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Review

Childhood obesity, bone development, and cardiometabolic risk factors

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ABSTRACT

Osteoporosis and obesity are both major public health concerns. It has long been considered that these are distinct disorders rarely found in the same individual; however, emerging evidence supports an important interaction between adipose tissue and the skeleton. Whereas overweight per se may augment bone strength, animal studies suggest that the metabolic impairment that accompanies obesity is detrimental to bone. Obesity during childhood, a critical time for bone development, likely has profound and lasting effects on bone strength and fracture risk. This notion has received little attention in children and results are mixed, with studies reporting that bone strength development is enhanced or impaired by obesity. Whether obesity is a risk factor for osteoporosis or childhood bone health, in general, remains an important clinical question. Here, we will focus on clarifying the controversial relationships between childhood obesity and bone strength development, and provide insights into potential mechanisms that may regulate the effect of excess adiposity on bone.

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1. Introduction

Osteoporosis and obesity are both major public health concerns. Since the 1970s, obesity rates have doubled in adults aged 20 years or older and have tripled in children and adolescents aged 6–19 years (Flegal et al., 2002; Ogden et al., 2006). It was estimated recently that the direct costs associated with obesity in the US is approximately $80 billion per year, representing ~10% of the national health expenditures (Finkelstein et al., 2003). In the realm of osteoporosis, it is estimated that 1 in 2 women and 1 in 3 men over the age of 50 will experience an osteoporotic-related fracture in their lifetime (Johnell and Kanis, 2005). The estimated US healthcare costs associated with osteoporosis amounted to $18 billion in 2002 and is projected to approach $45 billion by 2020 (Melton, 2003). It has long been considered that obesity and osteoporosis are distinct disorders rarely found in the same individual; however, emerging evidence supports an important interaction between adipose tissue and the skeleton (Reid, 2002; Rosen and Bouxsein, 2006).

Adipose tissue was once considered just a passive reservoir for energy storage; however, it is now known to play a role in energy metabolism, neuroendocrine function and immune status. Likewise, analyses from cellular and molecular studies also suggest that adipose tissue plays a significant role in bone metabolism (Reid, 2002; Rosen and Bouxsein, 2006). Mechanisms involving bone and

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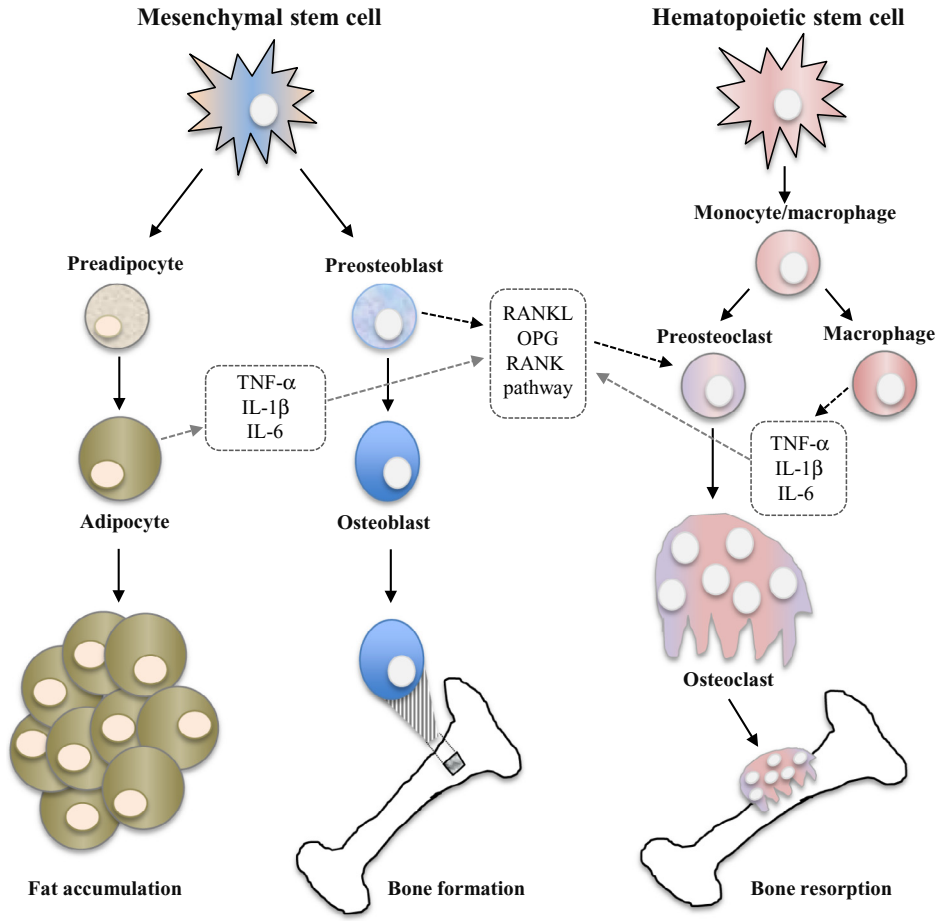

