

11-30-2000

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CLINICAL REVIEW 117

Hormonal Determinants and Disorders of Peak Bone Mass in Children*

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PEAK BONE MASS can be defined as the maximal bone mineral density that is accrued during growth and development plus subsequent consolidation that continues during early adulthood (1). The precise age at which peak bone mineral density is acquired is still unknown and may be site dependent. It is generally accepted that maximal bone density is present during the third to fourth decade, but this assumption is based upon data derived from studies using densitometry techniques that are less precise than newer methods. Normative data are derived primarily from cross-sectional studies of adolescents and young adults, such as cohorts of the National Health and Nutrition Examination Survey (NHANES). Differences in absolute density depend on the various techniques used for assessing bone density [*i.e.* single photon absorptiometry, dual energy x-ray absorptiometry (DEXA), quantitative computed tomography (QCT)] and differences using the same method among different machines, emphasizing the importance of methodology, including the type of machine used when referencing normative databases. There are also ethnic differences in bone density, with blacks reported as having higher bone density than whites. There are gender differences in bone density during childhood and adolescence due to differences in the timing of growth and puberty, resulting in females reaching peak bone mass earlier than males, although bone density values at peak bone mass are similar between the sexes. An individual's height, bone size, and skeletal age may all impact bone density values, particularly in growing children and adolescents. These variables should be considered when assessing the normality of an individual's bone density, but unfortunately current reference data do not include information on these variables. More recent investigations have suggested that peak bone mass may be attained as early as late adolescence in the hip and spine (1). In healthy adolescents, bone mass increases throughout childhood, with max-

imal bone mass accrual occurring in early to midpuberty and slowing in late puberty (2–5). However, most published studies are cross-sectional and do not include individuals in sufficient numbers encompassing the entire age span of interest (*i.e.* teens to fourth decade) followed prospectively to definitively determine the age at which peak bone mass is attained. Longitudinal data from healthy girls demonstrate that the gain in bone mass is most pronounced between 11–14 yr of age and falls significantly after 16 yr of age and/or 2 yr after menarche, as shown in Fig. 1 (4, 5). These data suggest that there is a critical window in time to maximize bone density in early and midadolescence, and the majority of bone mass will accumulate by late adolescence. It has been shown in adult patients that each SD reduction in bone density is associated with a doubling of fracture risk. In children, as in adults, fracture rates have also been shown to be higher in individuals with a lower bone mineral content (6). Because an individual's bone density is determined by peak bone density and the degree of later bone loss, an understanding of the factors responsible for maximizing peak bone mass is critical for preventing fractures in later life. In this review, the factors that influence the attainment of peak bone mass, particularly hormonal determinants and disorders, will be considered.

Genetic determinants of peak bone mass

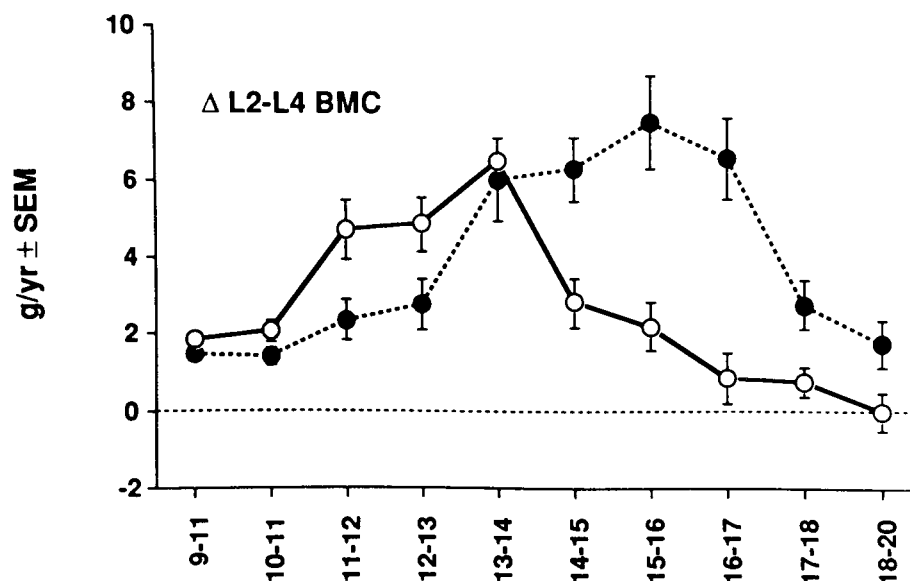
There are important genetic determinants of bone density, as suggested by studies of twins and families (7–9), and the specific inherited factors involved are under investigation. Polymorphisms in the gene encoding the 1,25-dihydroxyvitamin D receptor may in part underlie genetic variation in bone mass (10–12). Studies examining the relationship between vitamin D receptor (VDR) polymorphisms and bone density have provided conflicting results, and a meta-analysis of studies in adults suggest that the VDR genotype makes a small contribution to observed bone density (11). In contrast, in a genetically homogeneous population of children, Sainz *et al.* reported that VDR polymorphisms accounted for a significant (>1 SD) difference in femoral and vertebral bone density between the homozygous recessive (*aa, bb*) and the dominant (*AA, BB*) genotypes (12). These data suggest that genotype may be of greater importance in predicting bone density early in life before age- and gonadal

Received May 10, 2000. Revision received August 2, 2000. Accepted August 9, 2000.

