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The Impact of Fat and Obesity on Bone Microarchitecture and Strength in Children

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Abstract

A complex interplay of genetic, environmental, hormonal, and behavioral factors affect skeletal development, several of which are associated with childhood fractures. Given the rise in obesity worldwide, it is of particular concern that excess fat accumulation during childhood appears to be a risk factor for fractures. Plausible explanations for this higher fracture risk include a greater propensity for falls, greater force generation upon fall impact, unhealthy lifestyle habits, and excessive adipose tissue that may have direct or indirect detrimental effects on skeletal development. To date, there remains little resolution or agreement about the impact of obesity and adiposity on skeletal development as well as the mechanisms underpinning these changes. Limitations of imaging modalities, short duration of follow-up in longitudinal studies, and differences among cohorts examined may all contribute to conflicting results. Nonetheless, a linear relationship between increasing adiposity and skeletal development seems unlikely. Fat mass may confer advantages to the developing cortical and trabecular bone compartments, provided that gains in fat mass are not excessive. However, when fat mass accumulation reaches excessive levels, unfavorable metabolic changes may impede skeletal development. Mechanisms underpinning these changes may relate to changes in the hormonal milieu, with adipokines potentially playing a central role, but again findings have been confounding. Changes in the relationship between fat and bone also appear to be age and sex dependent. Clearly, more work is needed to better understand the controversial impact of fat and obesity on skeletal development and fracture risk during childhood.

Keywords

Obesity; Children; Fat; Bone Microarchitecture; HRpQCT; Adipokine

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Introduction

Pediatric osteoporosis is often characterized by failure to accrue optimal bone mass and structural adaptations that consequently increase susceptibility to fractures. Whereas the focus in pediatrics has historically been on optimizing peak bone mass [1], mounting evidence demonstrates that modeling adaptions which occur during growth lead to important structural changes independent of bone mass that may not only determine peak bone strength (and thus resistance to fracture) [2], but also track throughout life [3]. However, traditional approaches (e.g., dual-energy X-ray absorptiometry [DXA]) for skeletal assessments in growing children have neither the sensitivity nor specificity for optimal fracture risk assessment and are unable to assess critical aspects of bone' s complex design [4]. Thus, in recent years, there has been a shift towards measuring biomechanically relevant determinants of bone strength in children.

Like osteoporosis, obesity has also become a world-wide public health concern, reaching epidemic proportions globally [5], even in children. Indeed, data from the World Obesity Federation indicate that the prevalence of childhood overweight and obesity has risen substantially over the past three decades in several low-, middle-, and high-income countries [6]. For example, recent survey data in the United States show that 17% of children are obese [7]. Beyond the predominantly consistent observation that obese children are overrepresented in fracture groups [8–18] (Table 1), emerging evidence from both translational and basic cellular/molecular studies suggests that adipose tissue can have a multitude of effects on bone metabolism [19, 20]. Despite great strides, our understanding of the relationship between adipose tissue and bone is still evolving, with recent evidence indicating that the effect of adipose tissue on bone may be fat-depot specific. Indeed, pathogenic depots such as visceral fat may exert negative effects on bone, whereas non-pathogenic fat depots appear to mediate positive skeletal effects [21].

Specific skeletal sites (e.g., weight-bearing versus non-weight-bearing) as well as skeletal compartments (e.g., cortical versus trabecular) may also be differentially affected by obesity. In children, these complex interactions between fat and bone are further complicated by both skeletal growth and a rapidly changing hormonal environment. It is likely that this complexity contributes to the consistent finding that overweight and obese children are overrepresented in fracture groups (Table 1), and why this effect may be most noticeably observed in the peripubertal years. Indeed, during this critical period of rapid skeletal growth, it may be that excessive adiposity provides an additional insult on the skeleton at a microarchitectural level.

Importance of assessing bone structure and strength during growth in children

Because multiple components of adult bone strength are established during growth [1], the value of accurately measuring bone geometry and microarchitecture *in vivo* in children and adolescents has become increasingly evident. Fortunately, the more recent development and application of alternative tools, such as magnetic resonance imaging (MRI) and peripheral quantitative computed tomography (pQCT), has made it feasible to accurately estimate

volumetric BMD (vBMD) and bone structural parameters (e.g., periosteal and endocortical surfaces) in children and adolescents *in vivo*. Such information is valuable because these parameters can be utilized to calculate indices of bone strength (e.g., bone strength index [BSI] at metaphyseal sites and strength-strain index [SSI] at diaphyseal sites). It is noteworthy that BSI and SSI have been shown to predict up to 85% of the variance in bone failure properties in human cadaveric tissues [22]. In recent years, additional technologic advances have occurred, including high-resolution pQCT (HRpQCT), a method which essentially allows for the safe performance of a virtual *in vivo* "non-invasive bone biopsy" of the distal radius and tibia. Indeed, by applying novel advances in image acquisition and analysis, this technique can evaluate bone macro- and microarchitecture (e.g., trabecular connectivity, cortical thickness, vBMD, and porosity), as well as micro-finite element (μFE)-derived bone strength (i.e., failure load), to better understand skeletal development and fracture risk in children and adolescents [23–25]. Application of these techniques will be crucial toward improving our knowledge of the underlying biomechanical factors that influence fracture risk during growth, as well as the impact of fat and obesity on bone microarchitectural development and strength during growth.

