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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.

Keywords

Obesity; Children; Fat; Bone; Inflammation; Insulin resistance

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 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 (Peters 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 regulator 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 bone resorption by osteoclasts and bone formation by osteoblasts (Einhorn, 1996). Modeling refers to alterations in the shape of bone, whereas remodeling refers to turnover of bone that does not alter its shape. The balance between modeling and remodeling differs between the growing and adult skeleton. In the former, modeling is the dominant mode, whereas in the latter, remodeling is dominant. Modeling, seen in early childhood up to early adulthood, is the process in which bones become larger, heavier, and denser; hence, osteoblastic activity exceeds osteoclastic activity. Bone remodeling begins to take over in adulthood, where bone mass undergoes constant and equal removal of old bone and renewal with newly formed bone (Parfitt, 1982). An equilibrium exists between bone resorption and formation until the fourth or fifth decade of life, when bone resorption begins to supersede the continually declining bone formation process (Frost, 1990). Any disorder or condition that alters bone formation or enhances bone resorption during the lifespan will lead to suboptimal bone turnover dynamics, presumably leading to a greater risk of osteoporotic fracture. Because bone integrity in childhood is likely to have biologically relevant effects on skeletal competence in advanced age (Baxter-Jones et al., 2011), it is important to understand the factors, including obesity, that influence bone in childhood.

Pediatric obesity has reached epidemic proportions globally (Wang and Lobstein, 2006). The dire consequence of childhood obesity is that it increases the risk for metabolic conditions such as hypertension, type 2 diabetes, and cardiovascular diseases (Weiss et al., 2004). Now, there is increasing concern that being overweight may be associated with suboptimal bone strength development, as there is mounting evidence linking childhood obesity to skeletal fractures (Table 1). Inevitably, the potential for increasing adiposity to negatively effect pediatric skeletal integrity is a subject of growing interest.

Determination of body mass index (BMI) is recommended for classification of overweight and obesity. For children and adolescents, BMI is age- and sex-specific to reference curves such as those published by the Centers for Disease Control and Prevention (CDC) (Kuczmarski et al., 2000) and the World Health Organization (WHO) (de Onis et al., 2007). According to the CDC, a BMI above the 85th and 95th percentiles are considered to be overweight and obese, respectively. The WHO defines obese as a BMI > 3 standard deviations above the WHO growth standard median.

With the emergence of dual energy X-ray absorptiometry (DXA) in the 1990s as a clinical instrument to assess bone mineral density (BMD) and soft tissue mass, great strides were made in furthering our understanding of factors influencing bone health in adults and bone mineral accrual in the growing skeleton. BMD and bone mineral content (BMC) can be measured with precision by DXA at the lumbar spine, total hip, wrist, and whole body. BMD has been applied to establish normal patterns that differ between different race/ethnic groups and that permit the precise and accurate quantification of bone mass according to age, group, and sex (Kanis, 2002). DXA has proven to be a valuable two-dimensional bone imaging technique, but because DXA calculates areal, and not volumetric, BMD and since

the bone area does not increase at the same proportion as bone volume during growth, the true BMD of children and adolescents might be overestimated for large bones and underestimated for small bones. Therefore, BMC is recommended as the bone measure to assess bone mass status in children and adolescents (Gordon et al., 2008).

Recently, peripheral quantitative computed tomography (pQCT) was proposed as an imaging tool for the study of both trabecular and cortical bones in adolescents and adults. This proposal is based on the capacity of this method to evaluate volumetric bone density and bone geometry, providing a better understanding of bone strength (Zemel et al., 2008). Although the contrast resolution of pQCT is lower than that of magnetic resonance imaging, the low costs of this method favor its use for the evaluation of large population samples. However, studies are needed to determine reference ranges and measurement sites and to standardize devices and software. Since children and adolescents are in the phase of growth, the exact and most consistent site of measurement needs to be determined (Zemel et al., 2008).

3. Clinical evidence for obesity and bone relationships during childhood

In adults, a high body mass index (BMI) or being obese has long been thought to be protective against osteoporosis and related fractures (Reid, 2002, 2008). Contrary to the notion that obesity may also protect children from fractures, a recent study reviewing medical records of 913,178 children aged 2–19 years reported that moderately obese and extremely obese children had an increased odds ratio (OR, 1.23 and 1.42, respectively, with 95% CI, 1.12–1.35 and 1.26–1.61, respectively) of fracture compared to normal weight children (Kessler et al., 2013). A higher fracture risk in obese children may be the result of greater forces generated during a fall, a lifestyle contraindicative to strong bones, and/or excess fat tissue that impairs bone strength development (Frost, 1997). Given the current state of increasing pediatric obesity along with reports of high fracture rates in obese children, it is vital to understand the effects of adiposity on the skeleton since achieving optimal bone mass and size during growth will presumably reduce the risk of osteoporotic fractures later in life (Hui et al., 2003).

An obligatory level of fat is required for the initiation of skeletal maturation; however, excess adiposity, while associated with increased bone size, may have an adverse effect on bone quality. Across the pubertal years, body fat has been associated with larger bones in boys, and larger and denser bones in girls (Streeter et al., 2013). However, accelerated skeletal growth and greater bone size may not translate into reduced fracture risk (Kessler et al., 2013). In fact, a recent fracture study in females aged 4–15 years reported that those who sustained a fracture were more overweight and had a smaller cross-sectional area at the non-fractured forearm compared to the non-fracture group (Skaggs et al., 2001). Since differences in bone mass and size are apparent between males and females during puberty (Gilsanz et al., 1997), it is possible that gender may affect the association between obesity and bone outcomes. In a study of adolescents, total body fat mass was associated with bone mass in females but not males (Sayers and Tobias, 2010). In a case–control study of children with and without fractures, it was found in girls that the prevalence of overweight/obesity was greater in those presenting with fracture at either upper or lower limb; however, in boys,

the prevalence was greater only in those with fracture at the lower limb (Valerio et al., 2012). Race may be another important factor in the bone–fat relationship (Pollock et al., 2011b, 2011c). The National Health and Nutrition Examination Survey, 2003–2006, estimated that the overweight prevalence among black females, aged 12–19 years, was almost double the rate for white females (28% versus 15%) (Ogden et al., 2008). If the effect of obesity on bone is independent of race, skeletal health in this population could be a public health concern.