Fig. 1. Interrelationships between fat accumulation, bone formation, and bone resorption. Mechanisms involving fat and bone are intricate by nature, since both adipocytes and osteoblasts originate from mesenchymal stem cells in bone marrow. Osteoclasts originate from monocyte/macrophage precursors of hematopoietic stem cells. Adipocytes and macrophages can secrete several cytokines such as TNF-α, IL-1β, and IL-6, which are capable of stimulating osteoclast activity and bone resorption via regulation of the RANKL/RANK/OPG pathway. OPG, a decoy receptor secreted by preosteoblasts, acts as a decoy receptor to RANKL, and therefore inhibits osteoclast activation and bone resorption. TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6.

fat are intricate by nature, since both adipocytes and osteoblasts originate from mesenchymal stem cells in bone marrow, and factors that stimulate adipogenesis typically inhibit osteoblast differentiation (Rosen and Bouxsein, 2006) (Figure 1). What ultimately determines the fate of bone marrow stem cells is not fully understood and is the subject of ongoing investigation.

Several intracellular signals and phenotype-specific transcription factors have been shown to influence the mesenchymal stem cell into either bone or fat cells. Simplistically, activation of the Wnt/β-Catenin pathway (Piters et al., 2008) and increased expression of transcription regulators such as the Runt-related transcription factor-2 (Runx2) (Ducy et al., 1997), osterix (Nakashima et al., 2002), and Msx2 (Satokata et al., 2000) have all been attributed to promote osteoblastogenesis. Estrogen has been shown to increase bone formation with associated inhibition of fat formation (Dang et al., 2002). On the other hand, members of the CCAAT/enhancer binding protein (C/EBP) family of transcription factors are characterized as regulators of adipogenesis (Tontonoz and Spiegelman, 2008). The transcription factor peroxisomal proliferator-activated receptor gamma (PPAR-γ) is seen as the master regular of fat formation within bone marrow, and activation of PPAR-γ favors differentiation of stem cells into adipocytes rather than osteoblasts (Rzonca et al., 2004).

Clinical investigations have established that a high body weight and obesity are positively correlated with bone mass and that a low body weight or loss of weight is associated with bone loss and fracture risk (Shapses et al., 2011). The greater bone mass in obesity may result from the greater mechanical load on bone due to excess weight or hormones produced by the excess adipose tissue. Furthermore, the regional distribution of fat may influence bone mass independently of obesity (Pollock et al., 2010, 2011a; Tarquini et al., 1997; Warming et al., 2003). Specific bone sites may also be affected differently depending on whether they are load-bearing or by the cortical:trabecular content of a particular bone (Laing et al., 2013; Pollock et al., 2007, 2011b). This weight–bone relationship is not gender specific and it is also found in children, although severe obesity at greater levels of adiposity observed typically only in Western countries may attenuate the positive effect on bone mass and/or bone quality in children (Shapses et al., 2011). Although obesity is associated with a higher bone mass, the impact of excess adiposity on bone quality, especially modification of the trabecular and cortical compartments, presents a more complicated picture that may actually lead to an increase in fracture risk. Thus, whether obesity is a risk factor for suboptimal bone strength development remains an important clinical question. In this review, we will focus on clarifying the controversial relationships between childhood obesity and bone health, and provide insights into potential mechanisms that may mediate the effect of excess fat accumulation on bone.

2. Evaluation of bone health in the developing skeleton

To maintain its functions, bone tissue is constantly turned over by processes referred to as modeling and remodeling, which involves