Fractures in children and adolescents

Fractures are a common occurrence in the pediatric population. One of the leading causes of hospital admission following injury [26], fractures occur in approximately one in three children who are otherwise healthy [27, 28]. Further, children who suffer a fracture are 2- to 3-fold more likely to sustain a repeat fracture as compared to age-matched peers with no fracture history [9]. Importantly, fracture incidence in children has increased over the past 30 years [29]; thus, a greater effort is needed to identify the key biomechanical and functional parameters that determine bone strength and fracture risk in children and adolescents and to refine our knowledge of the risk factors that influence those parameters. As now recognized, a complex interplay of genetic, environmental, hormonal, and behavioral factors [30–33] affect bone strength, several of which (e.g., low birth weight, inadequate dietary calcium intake, excess soft drink consumption, insufficient vitamin D levels, physical inactivity, and obesity) have also been associated with childhood fractures [9, 13, 15, 16, 34–39]. These factors tend to be associated with precipitating events (e.g., falls) and underlying predisposition (e.g., suboptimal skeletal accrual and/or impaired bone structure), and the latter can have long-term negative consequences for bone health and fracture risk. Moreover, associations with earlier age at first fracture [40] and obesity [9, 13, 15, 16, 39] implicate developmental or behavioral traits, respectively, that could extend into adulthood. Thus, interventions designed to affect modifiable risk factors could potentially have an important impact on skeletal development and subsequent fracture risk.

It has become increasingly clear that fractures during growth are associated with skeletal fragility [41, 42]. Although fractures can occur at any time and at any skeletal site, forearm fractures are most common in normal healthy children, with an incidence that peaks during the early adolescent growth spurt [27, 28]. However, whereas fractures due to high trauma (e.g., motor vehicle accidents) are likely to occur regardless of bone strength, fragility fractures (i.e., due to moderate/mild trauma) may result from underlying skeletal deficits. Interestingly, studies using HRpQCT to assess bone microarchitecture in children and

adolescents have suggested that transient thinning and decreased load sharing by the cortex during the pubertal growth spurt may account for the peak in forearm fracture incidence that coincides with rapid skeletal accrual [23, 43]. Potential contributing factors may include enhanced bone turnover during peak longitudinal growth leading to increased cortical porosity and/or a lag in endocortical apposition, which may transiently induce a transient deficit in bone strength, thereby leaving the already thin metaphyseal cortex particularly vulnerable to fracture [44, 45]. Given that the timing of these cortical bone changes virtually mirrors the peak in forearm fracture incidence in early adolescence [27, 28], it is logical to ask whether children with forearm fractures have deficits in bone microarchitecture and strength. Using HRpQCT imaging, recent work has demonstrated that children and adolescents with forearm fractures due to mild trauma have significant deficits in failure load at the radius, worse fall load-to-strength ratios, and significantly thinner metaphyseal cortices [25]. By contrast, boys and girls with moderate trauma fractures have bone parameters which are virtually identical when compared to peers (matched for various confounding factors) with no fracture history [25]. From these data, it can be inferred that forearm fractures during growth appear to have two distinct etiologies: those which occur due to underlying skeletal deficits and result in fractures in response to mild trauma versus those which occur due to more significant trauma in the setting of normal bone strength [25]. Future studies are needed to define the key risk factors, such as obesity, that potentially influence fracture risk in children and adolescents who suffer mild trauma fractures.

Important considerations when examining fat-bone relationships during childhood

Peak bone mass is dependent on bone mass accrual during childhood and adolescence and may be a determinant of fracture risk in adulthood [1]. Achieving an optimal peak bone mass during adolescence is thought to prevent or delay the onset of osteoporosis in later life by up to 13 years [46]. Bone mass ‘ tracks’ through childhood and adolescence due to the strong influence of heredity and genes [47], but environmental factors may lead to a deviation from the predicted developmental path. Despite the profound changes in skeletal structure and architecture during growth, there remains a paucity of longitudinal studies examining the impact of obesity on skeletal development particularly in respect to changes in skeletal microarchitecture. When studying the effect that increasing body mass has on children's bones, two outcomes need to be considered: the relative influence that increasing fat mass or lean mass have on the size, geometry, mineral content, and architecture of bones and whether these changes confer a structural disadvantage, leading to an increased fracture risk. Normally, fat mass rises during growth and puberty; the effect the maturational increase in fat mass on skeletal development, microarchitecture and maturation may potentially be different compared to the presence of excess fat mass from obesity. Thus, the relationship between fat mass and bone during childhood must be considered in the context of the quantity and distribution of fat. Skeletal maturity must also be considered as obese children enter puberty earlier and thus bone development may vary as a consequence of earlier skeletal maturation and consolidation [48].