Determining whether excess adiposity is either beneficial or detrimental to the growing skeleton has been challenging. Whereas some studies report greater bone mass in overweight children and adolescents compared to their healthy weight peers (Clark et al., 2006; Ducher et al., 2009; Leonard et al., 2004), others conclude that obesity is linked to lower bone mass or that extra weight from fat mass had no effect on bone mass (Petit et al., 2005; Pollock et al., 2007, 2011b; Wosje et al., 2009). Discrepancies in these childhood bone–fat investigations may be attributed, in part, to the methodological limitations when comparing bone mass between overweight and healthy weight children of the same age. At any given age, a wide variation exists among children in stature, body composition, rate of growth, and timing and tempo of biological maturation. Since overweight compared to healthy weight children of the same age are generally further advanced in maturation, their skeletal development is likewise more advanced, because of increased hormonal activity than their healthy weight peers. Another limitation of the aforementioned pediatric bone–fat investigations is that biochemical parameters indicative of metabolic abnormalities in the overweight children were not reported. Comorbidities associated with adult obesity, such as hypertension, dyslipidemia, and insulin resistance, also occur in children and adolescents (Weiss et al., 2004), and more importantly, the prevalence of these metabolic abnormalities are increasing alongside childhood obesity (Johnson et al., 2009). Since adult investigations have linked lower bone mass to metabolic syndrome (Hwang and Choi, 2010; von Muhlen et al., 2007) as well as individual components of the metabolic syndrome such as hypercholesterolemia (Tanko et al., 2003) and hyperglycemia (Petit et al., 2010), it is possible that discrepancies in prior pediatric bone–fat studies could have been attributed to metabolic abnormalities present in some but not all overweight subjects. This notion seems plausible given that elevated glucose concentrations have been shown in vitro to inhibit bone mass accrual (Balint et al., 2001) combined with additional evidence suggesting that oxidized lipids direct un-differentiated mesenchymal stem cells toward adipocyte rather than osteoblast differentiation (Parhami et al., 1997).

In an effort to provide better insight into the childhood bone and fat relationship, our research work has focused solely on overweight and obese children with and without metabolic abnormalities (i.e., cardiometabolic risk factors such as high waist circumference, blood pressure, fasting glucose, triglycerides, and low HDL-cholesterol). In our pediatric investigations (Pollock et al., 2010, 2011a, 2011d), metabolic abnormalities were characterized as cardiometabolic risk factors (CMR) and defined according to the National Cholesterol Education Program Adult Treatment Panel III definition modified for age (“American Academy of Pediatrics: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents,” 1992; Cook et al., 2008; Daniels and Greer, 2008). Specifically, these risk factors were defined accordingly: (1) waist circumference 90th

percentile for age and gender; (2) HDL cholesterol 40 mg/dL; (3) triglycerides 110 mg/dL; (4) systolic or diastolic blood pressure 90th percentile for age, gender, and height; and (5) fasting glucose 100 mg/dL. In overweight (OW) adolescents aged 14–18 years, we compared total body bone mass, as measured by DXA, between those with and without cardiometabolic risk factors (CMR) (Figure 2) (Pollock et al., 2011a). We found that compared to OW + Healthy group, total body bone mass was 5.4% lower in the OW + 1CMR group and 6.3% lower in the OW + 2CMR group. Given that the CMR groups were carrying significantly greater total body fat mass loads (an average of 9-lbs of fat mass in the OW + 1CMR group and 22-lbs of fat mass in the OW + 2CMR group) than the OW + Healthy group, it appears that excess weight from the fat mass provides no additional weight-loading benefit to bone mass. These findings suggest that if cardiometabolic risk factors are present alongside being overweight, it could have a negative effect on bone. More importantly, it is possible to hypothesize that if the extra weight from fat mass provides no additional influence to bone, an overweight adolescent with metabolic abnormalities may be more susceptible to fracture because traumatic impact forces generally scale with body weight (Davidson et al., 2003; Kim et al., 2013). However, further work is required to establish this connection.

Even in adults, the associations of metabolic syndrome with bone mass have not been extensively explored, and the results have been mixed. Whereas some authors have reported greater bone mass in adults with metabolic syndrome (Kinjo et al., 2007), others have shown the opposite relationship (Hwang and Choi, 2010; von Muhlen et al., 2007). These conflicting reports may be due, in part, to the heterogeneous samples studied (e.g. age, co-morbid disease status and medication use) and potentially of greater importance, the lack of consideration of the generally larger body size in metabolic syndrome patients compared to controls. If the latter is not considered, the effect of body size on bone mass could lead to misinterpretations when comparing individuals of different stature and body composition.

Recent studies have challenged the traditionally accepted view that obesity is beneficial to the growing skeleton (Petit et al., 2005; Pollock et al., 2007, 2011b; Wosje et al., 2009); however, it is apparent that a phenotype, beyond total fat accumulation, is needed to explain the complex relationship between developing bone and obesity. Given that the relationship between type 2 diabetes and osteoporotic fractures is increasingly being recognized (Schwartz and Sellmeyer, 2007), it is possible that insulin resistance may be the culprit linking poor bone health and childhood obesity. In our adolescent study (Pollock et al., 2011a), homeostasis model assessment of insulin resistance (HOMA-IR), a surrogate measure of insulin resistance based on fasting insulin and glucose, explained a significant proportion of the variance in total body bone mass. Thus, it is plausible that insulin resistance may explain, in part, the association between obesity and suboptimal bone mass. Evidence to support this notion was first reported in a cohort of overweight Hispanic-American children in which total body BMC was inversely associated with markers of insulin resistance, as determined by oral glucose tolerance test (Afghani et al., 2005). Similarly, in a recent study of overweight prepubertal children (Pollock et al., 2010), our group observed lower bone mass in the children with pre-diabetes compared to those with normal glucose levels. Taken together, these studies indicate that abnormal glucose regulation has a negative effect on the growing skeleton. The mechanism for the potential

negative effect of insulin resistance on bone development is currently unknown; however, some hypotheses include decreased osteoblast function, increased osteoclast and osteocyte functions, excessive nonenzymatic glycation, and alterations in vitamin D endocrine function (Figure 3).

It is also possible that obesity during childhood promotes both low bone mass accrual and risk for diabetes through events that are mechanistically associated. Recent animal data have uncovered the presence of a “bone-fat-pancreas” axis that regulates energy homeostasis, coordinates energy partitioning between bone and adipose tissue, and impacts insulin sensitivity.

