fragility and increased risk of fractures in obesity, despite an apparent increase in BMD, directing cause related treatment approaches for the same in the near future.

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