Fracture risk in obese children

Obese children are at a greater risk of fracture (Table 1), suggesting that the ‘ excessive’ accumulation of fat mass may have a detrimental impact on the skeleton either directly or by limiting gain in bone mass in proportion to body size. Additional plausible explanations for this higher fracture risk include a greater propensity for falls (e.g., due to poor balance and abnormalities in gait [49]), greater force generation upon fall impact [50], unhealthy lifestyle habits (e.g., low physical activity levels, inadequate dietary calcium intake), and excessive adipose tissue that may have direct or indirect detrimental effects on skeletal development [21, 51]. In addition, it is known from pediatric cases of slipped capital femoral epiphyses [52] and tibia vara [53] that extreme mechanical loading on the skeleton from excessive adiposity can result in skeletal complications.

Cross-sectional study evidence for a relationship between adiposity and bone strength

To date, several cross-sectional studies of adiposity and DXA-derived bone mineral content (BMC) and areal bone mineral density (aBMD) in children and adolescents have reported conflicting findings [54–59] with studies demonstrating that fat mass is either positively [54, 55], negatively [56, 57], or not related [58, 59] to bone mass and density. However, much of this confusion may stem from reliance on DXA imaging which has inherent limitations for skeletal assessment in growing children and adolescents [60, 61]. Thus, in order to gain insight into why overweight and obese children are more prone to fractures, it is important to consider the underlying skeletal parameters that determine bone quality and strength.

Several studies, summarized in Table 1, have used either conventional CT or standard pQCT to examine the influences of fat mass on bone geometric parameters and vBMD in children and adolescents. For example, Janicka et al. [62] used conventional CT imaging in 300 mature adolescent males and females and reported that total body fat mass (TBFM) was not associated with vertebral or femoral bone size. In contrast, Pollock et al. [63] used pQCT imaging in 115 late adolescent females and reported that those with a higher body fat percentage (>32%) had significantly lower bone size and cortical bone strength (SSI) at both the radius and tibia as compared to age- and sex-matched controls with a normal body fat percentage. It is also noteworthy that with pQCT imaging of 445 early pubertal boys and girls (aged 9–11 years), Wetzsteon et al. [64] reported that overweight (BMI ≥85th percentile) children had greater indices of bone strength at the tibia as compared to normal weight children (BMI ≤75th percentile), but that bone strength was adapted to lean mass rather than fat mass. Thus, because overweight and obese children have greater skeletal muscle mass relative to their height [54], positive associations between body weight and bone parameters might be accounted for by increased muscle mass alone. This possibility is supported by studies demonstrating that children with excess adiposity have lower bone mass [56] and suboptimal bone structural parameters [65] relative to their body size, which may contribute to the increased fracture risk observed in obese children [8–18] (Table 1). Consistent with this possibility, several lines of evidence support the notion that muscle forces and muscle-secreted factors (so-called “myokines”) can result in mechanical coupling

and muscle-bone crosstalk, respectively, that both stimulate bone formation [2, 66]. Therefore, greater lean mass in obese children may having positive effects on the skeleton, although in the case of severe obesity, excessive fat mass and in particular accumulation of pathogenic fat, may attenuate these lean mass effects by negatively modifying bone microarchitecture within trabecular and cortical compartments.

The potential adverse effects of excess adiposity on skeletal development may also be skeletal site-specific, which led to the proposal that despite augmenting bone size, excessive fat mass may in fact impair bone quality [51]. To test this premise, Farr et al. [67] used HRpQCT in boys and girls (aged 8–15 years) and found that fat mass may have differential associations with bone microarchitecture and bone strength (as assessed by micro-finite element analysis [μFEA]) at non-weight-bearing versus weight-bearing (tibia) skeletal sites. After adjusting for potential confounders, the relationship between fat mass and radial bone strength was essentially non-existent, whereas positive (albeit weak) associations were observed between fat mass and tibial bone strength. In addition and consistent with previous studies, data from this same cohort of children clearly indicated that muscle mass is strongly associated with both cortical and trabecular microarchitecture as well as μFEA-derived bone strength at both the radius and tibia. Thus, these findings emphasized the importance of muscle mass for optimizing bone microarchitecture and strength during childhood and adolescence, and suggested that the strength of the distal radius does not commensurately increase with excessive gains in fat mass during growth. Rather, this may result in a mismatch between the strength of the radius and the load experienced by the distal forearm during a fall, a load which is greater in obese individuals. Collectively, these observations may at least in part explain why obese children are overrepresented in forearm fracture groups (Table 1). Notwithstanding, while there is increasing concern that obesity may be associated with the suboptimal development of bone strength, there is also a lack of longitudinal data to support cross-sectional findings. Inevitably, there is a need for carefully designed longitudinal studies using appropriate methodologies to definitively establish the level at which excess adiposity may negatively affect pediatric skeletal integrity, and whether any deficits that occur during periods of rapid skeletal growth are temporary or extend into adulthood.