In mice lacking the gene for osteocalcin, a bone-derived protein and well-known biomarker of bone formation, Lee et al. (2007) observed phenotypes of glucose intolerance, insulin resistance, and visceral obesity. When recombinant osteocalcin was administered to the animals, improvements in glucose tolerance and insulin secretion were observed (Lee et al., 2007). In a mouse model lacking the gene for the insulin receptor in osteoblast (Ob- IR), Fulzele et al. (2010) demonstrated lower postnatal bone mass acquisition in the Ob- IR mice compared to controls. Along with decreased bone formation, the Ob- IR mice displayed marked peripheral adiposity and insulin resistance that was accompanied by decreased osteocalcin concentrations. When recombinant osteocalcin was administered in this study, the researchers observed improvements in glucose tolerance and insulin sensitivity (Fulzele et al., 2010). In support of the animal studies linking osteocalcin and insulin sensitivity (Fulzele et al., 2010; Lee et al., 2007; Yoshikawa et al., 2011), we reported associations between higher insulin sensitivity and greater osteocalcin levels in cohorts of obese children (Pollock et al., 2011d) and obese adults (Gower et al., 2013).

These novel relationships described above between osteocalcin and glucose-insulin metabolism appear to be regulated via leptin (Hinoi et al., 2008), an adipocyte-derived hormone that is strongly and positively correlated with fat mass levels (Hamrick and Ferrari, 2008). Animal studies reveal that leptin treatment elicits a bimodal response, where low doses of leptin can stimulate bone formation and prevent bone loss, but higher concentrations of leptin actually suppress bone formation and increase bone resorption (Martin et al., 2007). Thus, one way in which high levels of adiposity may inhibit the accumulation of bone mass during growth is via hyperleptinemia. Though the basic mechanisms underlying this biphasic effect are unclear, they may involve leptin receptor downregulation, which is known to occur with increases in endogenous leptin due to increased food intake or adiposity (Martin et al., 2000). Given that obesity, insulin resistance, and type 2 diabetes are related disorders of energy metabolism, further investigation of the bone-fat-pancreas axis is warranted.

Another significant finding in our pediatric studies was that the influence of adiposity on bone mass may depend on the manner in which the fat mass accumulates (Pollock et al., 2010, 2011a). A limitation of previous pediatric investigations of fat-bone relationships, which were inconclusive, was that most did not investigate the separate influence of total and central adiposity on bone. Given that metabolic abnormalities are more strongly associated with central rather than total adiposity (Fox et al., 2007), it is possible that this

type of fat accumulation could affect developing bone distinctly, which could be another potential explanation for the conflicting pediatric data of the bone-fat relationship. In our study of overweight pre-pubertal children (Pollock et al., 2010), we found that both total adiposity (total body fat mass measured by DXA) and central adiposity (visceral adipose tissue measured by magnetic resonance imaging) have significant but opposing relations with total body bone mass. Whereas total body fat had a positive association with bone mass, visceral fat had a negative relationship with bone mass. In our regression analyses, however, it was visceral fat, rather than total body fat, that was the conclusive independent predictor of bone mass. Similarly, this relationship between visceral fat and bone mass was also observed in our adolescent study (Figure 4) (Pollock et al., 2011a). Taken together, it seems that increased central adiposity, which is more clinically relevant for metabolic abnormalities than increased total body adiposity, could play an adverse role in bone health.

4. Biologic mechanisms for the bone-fat connection

Osteoblasts and bone marrow adipocytes share a common mesenchymal stromal cell progenitor and, consequently, the abundance of mature cells is not only dependent on the availability of that common progenitor but also on the direction of differentiation toward one lineage, since signals that skew differentiation toward one phenotype can suppress the development of the other (Figure 1). Bone marrow adipocytes share many features of extramedullary adipocytes (i.e., the adipocytes residing in adipose tissue) (Shockley et al., 2009); and therefore, factors that modulate metabolic function and cell fate in peripheral adipose depots may also affect marrow adipocytes. Historically, adipocytes in the marrow were regarded as passive “placeholders” to fill the space not needed for hematopoiesis (Gimble et al., 1996). However, more recently, it has been recognized that these cells play an active role in the marrow, most likely as a source of paracrine factors, as well as being a receptacle for energy storage (Gimble et al., 1996). Consequently, marrow adipocytes may secrete bone-modulating adipokines, such as leptin and adiponectin, directly into the local microenvironment, which influence the function of osteoblasts (Lecka-Czernik, 2012). In addition, recent evidence suggests that bone marrow pre-adipocytes also secrete factors into the bone marrow microenvironment that modulate the lineage commitment of mesenchymal progenitors (Abdallah and Kassem, 2012), influencing the abundance of adipocytes relative to osteoblasts. As a repository of energy storage and expenditure, marrow adipocytes have been found to share characteristics with brown adipocytes, which are primarily involved in thermogenesis and energy dissipation (Krings et al., 2012). Increased marrow adiposity during puberty, when bone mass accrual reaches a peak (Kawai and Rosen, 2010), also supports the notion that marrow adipocytes may act as an energy reservoir. However, although marrow adiposity is associated with increased energy availability, it may also result in a reduction in bone mass, bone formation (Di Iorgi et al., 2008; Justesen et al., 2001; Verma et al., 2002) and bone mineral density (BMD) (Bredella et al., 2011; Shen et al., 2007), with the latter being a strong predictor of fracture risk (Johnell et al., 2005).

4.1. Obesity, inflammation, and insulin resistance

Obesity is frequently associated with chronic systemic inflammation and metabolic alterations, which predispose to the development of type 2 diabetes and cardiovascular

disease (Van Gaal et al., 2006). Activation of the immune system and chronic low-grade inflammation may link excessive fat accumulation to obesity-related metabolic dysregulation (Elenkov et al., 2005; Esser et al., 2014; Stofkova, 2009). The activation of the immune system in obesity is not only reflected by higher circulating concentrations of proinflammatory cytokines, but also by infiltration of macrophages and other immune cells in adipose tissue, liver, muscle and pancreas. Immune cell populations shift toward a proinflammatory profile with a production of pro-inflammatory cytokines, which both affect insulin signaling in peripheral tissues and induce β -cell dysfunction and subsequent insulin secretion defect (Esser et al., 2014).

At the level of adipose tissue, systemic inflammation may be initiated by dysfunction of adipocytes (Esser et al., 2014). Adipocyte dysfunction may be caused by intracellular “toxins”, such as ceramides or other lipids (Vandanmagsar et al., 2011), which accumulate in adipose tissue during weight gain. However, not all obese individuals develop chronic systemic inflammation, metabolic or cardiovascular diseases (Stefan et al., 2008). Therefore, there must be factors that protect a subgroup of obese individuals against these obesity-related traits. It has been suggested that heterogeneity in body composition, fat distribution and adipose tissue function maybe more important to determine the individual cardiometabolic risk than body fat mass.