Longitudinal impact of fat mass on bone health during skeletal growth

Much of the information relating to the impact of excess fat mass on the developing skeleton has come from amalgamating cross-sectional studies of obese children at different ages. However, changes identified from cross-sectional studies may not necessarily reflect changes that occur in skeletal development over time [68]. Generally, bone mass in childhood is a strong predictor of bone status in young adulthood, a process termed ‘ tracking’ [69]. Greater gains in lean mass can improve bone mass gains during skeletal maturation in excess of the normal predicted bone mass in adulthood. In contrast, excess fat mass appears to limit the effect of lean mass on skeletal maturity or can negatively impact on the normal tracking process of skeletal maturation [70]. At a microarchitectural level, greater longitudinal gain in fat mass during puberty appears to negatively impact the cortex of the appendicular skeleton with reductions observed in cortical BMD, thickness, and area at increasing levels of fat mass [68, 71]. However, the same negative relationship between

increasing adiposity and cortical or trabecular bone compartments does not appear to be present in earlier childhood [72]. Others have suggested that fat mass positively predicts either bone size in isolation [73], or improves bone size and mineral content independently during early childhood [71]. Whatever the influence of fat mass on skeletal development, bone mass and additionally bone strength are more strongly influenced by an increase in lean mass in overweight children [64, 74]. However, stating that excess fat mass in childhood has a negative or positive impact on skeletal development may well be overly simplistic and outcomes may vary according to age and pubertal development. During the first year of life, both fat and lean mass are associated with gain in total body BMC in both sexes [75]. As children enter puberty, the positive relationship between fat mass and bone appears to attenuate and then reverse [76], although this changing relationship may be confined to females [68, 76]. Moreover, despite the age-related impact of fat mass in females, menarche may modify this relationship, suggesting that hormonal changes during puberty may additionally affect fat-skeletal interactions [68]. Others have suggested that the negative impact of adiposity on skeletal development may happen prior to puberty [77, 78], and that the negative impact of childhood and adolescent obesity on bone persists through the post-pubertal years and into early adulthood [79].

The contradictory findings among studies may in part relate to the degree of childhood adiposity, fat mass distribution, and metabolic profile. Longitudinal studies utilizing DXA and pQCT indicate that a ‘ fat mass threshold’ may exist in childhood at which the effects of increasing fat mass change from positive to detrimental [68, 71] and that these changes may predominate in the cortex [71]. However, the curvilinear relationship proposed between escalating fat mass and bone may be confined to females [68, 71]. Co-morbidities relating to obesity such as cardiovascular risk and the metabolic syndrome are more closely related to an increase in visceral adiposity [80, 81]. Variation in the relationship between adiposity and bone at different ages may also relate to fat distribution, a factor that is rarely considered in pediatric studies. Cross-sectional studies in children assessing fat distribution in relation to bone mass, architecture and strength demonstrate that android fat distribution or visceral fat appears to be detrimental to bone with the greatest impact on the skeletal cortex [71, 82, 83]. Metabolic status may also influence findings relating to the fat-bone relationship in childhood. For example, overweight prepubertal children with pre-diabetes have lower total body BMC, compared to overweight children without pre-diabetes suggesting that the metabolic consequences of escalating adiposity may unfavorably impact on bone mass accrual at a critical stage of development [84].

The impact of bariatric surgery on bone health in adolescents

Adolescents who undergo Roux-en-Y gastric Bypass (RYGB) experience dramatic weight loss, losing 58% to 73% of their excess weight by 1 year [85–87]. In the adult population, bariatric surgery results in a reduction in BMC, area, and density particularly in relation to malabsorptive procedures [88]. The relevance of the bone loss is debatable with some suggesting that bone loss and reduction in BMD is detrimental [89, 90], while others suggest that the reduction in bone mass with increase in bone turnover following bariatric surgery equates to a normalization of bone following an adaptive gain in bone mass from the increased in force from excessive weight gain [91, 92]. Bone loss results from a reduction of

BMD in both the cortical and trabecular compartments and appears to develop centrally and peripherally. After 24 months following gastric-bypass surgery, 5–10% bone loss is seen at the hip and spine largely due to a reduction in trabecular vBMD, with the greatest decline observed from 12–24 months [93]. Micro-architectural changes at the distal tibia identified by HRpQCT include a reduction in trabecular number, an increase in trabecular separation with greater inhomogeneity within the trabecular envelope and cortical thinning [94]. Although a reduction in radial vBMD has been reported following gastric bypass surgery [95], microarchitectural changes predominate in the tibia, suggesting that a reduction in mechanical load is responsible for bone loss [94]. Moreover, bone loss at both peripheral and central skeletal locations persists beyond the period of weight loss implying that additional mechanisms may be responsible for bone loss following bariatric surgery that include nutritional deficiencies, and alterations in adipokines and gut-derived appetite-regulatory hormones [92]. Interestingly, the clinical impact of skeletal change following bariatric surgery manifests later with an increase in fracture risk observed 3-years post-operatively [96–98]. Vitamin D deficiency, hyperparathyroidism and calcium malabsorption following malabsorptive procedures such as RYGB is of concern [99] particularly in a background of vitamin D deficiency in obese patients pre-operatively [100]. However, across clinical practice guidelines there remains lack of agreement as to the post-operative supplementation of vitamin D with recommended doses ranging from 3000 IU daily to 50,000 IU 1–3 times weekly [101]. There are very few studies in adolescents assessing the impact of profound weight loss on bone secondary to bariatric surgery. Rapid and marked weight loss is related to a reduction in fat mass, as lean mass increases post-operatively [102]. Importantly, adolescence and early adulthood are periods during which approximately 25% of total body bone mass is accrued. Thus a reduction in bone mass following bariatric surgery could have profound short- and long-term effects on the developing skeleton. Following RYGB, adolescents show a decline in whole-body BMC and BMD over a 2-year period with weight partially accounting for this effect. The mean reduction in BMD z-score over a 2-year period in two separate patient cohorts was 1.5 but age-adjusted Z-scores for BMD and BMC remained within normal limits, thus suggesting that bone loss normalizes with weight loss [102, 103]. Further work, however, is required to determine whether bone loss continues beyond a 2-year period in adolescents leading to low bone mass, lower peak bone mass in early adulthood, increased fracture risk in the short and long term, and to understand the impact of microarchitectural changes in adolescents following bariatric procedures.

Biological mechanisms linking adiposity and bone during childhood

Multiple factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, and the endocrine environment. There is general agreement in the literature that exercise augments bone mass [104, 105] either by a direct osteogenic action and/or augmenting muscle mass. Gains in bone mass and relative bone strength are determined by the type of exercise, the timing in relation to pubertal onset (with the greatest gains elicited if exercise is commenced prior to puberty) and the intensity of the exercise [106, 107]. These changes are likely to result in

skeletal adaptation which will be dependent on gender, pubertal stage, and degree of adiposity.

The impact of childhood obesity on the endocrine environment

In children and adults with high level of visceral adiposity, physiological secretion of growth hormone (GH) secretion is impaired which in turn may impact on bone mass accrual and skeletal integrity [108–110] as GH promotes myogenesis and osteoblastogenesis and regulates the hepatic generation of insulin-like growth factor 1 (IGF-1) which promotes chondrogenesis at the growth plate and osteoblast proliferation and activity. IGF-1 also acts indirectly to promote renal tubular reabsorption of phosphate and on the synthesis of calcitriol [111]. Impaired GH secretion may be compounded by highly caloric low protein diets in obese children that impacts on the synthesis of IGF-1 [112, 113].

Androgens stimulate the differentiation and proliferation of osteoblasts via androgen receptors [114, 115], decrease osteoblast and osteocyte apoptosis, and indirectly and directly modify osteoclastogenesis in favor of a reduction in bone resorption [116]. Indirectly, androgens upregulate Transforming Growth Factor β (TGF)-β and Insulin-like Growth Factors (IGFs) promoting bone formation [117] and downregulate Interleukin 6 (IL-6); thus, inhibiting osteoclastogenesis [118]. Higher levels of adrenal androgens are seen in obese prepubertal children [119] and thus may in part account for the higher body size adjusted bone mass that some have observed in this age group [55]. The subsequent onset of puberty is usually closely preceded by an increase in adrenal androgens and pubertal growth acceleration is reliant on the synergistic action of GH and androgens. Androgens can be aromatized via the cytochrome P450 aromatase enzyme complex into 17β-estradiol. As fat depots contain aromatase, childhood obesity may result in the increased aromatization of testosterone and other androgens to estrogens [116]. During pubertal progression, levels of testosterone and DHEAS appear to be higher in obese females [119]. Thus, although these relationships are complex, adrenal androgens may have a more potent effect on pubertal skeletal development in obese females, potentially contributing to sex differences in cortical bone mass [55, 71].