Weight gain leads to the accumulation of adipose tissue by an increase of adipocyte volume (hypertrophy) or number (hyperplasia). The expansion of adipose tissue significantly influences adipocyte biology and subsequently impairs whole-body glucose homeostasis. Hypertrophy of adipocytes is considered a key event associated with a loss of insulin sensitivity both in lean and obese conditions (Cotillard et al., 2014; Salans et al., 1968). Individuals with larger adipocytes typically have elevated proinflammatory factors including leptin, interleukin-1 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1) (Skurk et al., 2007), reduced levels of the insulin-sensitivity related adipokine adiponectin and IL-10 (Kloting et al., 2010; Skurk et al., 2007), and increased basal and catecholamine-stimulated lipolysis (Laurencikiene et al., 2011). In obese individuals, adipocyte hypertrophy seems to be associated with deleterious effects on inflammation and glucose metabolism.

4.2. Inflammation and bone

A recent development in obesity research is the concept that increased adiposity is characterized by greater systemic inflammation. The basis for this notion is that inflammatory-related factors, including various cytokines and acute phase proteins, are increased in obesity, particularly abdominal obesity (Trujillo and Scherer, 2006). As adipocytes and macrophages within fat can secrete cytokines and acute phase proteins, it is considered that increasing visceral fat accumulation contributes to greater production of these inflammatory-related factors, thus leading to chronic low-grade systemic inflammation, a well-known risk factor for cardiovascular disease and diabetes (Kershaw and Flier, 2004).

Our understanding of bone turnover has increased considerably with the discovery of the key molecular drivers of osteoclastogenesis, receptor activator of nuclear factor- κ B ligand (RANKL) and osteoprotegerin (OPG) (Vega et al., 2007). Osteoblasts have been revealed to

regulate osteoclast activity through the expression of RANKL and OPG (Figure 1). RANKL is expressed on the osteoblast cell surface and binds to its receptor, RANK, on the surface of hematopoietic precursor cells to stimulate osteoclast differentiation and maturation in the presence of macrophage colony stimulation factor (Yasuda et al., 1998). OPG, a decoy receptor secreted by osteoblasts, binds RANKL to prevent activation of RANK, and therefore prevents osteoclast activation and bone resorption (Lacey et al., 1998). Clinically, it has been demonstrated in postmenopausal women that elevated osteoclastic activity and increased bone resorption is positively associated with upregulation of RANKL (Cao et al., 2005; Eghbali-Fatourehchi et al., 2003).

Proinflammatory cytokines including TNF- α , IL-1, and IL-6 are key mediators in the process of osteoclast differentiation and bone resorption. Chronic inflammation and increased proinflammatory cytokines induce bone resorption and bone loss in patients with periodontitis (Van Dyke and Serhan, 2003), pancreatitis (Mann et al., 2003), inflammatory bowel disease (Bernstein et al., 2003), and rheumatoid arthritis (Romas et al., 2002). It has also been established that upregulated proinflammatory cytokines are primary mediators of osteopenia or osteoporosis. The accelerated bone loss at menopause is linked to increased production of proinflammatory cytokines including TNF- α , IL 1, and IL-6 (Mundy, 2007). These proinflammatory cytokines are capable of stimulating osteoclast activity through the regulation of the RANKL/RANK/OPG pathway (Khosla, 2001; Pfeilschifter et al., 2002). In mice lacking IL-1 β and TNF genes (Vargas et al., 1996) or over-expressing TNF- α decoy receptor (Ammann et al., 1997), ovariectomy did not cause bone loss. Blocking the action of IL-1 with an IL-1 receptor antagonist or the signaling of TNF- with a TNF-binding protein decreased osteoclast formation and bone resorption in ovariectomized mice (Kimble et al., 1995). The significant increase in the development of osteoarthritis in obese human subjects is another evidence that chronic inflammation influences bone metabolism (Anandacoomarasamy et al., 2008).

4.3. Insulin resistance, type 2 diabetes, and bone

Although type 1 diabetes is known to have negative effects on bone metabolism (Albright and Reifenstein, 1948; Schwartz et al., 2001), it was not until recently that type 2 diabetes, which is increasing globally as a consequence of the obesity epidemic, is considered a potential risk for skeletal fractures (Holmberg et al., 2006; Melton et al., 2008). The low bone mass typically associated with type 1 diabetes is thought to contribute to the greater number of skeletal fractures observed in type 1 diabetes patients than in controls (Buysschaert et al., 1992; Hofbauer et al., 2007). Type 2 diabetes patients, on the other hand, are generally characterized with high BMC and BMD (Buysschaert et al., 1992; van Daele et al., 1995), although reduced bone size and structure, assessed by 3-dimensional bone imaging, have recently been reported in type 2 diabetic adult men (Petit et al., 2010). This finding, along with animal work (Ahmad et al., 2003), suggests that increased bone fragility in type 2 diabetes may not be discerned as much from bone mass as other aspects of skeletal strength such as bone size and structure. The exact underlying mechanism for how impaired glucose metabolism leads to suboptimal bone strength is still elusive; however, some hypotheses include decreased osteoblast function, increased osteoclast and osteocyte

functions, excessive nonenzymatic glycation, and alterations in vitamin D endocrine function (Figure 3).

Co-culture and animal studies have revealed that uncontrolled high glucose levels may have direct and indirect deleterious effects on osteoblast function and bone formation. At the cellular level, a recent in vitro study in human osteoblast-like MG-63 cells demonstrated that a hyperglycemic condition suppressed cell growth, mineralization, and expression of various osteogenic markers including Runx2, type I collagen, osteocalcin and osteonectin, but inversely promoted expression of adipogenic markers such as PPAR- γ , adipocyte fatty acid binding protein, resistin, and adiponectin (Wang et al., 2010). Consistent with the in vitro findings, a histomorphometric analysis in streptozotocin-induced diabetic mice showed increases in osteoclast numbers and expression of osteoclastogenic mediators, including TNF- α , macrophage colony stimulating factor (M-CSF), and RANKL (Kayal et al., 2007). Moreover, there were upregulations of PPAR- γ , adipocyte fatty acid binding protein, and resistin mRNAs, as well as increases in lipid-dense adipocytes in the bone marrow of tibias of these streptozotocin-induced diabetic mice (Botolin et al., 2005). It is thus plausible that, in addition to direct interference with osteoblast function and bone formation, insulin resistance and type 2 diabetes may also induce lipid accumulation in the marrow of long bones, thereby leading to expansion of the bone marrow cavity and thinning of the cortical envelope to make the bone more fragile. In addition, the osteoblast to adipocyte shift may also reduce the number of differentiated osteoblasts available for bone formation.