Increased insulin production in obese children and adults may exert an anabolic effect on bone. In response to physiological doses of insulin, cultured osteoblasts show increased proliferation, collagen synthesis, alkaline phosphatase production, and glucose uptake [120] and hyperinsulinaemia following insulin administration stimulates osteoblast activity and increases mineral apposition rates in rats [121]. However, despite high bone mass in adults with type 2 diabetes, bone quality is impaired and fracture risk is high suggesting that in the hyperinsulinaemic state, bone quality is impaired [122, 123]. To date, there are no studies in children to determine whether changes in skeletal ‘ integrity’ secondary to hyperinsulinaemia occur as a result of chronic exposure to high blood glucose and insulin resistance.

Childhood obesity, adipokines, and skeletal development

In addition to the impact of childhood obesity on hormones that direct physiological function during growth and development, adipokines (hormones produced by fat) also

influence skeletal development. Leptin is elevated in obese children and adults. Both *in vitro* and *in vivo* studies suggest that leptin acts directly via osteoblast receptors on human marrow stromal cells to promote osteoblast proliferation and differentiation [124], whilst inhibiting adipocyte differentiation and osteoclatsogenesis through generation of osteoprotegerin [124, 125]. In contrast, *in vivo* studies in tail-suspended rats demonstrate that lower doses of leptin appear to be osteoprotective, but at higher doses bone loss is increased by bone resorption and reduced bone formation [126]. Although complex, this may explain why at levels of leptin associated with obesity in children, leptin appears to be associated with a reduction in bone mass and trabecular thickness and an increase in cortical porosity [127–129] whereas in cohorts of predominantly normal weight children, these associations are not demonstrated [130–132]. The dose-dependent relationship between leptin and bone thus mimics the curvilinear relationship observed between visceral adiposity and cortical bone [71] and therefore may in part provide a mechanistic explanation for this finding. Children with congenital leptin deficiency are profoundly overweight yet they appear to have normal age and sex-related whole body BMD despite being hypogonadal and having hyperparathyroidism [133, 134], which is further supported by a recent report of two children with mutations in the leptin receptor demonstrated a high bone mass phenotype [135]. Thus, findings in human mutations suggest leptin deficiency may be protective to the developing skeleton. These findings also support findings from mouse models demonstrating an anti-osteogenic indirect action of leptin on bone via hypothalamic pathways [136–138]. Conversely, despite adiponectin being produced by adipocytes it is lower in obesity. Adiponectin deficiency in mice leads to a reduction in BMC and bone strength of the femur and lumbar vertebrae [139] but in studies of both children and adults have shown that an inverse relationship between adiponectin and total body and regional bone mass exists [140–142]. Resistin can stimulate the proliferation of osteoblasts but has a more potent effect on osteoclastogenesis by increasing the number of osteoclasts and activating the NF-κB promoter [143]. Visfatin is as a novel adipokine preferentially expressed in visceral adipose tissue and can promote osteoblast proliferation and bone mineralization, but inhibits osteoclast differentiation. Vaspin, Chimerin, and Omentin-1 also directly or indirectly affect bone cell fate *in vitro* [144].

Alterations in gut peptides

Peptide YY (PYY) is an anorexigenic peptide secreted primarily by endocrine L cells of the distal gut. Levels of PYY increase after food intake and PYY promotes satiety by binding to Y2 receptors of neuropeptide Y (NPY) within the hypothalamus and by inhibiting NPY secretion. PYY-deficient mice (Pyy(−/−)) have osteopenia with a reduction in trabecular bone mass and a deficit in bone strength. PYY levels are lower in obese adults and the elevation of PYY seen after a meal in lean subjects is blunted in obesity [145, 146]. However, clinical studies have mainly focused on patients with anorexia nervosa and amenorrhoeic athletes. PYY is elevated in these patient groups and is paradoxically associated with a low bone mass [147]. Ghrelin, a gut-derived GH secretogogue that promotes osteoblast proliferation via the growth hormone secretogogue receptor 1a (GHS-R1a) is involved in energy homeostasis and is reduced in obesity. In healthy adolescent girls, ghrelin positively predicts total body and regional BMC [148], but is a negative predictor of

BMC in obese post-menarcheal adolescent females [149]. However, ghrelin' s influence on bone mass may be isoform dependent, whereby acylated ghrelin may negatively impact on bone mass in lean children whereas desacyl ghrelin positively predicts bone mass in obese children [150].

Future directions

One of the clear challenges in determining the impact of fat and adiposity on the developing skeleton is the ability to accurately determine 3-dimensional changes over time in bone structure and to apply appropriate models to determine bone strength and assess fracture risk. The advent of HRpQCT has allowed more accurate determination of cortical and trabecular bone compartments that include measurements of trabecular separation, width, and heterogeneity as well as cortical porosity and proxy measures of bone strength. However, HRpQCT measurements are confined to the distal tibia and radius and thus may not represent changes in other regions of the axial and appendicular skeleton. Further, HRpQCT poses additional challenges in children as the site measured changes as children grow, making comparative studies between different age groups challenging. Developments in MR (magnetic resonance) skeletal imaging may provide alternative solutions in the future. The recent use of MR ultrashort TE (UTE) has enabled the quantification of cortical bone parameters [151, 152], including cortical bone water concentration [153] and cortical bone porosity [154]. Additionally, analysis of textural features of MRI sequences using statistical modelling provides information about the trabecular compartment which correlates closely with HRpQCT parameters but requires further refinement and development beyond peripheral skeletal sites [155].

The timing, rate and extent of changes in body composition appear to impact on skeletal structure and geometric development. Future prospective studies of both weight-bearing and non-weight-bearing skeletal sites are necessary to examine the site-specific differences in the effects of fat on bone in males and females and whether the relationships between subcutaneous and visceral adiposity and bone mechanics and microarchitectural parameters influence fracture risk at specific skeletal sites. Similarly, whilst lean mass is clearly associated with gains in bone mass and favorable changes in cortical and trabecular bone, the mechanism(s) underpinning this change is not clear. Further work is required to determine the role of myokines in skeletal development [156], the interaction of myokines and adipokines, the relative composition of muscle in relation to skeletal phenotype and change, and whether additional factors are responsible for a concomitant increase in muscle and skeletal development.

Conclusions

There remains little resolution or agreement about the impact of obesity and adiposity on skeletal development and the mechanisms underpinning these changes. Limitations in imaging modalities, short duration of follow-up in longitudinal studies, and differences among cohorts, may all contribute to confounding results. Nonetheless, a linear relationship between increasing adiposity and skeletal development seems unlikely. Fat mass may confer advantages to the developing cortical and trabecular bone compartments, provided that gains

in fat mass are not excessive. However, when fat mass accumulation reaches excessive levels, unfavorable metabolic changes may impede skeletal development. Mechanisms underpinning these changes may relate to changes in the hormonal milieu, with adipokines potentially playing a central role, but again findings have been confounded. In an era where bariatric surgery is rapidly becoming a mainstay for treatment for morbid obesity in post-pubertal adolescents, understanding the effect of excessive fat mass on the developing skeleton and the subsequent risk of fracture is vital as the rapid weight loss may result in profound skeletal alterations in both the short- and long-term. Changes in the relationship between fat and bone also appear to be age and sex dependent. Clearly, more work is needed to better understand the controversial impact of fat and obesity on skeletal development and fracture risk during childhood.

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Table 1

Summary of some of the key studies examining the relationships of fat and obesity with bone parameters and fractures in children and adolescents

Study	Geographical Area	Age, y; Sex	Cases	Controls	1° Skeletal Outcome / Fracture Assessment	Purpose	Summary of Key Findings
Goulding et al. 1998; REF [8]	Dunedin, New Zealand	3–15; F	100 DFF	100 non-fracture	DXA / Medical records	To determine associations of bone density and adiposity with recent history of DFF	Girls with a DFF have lower bone density and higher adiposity vs their non-fracure peers
Goulding et al. 2000 [REF 9]	Dunedin, New Zealand	10 ± 2.9; F	82 DFF	80 non-fracture	DXA / Medical records	To examine predictors of incident fractures (over 4 years) during childhood	Girls with lower bone density and a higher BMI were at increased risk of sustaining incident fractures
Skaggs et al. 2001; [REF 10]	California, USA	4–15; F	50 DFF	50 non-fracture	CT / Medical records	To examine bone macro-structural parameters in girls with a recent DFF	Girls with a DFF had smaller radial bone size and higher adiposity vs their non-fracture peers
Goulding et al. 2001; [REF 11]	Dunedin, New Zealand	3–19; M	100 DFF	100 non-fracture	DXA / Medical records	To test whether boys with a DFF differ from non-fracture boys in bone density or adiposity	Boys with a DFF have lower aBMD and higher adiposity vs their non-fracture peers
Davidson et al. 2003; [REF 12]	Dunedin, New Zealand	4–17; M	25 obese (BMI ≥95th)	25 NW (BMI ≤85th)	DXA / Medical records	To compare risk of DFF in obese boys vs NW boys	Obese boys were at significantly greater risk of DFF vs their NW peers
Goulding et al. 2005; [REF 13]	Dunedin, New Zealand	5–19; F & M	90 children with ≥2 DFFs	None	DXA / Medical records	To establish risks factor for repeat DFFs in children	Children with repeat DFFs have lower radial aBMD and higher adiposity
Taylor et al. 2006; [REF 14]	Washington DC, USA	12 ± 2.8; F & M	227 SO (BMI ≥95th)	128 NW	DXA / Medical records	To examine the fracture risk in SO children vs their NW peers	SO children had a greater prevalence of fractures vs their NW peers
Janicka et al. 2007; [REF 62]	California, USA	13–21; F & M	300 healthy adolescents and young adults		CT / None	Cross-sectional study of TBFM and vBMD/ bone structure at cortical and trabecular sites	TBFM was either not associated or negatively associated with vBMD and cortical bone structure
Pollock et al. 2007; [REF 63]	Athens, Georgia, USA	18–19; F	115 late adolescents stratified based on percentage body fat (normal <32%; high ≥32%)		pQCT / None	Cross-sectional study of associations between % body fat and vBMD/ bone structural parameters at the radius and tibia	After adjusting for covariates, including muscle size, % body fat was negatively associated with several cortical bone structural parameters
Wetzsteon et al. 2008; [REF 64]	British Columbia, Canada	9–11; F & M	445 children; 302 NW (BMI ≤ 75th) and 143 overweight (BMI ≥85th)		pQCT / None	Longitudinal study of relationships between body composition and tibial parameters	In overweight children, indices of bone strength adapted to greater lean mass, but did not adapt to excess body fat
Gilsanz e al. 2009; [REF 82]	California, USA	15–25; F	100 healthy adolescents and young adults		CT / None	Cross-sectional study of regional fat deposition on femoral structure/ strength	SF was positively associated with bone whereas negative associations were observed between VF and bone
Dimitri et al. 2010; [REF 15]	Sheffield, UK	Obese = 12.1 ± 2.9; NW = 10.6 ± 3.2; M	52 obese (BMI ≥99.6th BMI)	51 NW	DXA / Medical records	To determine differential effects of obesity on bone size/ mass accoring to fracture history	Children who were obese and had a history of fracture had smaller bones as compared to their NW peers
Sayers et al. 2010; [REF 76]	Southwest England, UK	14 ± 0.2; F & M	3,914 children and adolescents		DXA / None	Cross-sectional study exploring relationships among sex, puberty, body composition, and hip structure	As children enter puberty, a positive relationship between adiposity and indices of hip structure appeared to attenuate and then reverse, although