Uncontrolled high glucose levels in conditions of insulin resistance and type 2 diabetes lead to accumulation of advanced glycosylation end-products (AGE) in the organic bone matrix by a process known as nonenzymatic glycation (Monnier et al., 1984; Vashishth, 2007). Hemoglobin A1c is a common example of an early-stage glycation product. The production of AGE are associated with osteoblast apoptosis and inhibition of osteoblast differentiation, thus leading to reduced osteoblast function (Alikhani et al., 2007). In contrast to normal enzymatic cross-linking in collagen (with pyridinoline, for example), which gives bone its toughness and scaffolding properties, AGE crosslinks lead to biomechanically more brittle bone that has lost its toughness and is less able to deform before fracturing (Tang et al., 2009). Pentosidine, when measured in urine, was associated with a 42% increase in clinical fracture incidence in type 2 diabetes (Schwartz et al., 2009), and when measured in serum was increased in patients with type 2 diabetes who had vertebral fractures (Yamamoto et al., 2008). These data suggest that increased levels of AGE may render bone more fragile in conditions of insulin resistance and type 2 diabetes.

Bone mass and strength at any particular time reflects the bone turnover balance between bone formation and resorption. Increased AGEs may weaken bone by decreasing bone formation. There is evidence suggesting that AGEs interfere with normal osteoblast development (Kume et al., 2005) and function (Sanguineti et al., 2008). In addition, reduced bone formation also works in the opposite direction to further increase AGE, as, for example, with high bisphosphonate dosages (Tang et al., 2009). Clinical data have shown that bone turnover dynamics is reduced in type 2 diabetes, with a disproportionate reduction in bone formation (Dobnig et al., 2006;

Gerdhem et al., 2005). Bone formation markers measured in serum have generally been reduced in conditions of prediabetes (Pollock et al., 2011d) and type 2 diabetes (Kanazawa et al., 2009; Shu et al., 2012), although it still has not been established definitively that abnormal glucose metabolism is characterized by low bone formation. It is thought that the link between bone formation and glucose metabolism is regulated via leptin, an adipocyte-derived hormone. It has been shown that as leptin levels increase, there is a subsequent decrease in bone formation, which in turn depresses insulin sensitivity and secretion (Hinoi et al., 2009). Other data suggest that sclerostin, an osteocyte-derived protein with anti-anabolic effects on bone formation, is increased in type 2 diabetes (Gennari et al., 2012), although no relationships were found between circulating sclerostin levels and serum markers of bone formations. Interestingly, the known inverse relationship between parathyroid hormone (PTH) and sclerostin was not observed (Gennari et al., 2012), perhaps suggesting that there may be an absence in type 2 diabetes of the usual inhibitory effect of PTH on sclerostin production.

Circulating vitamin D levels are inversely correlated to insulin resistance and significantly lower in patients with type 2 diabetes (Joergensen et al., 2010; Parikh et al., 2012). Vitamin D is an essential factor of bone and muscle activities because vitamin D deficiency stimulates the production of PTH, which is a negative regulator of osteoblast functioning but a positive regulator of osteoclast functioning which then in turn reduces bone formation and increases bone resorption, respectively (Bouillon, 1991; Fowlkes et al., 2011). Type 2 diabetes-related vitamin D deficiency may also lead to reduced muscle strength because it lowers the rate of calcium absorption by the intestine and thereby reduces the activity of muscle (Gao et al., 2008; McNair et al., 1979), which may be a risk factor of bone fractures through increasing the rate of falling.

The mechanisms for suboptimal bone strength and increased fracture risk in obesity-related diabetes appear to include both material and structural abnormalities. These abnormalities could be interrelated since distorted collagen is also likely poorly mineralized. An overly glycosylated collagen matrix, confounded by reduced osteoblast differentiation, in the setting of increased cortical porosity, may lead to compromised biomechanical competence. Because the extent and the nature of collagen crosslinking are significant contributors to bone matrix quality, it is important to conduct additional studies to determine independent contributions to collagen and, ultimately, bone strength.

5. Conclusion

The effect of obesity on childhood bone development has emerged as an important area of investigation, as obese children have been a population over-represented in fracture groups of children. Although it has become clear that body mass is a significant determinant of bone mass and bone quality in children and adolescents, the influence of fat (particularly excessive amounts of fat) on bone during critical stages of bone strength development remains uncertain. Peak bone strength is a major determinant of bone health and fracture risk in later life and so there is a clear need for longitudinal studies covering pediatric populations to identify key factors regulating bone development and the relative changes in the relationship between fat and bone during growth. This knowledge will provide critical

information needed to maximize potential therapeutic interventions to counter the linked risks of obesity and osteoporosis, both major public health concerns.

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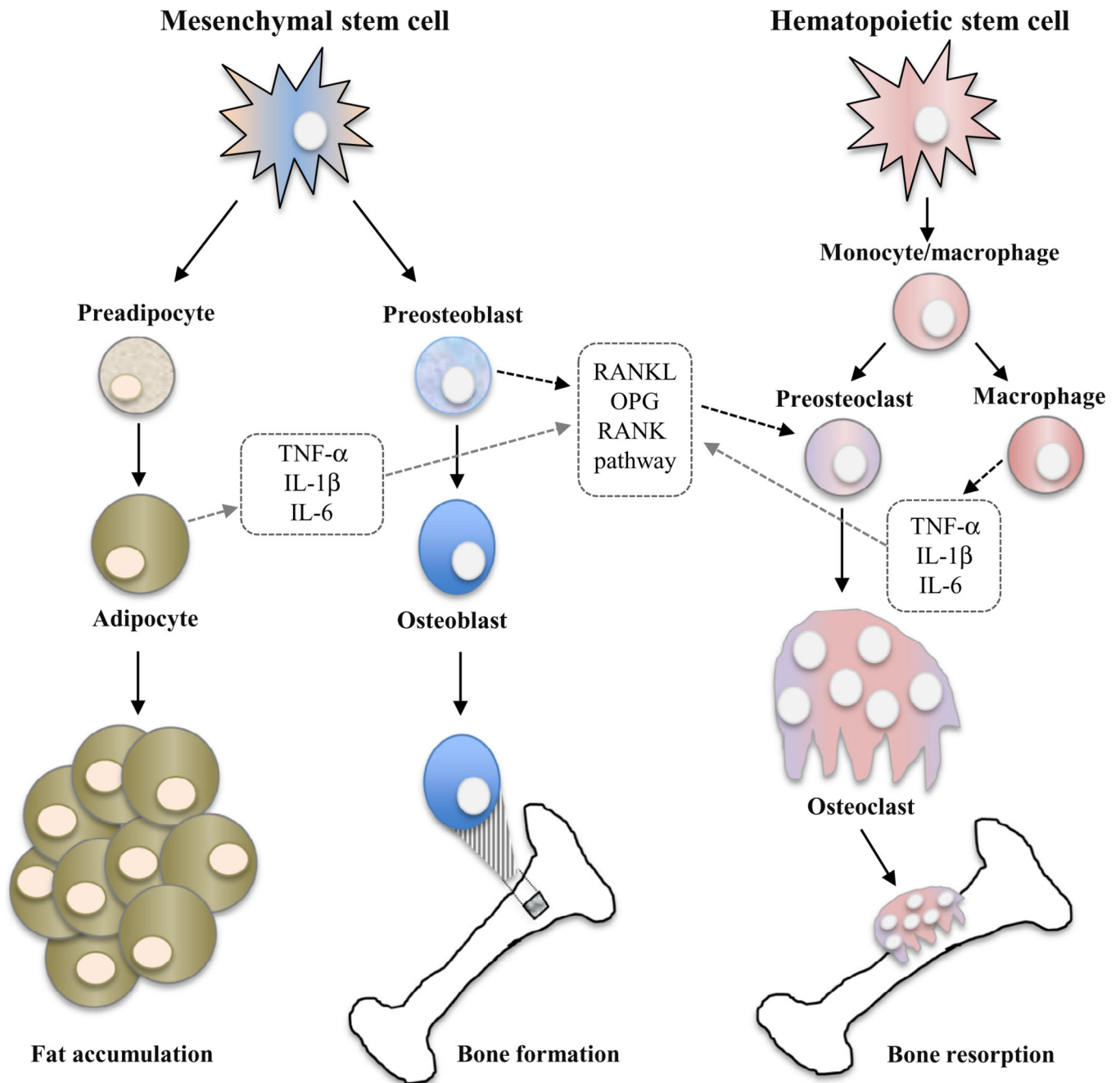


Fig. 1. Interrelationships between fat accumulation, bone formation, and bone resorption. Mechanisms involving fat and bone are intricate by nature, since both adipocytes and osteoblasts originate from mesenchymal stem cells in bone marrow. Osteoclasts originate from monocyte/macrophage precursors of hematopoietic stem cells. Adipocytes and macrophages can secrete several cytokines such as TNF- α , IL-1 β , 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 re-sorption. TNF- α : tumor necrosis factor- α ; IL-1 β : interleukin-1 β ; IL-6: interleukin-6.

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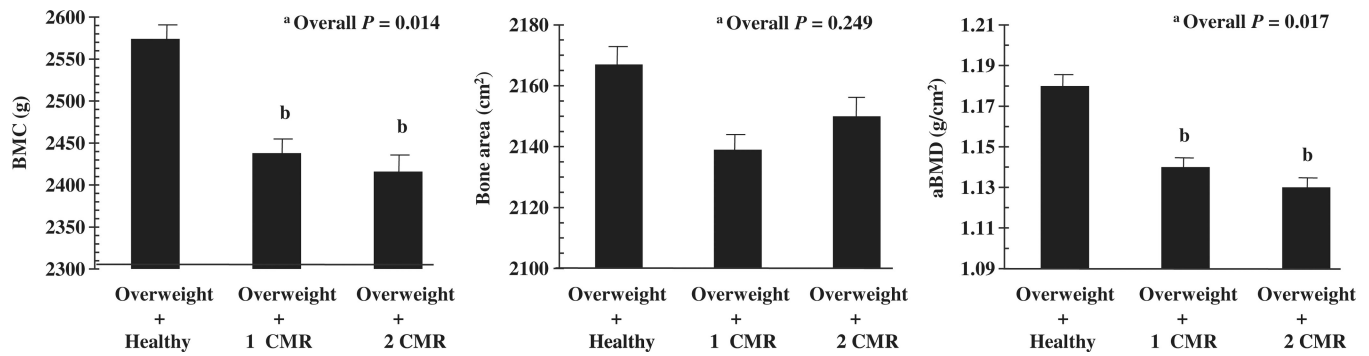


Fig. 2.

Mean (\pm SE) total body bone mineral content (BMC), bone area, and areal bone mineral density (aBMD) in overweight adolescents with no cardiometabolic risk factors (CMR) (healthy group, $n = 55$), overweight adolescents with one CMR (1 CMR group, $n = 46$), and overweight adolescents with two or more CMR (2 CMR group, $n = 42$). ^a Overall P-value on the basis of analysis of covariance, adjusted for age, sex, race, height and fat-free soft tissue mass. ^b $P < 0.05$, significantly different from healthy group (least squares difference adjustment for multiple comparisons). (From *J Pediatr*, Vol. 158, N.K. Pollock et al., Adolescent obesity, bone mass, and cardiometabolic risk factors, pp. 727–734. Copyright 2011, with permission from Elsevier.)