Study	Geographical Area	Age, y; Sex	Cases	Controls	1° Skeletal Outcome / Fracture Assessment	Purpose	Summary of Key Findings
							this may have been confined to girls
Russell et al. 2010; [REF 83]	Boston, Massachusetts, USA	12–18; F	15 obese (BMI ≥95th)	15 NW (BMI 15th-85th)	DXA / None	Cross-sectional study of associations between regional fat depots and vetebral bone	Visceral adipose tissue was negatively associated with veterbral bone density in obese girls
Wey et al. 2012; [REF 68]	South Dakota, USA	8– 18; F & M	370 children and adolescents		pQCT / None	Longitudinal study of body composition and bone parmeters at the radius and tibia	Greater longitudinal gain in fat mass appeared to negatively impact the cortex of the appendicular skeleton
Kessler et al. 2013; [REF 16]	California, USA	2–19; F & M	913,178 children and adolescents		None / Medical records	To investigate the relationship between adiposity (higher BMI) and lower limb fractures	Higher adiposity was associated with an increased risk of lower extremity fractures
Fornari et al. 2013; [REF 17]	3 Centers in California, USA	5 ± 2.5; F & M	992 fracture cases (230 LC & 762 SC)	None	None / Medical records	To determine whether children with a higher BMI are at increased risk for elbow fractures	Obese children were at higher risk of LC fractures (which are more severe than SC fractures) vs their NW peers
Laddu et al. 2013; [REF 71]	Tucson, Arizona, USA	8–13; F	260 children and adolescents		pQCT / None	Longitudinal study of TBFM or central adiposity to weight-bearing bone parameters	Higher levels of central adiposity may impair cortical bone development at weight-bearing skeletal sites in girls
Farr et al. 2014; [REF 67]	Rochester, Minnesota, USA	8–15; F & M	105 w/ DFF	93 non-fracture	HRpQCT / Medical records	Cross-sectional study of TBFM to bone microarchitecture and strength at the radius and tibia	Adiposity was not related to radial bone parameters, but was positevely associated with tibial bone parameters
Sabhaney et al. 2014; [REF 18]	Vancouver & Toronto, Canada	9.5 ± 4.2; F & M	1078 w/ fracture (316 obese)	1135 non-fracture	None / Medical records	To examine the relationship between BMI and risk of upper and lower limb fracture	Overweight and obese children were not at higher risk of limb fractures vs their non-fracture peers

Key: F = Female; M = Male; BMI = body mass index; TBFM = total body fat mass; DFF = Distal forearm fracture; DXA = Dual-energy X-ray absorptiometry; pQCT = peripheral quantitative computed tomography; HRpQCT = high-resolution pQCT; LC = lateral condyle; SC = supracondylar; SO = severly overweight; NW = normal weight.