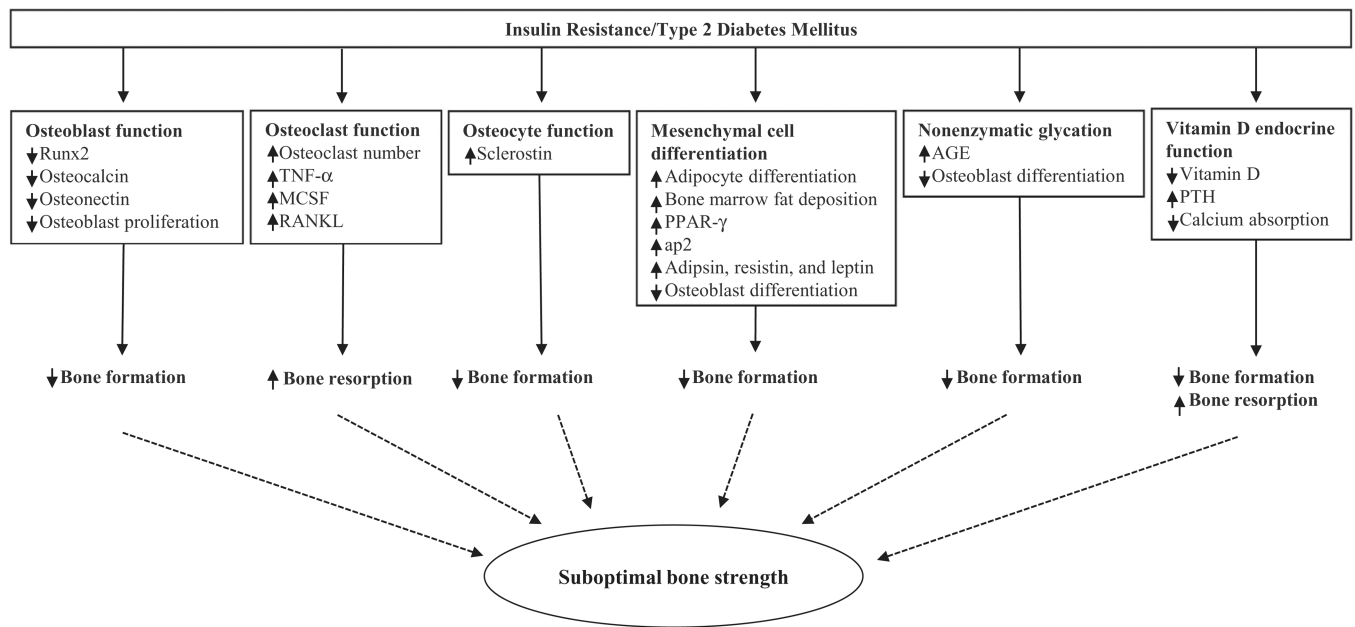


Fig. 3.

Possible pathways leading to suboptimal bone strength due to uncontrolled high glucose levels in conditions of insulin resistance and type 2 diabetes mellitus. The mechanism for how impaired glucose metabolism leads to suboptimal bone strength is still elusive. However, some hypotheses include decreased osteoblast function (i.e., decreasing Runx2, osteocalcin and osteonectin expressions and suppressing osteoblast proliferation), increased osteoclast function (i.e., inducing production of TNF- α , MCSF and RANKL, all of which are osteoblast-derived activators of osteoclast proliferation and differentiation), increased osteocyte function (i.e., increasing sclerostin expression), excessive nonenzymatic glycation (i.e., increasing AGE in the organic bone matrix and suppressing osteoblast differentiation), and alterations in vitamin D endocrine function (i.e., low circulating levels of vitamin D, thereby stimulating production of PTH and reducing calcium absorption). Runx2: Runt-related transcription factor; TNF- α : tumor necrosis factor- α ; MCSF: macrophage-colony stimulating factor; RANKL: receptor activator of nuclear factor- κ B ligand; PPAR- γ : peroxisomal proliferator-activated receptor gamma; ap2: adipocyte fatty acid binding protein; AGE: advanced glycosylation end-products; PTH: parathyroid hormone.

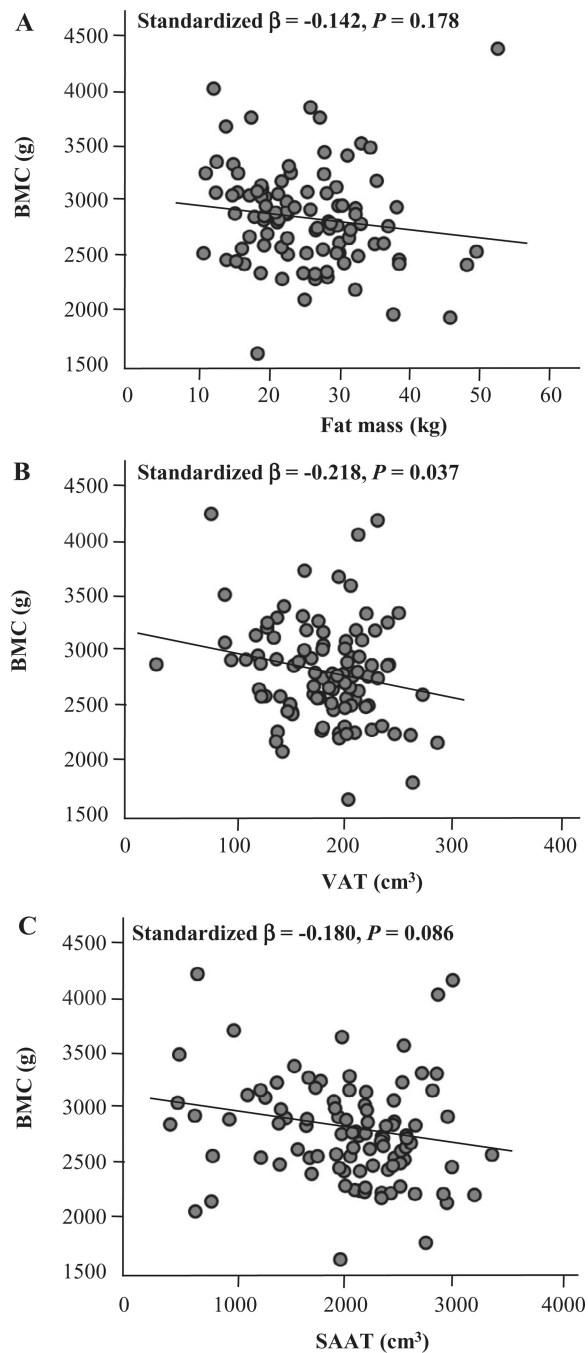


Fig. 4. Relationships between total body bone mineral content (BMC) and total and central adiposity in overweight adolescents. A, Fat mass versus total body BMC; B, visceral adipose tissue (VAT) versus total body BMC; and C, subcutaneous abdominal adipose tissue (SAAT) versus total body BMC. Relationships are adjusted for age, sex, race, height and fat-free soft tissue mass. N = 143. (From *J Pediatr*, Vol. 158, N.K. Pollock et al., Adolescent

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Table 1

Pediatric studies evaluating relationship of adiposity and skeletal fractures.

Study	Population	Obesity definition/adiposity measure	Bone measure/site and fracture assessment	Methodological/statistical approach	Overall study results
Goulding et al. (1998)	200 females with ($n = 100$) and without ($n = 100$) distal forearm fractures (average time of 47 days post-fracture); age: 3–15 years	<ul style="list-style-type: none"> BMI Total fat mass assessed by DXA 	<ul style="list-style-type: none"> Total body aBMD Spine aBMD Hip aBMD Radial aBMD Medical record of skeletal fracture 	To compare bone density of forearm fracture cases versus controls, matched for age and height.	Young females with forearm fractures had greater BMI, higher levels of fat mass, and lower aBMD at all skeletal sites than controls.
Goulding et al. (2000)	170 females with ($n = 82$) and without ($n = 88$) prior distal forearm fracture; age: 3–15 years at baseline	<ul style="list-style-type: none"> BMI 	<ul style="list-style-type: none"> Total body aBMD Spine aBMD Medical record of skeletal fracture 	To determine risk factors for occurrence of new skeletal fractures over a 4-year period.	In young females, previous forearm fracture, low total body aBMD, low spine aBMD, and high BMI each increase the risk of new skeletal fracture within 4 years.
Goulding et al. (2001)	200 males with ($n = 100$) and without ($n = 100$) distal forearm fractures (average time of 4 weeks post-fracture); age: 3–19 years	<ul style="list-style-type: none"> BMI Total fat mass assessed by DXA 	<ul style="list-style-type: none"> Total body aBMD Spine aBMD Medical record of skeletal fracture 	To determine factors associated with forearm fractures in young males.	Low total body aBMD, low spine aBMD, high BMD, and high adiposity each increased the risk of forearm fracture in young males.
Skaggs et al. (2001)	100 females with ($n = 50$) and without ($n = 50$) distal forearm fracture (average time of 4-weeks post-fracture); age: 4–15 years	<ul style="list-style-type: none"> BMI 	<ul style="list-style-type: none"> At the radius, the following CT-derived bone parameters were assessed at the distal site: <ul style="list-style-type: none"> Trab vBMD Total CSA 	To compare bone density and bone size of forearm fracture cases versus controls, matched for age, height, weight, and pubertal stage.	Young females with forearm fractures had a significantly smaller bone size (total CSA) and tend to be more overweight than controls. However, differences in vBMD between groups were not observed
Davidson et al. (2003)	50 males; age: 4–17 years	<ul style="list-style-type: none"> BMI 	<ul style="list-style-type: none"> Medical record of skeletal fracture 	To compare the relative likelihood of forearm fractures between obese (95th BMI percentile) and non-obese (<85th BMI percentile) male children and adolescents; matched for age, pubertal stage, and height.	Obese male children and adolescents were shown to have 1.7 times greater risk of forearm fracture compared to their non-obese counterparts.
Goulding et al. (2005)	90 children and adolescents having experienced 2 forearm fractures; age: 5–19 y	<ul style="list-style-type: none"> BMI 	<ul style="list-style-type: none"> Radial aBMD and BMC Medical record of skeletal fracture 	To determine factors associated with multiple forearm fractures during childhood.	A greater number of forearm fractures was associated with a higher BMI and lower radial aBMD and BMC.

Study	Population	Obesity definition/adiposity measure	Bone measure/site and fracture assessment	Methodological/statistical approach	Overall study results
Taylor et al. (2006)	355 children and adolescents; Age: 12.2 ± 2.8 y	• BMI	• Medical record of skeletal fracture	Nonoverweight (5–95th BMI percentile) versus overweight (>95th BMI percentile)	Overweight/obese children and adolescents were found to have greater prevalence of skeletal fractures than nonoverweight peers.
Pollack et al. (2008)	3,252 children and adolescents; age: 9–15 y	• BMI	• Medical record of skeletal fracture of the lower and upper extremities caused by motor vehicle crashes	To compare the relative likelihood of skeletal fractures between overweight/obese and normal weight children and adolescents.	The risk of skeletal fractures of the lower and upper extremities (due to motor vehicle crashes) was two and half times as great in overweight/obese versus normal-weight children.
Dimitri et al. (2009)	103 children and adolescents; age: 11.7 ± 2.8 y	• BMI • Total fat mass assessed by DXA	• Total body BMC, bone area, and aBMD • Lumbar spine BMC, bone area, and aBMD • Radial BMC, bone area, and aBMD • Medical record of skeletal fracture	To determine relations between total fat mass and bone parameters in four groups of children and adolescents: obese (99th BMI percentile) with and without prior fracture and normal-weight (<85th BMI percentile) with and without prior fracture; statistical control for gender, age, and weight or lean mass.	There was a consistent pattern of differences in BMC, bone area, and aBMD at the skeletal sites according to both obesity and prior skeletal fracture. Specifically, children and adolescents who fracture have smaller bones; the difference is substantially increased in those children and adolescents who have a history of skeletal fracture and are obese.
Kessler et al. (2013)	913,178 children and adolescents; age: 2–19 y	BMI	• Medical record of skeletal fracture of the lower extremities	To compare the relative likelihood of lower extremity fractures between obese, overweight, and normal weight children and adolescents.	The odds of foot, ankle, leg, and knee fractures were significantly higher in the overweight and obese children relative to their normal weight peers. There was no association between weight status and increased risk of fractures of the femur and hip.
Fornari et al. (2013)	1,345 children and adolescents; age: 5.0 ± 2.5 y	BMI	• Medical record of skeletal fracture of the upper extremities	To determine whether obesity status is a risk factor in the type and severity of upper extremity fracture (lateral condyle versus supracondylar humerus).	Obesity places a child at greater risk for sustaining a lateral condyle fracture versus supracondylar fracture. When these lateral condyle fractures occur, they are often more severe injuries compared to those in nonobese children.
Sabhaney et al. (2014)	2,213 children and adolescents; age: 2–17 y	BMI	• Medical record of skeletal fracture of the lower and upper extremities	To compare the relative likelihood of skeletal fractures between obese, overweight, and normal weight children and adolescents.	The odds of fracture were significantly higher in the lower extremity injuries among overweight relative to normal weight children, though an increased odds of lower extremity fracture was not observed among obese children compared with

Study	Population	Obesity definition/adiposity measure	Bone measure/site and fracture assessment	Methodological/statistical approach	Overall study results
normal weight children. There was no significant association between BMI and odds of fracture with upper extremity injuries or odds of complex fractures.					

BMI, body mass index; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; CT/QCT, axial quantitative computed tomography; aBMD, areal bone mineral density; BMC, bone mineral content; vBMD, volumetric BMD; CSA, cross-sectional area; trab, trabecular.