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* This work was supported in part by NIH Grants R01-DK-52625, M01-RR-01066, and T32-DK-07028–25.

FIG. 1. Gain in bone mass during adolescence. Yearly increase in spine bone mineral content (L2-L4) during adolescence in females (○) and males (●). (Reprinted with permission from *The Journal of Clinical Endocrinology & Metabolism*, 75:1062, 1992. Copyright © 1992 The Endocrine Society. All rights reserved.)



steroid-related factors affect bone mass. Studies in adults have suggested that calcium intake may be related to VDR genotype and bone density (13, 14). Similarly, in a study of prepubertal girls, dietary calcium intake correlated with change in bone density in those with homozygous dominant and heterozygous (*BB* and *Bb*) genotypes, but not in those subjects with the homozygous recessive (*bb*) genotype (15). These data suggest that VDR genotyping may be one factor determining the variation in bone density in children and could potentially be helpful in predicting benefits from calcium supplementation. Several other genetic loci that may play an important role in peak bone mass accrual are under investigation. A polymorphism in the Sp1 binding site of the collagen type 1 $\alpha 1$ gene (*COL1A1*) is one such candidate gene. This polymorphism is associated with decreased spinal bone density in prepubertal children with heterozygous (*s*) and homozygous recessive genotypes compared with the dominant (*S*) genotype, similar to findings in adult patients (16). The insulin-like growth factor I (*IGF-I*) gene is another important candidate due to its significant effects as a bone trophic hormone, although its role in peak bone mass has not been determined. The important role of estrogen in both male and female bone maturation and density suggests that estrogen receptor gene polymorphisms may also influence bone density. The *XbaI* restriction site of the estrogen receptor gene has been found to be related to bone density in studies of both adolescent boys and premenopausal young women (17, 18). Therefore, a growing number of candidate genes have been identified that may be important determinants of peak bone mass. Genetic studies in large populations with well characterized phenotypes will be critical in assessing the impact of these factors on peak bone mass.

Hormonal determinants of peak bone mass

The presence of osteopenia in patients with abnormal pubertal development demonstrates the critical impact of pubertal hormone changes on normal bone mineral acquisition. Adult patients with hypogonadotropic hypogonadism commonly have osteopenia, resulting from inadequate bone min-

eral accrual during puberty and/or abnormal bone remodeling after puberty as shown in Fig. 2 (19). Adult men with a history of constitutional delay of puberty have been reported to have decreased bone mass (20), although data are conflicting (21). Androgen receptors are located in growth plate osteoblasts in males and females and are thought to mediate the anabolic effects of testosterone in bone (22). However, estrogen appears to be the more important sex steroid involved in skeletal maturation and mineralization, although it is unknown whether estradiol acts directly on bone or indirectly by stimulating other mediators of bone growth (2-5, 23, 24). There are reports of rare patients with aromatase deficiency or estrogen receptor defects resulting in complete resistance; these subjects have a phenotype that includes tall stature and normal secondary sexual characteristics. However, these patients have osteoporosis and skeletal immaturity in adulthood despite normal androgen levels (25-27). Treatment of a male patient with aromatase deficiency with estrogen resulted in dramatic improvement in bone density and completion of skeletal maturation, indicating the critical role of estrogen in skeletal mineralization and maturation (see Fig. 3) (28). In young women, a high incidence of metatarsal stress fractures has been reported in ballet dancers, particularly in those with late age of menarche and long periods of secondary amenorrhea as shown in Fig. 4 (29). In female adolescents, lower lumbar bone density is seen in amenorrheic teens compared with those with normal menses, but the decrease in bone density is generally not significant when bone density is controlled for body weight (30-32). These data suggest that nutritional status, including nutritionally dependent growth factors, and gonadal status may be independent determinants of bone density. Estrogen deficiency, particularly in the setting of undernutrition, can lead to permanent osteopenia. Bachrach *et al.* found that one third of females who recover from anorexia nervosa during adolescence have persistent osteopenia (33). Women with anorexia nervosa who have disease onset during adolescence have lower spinal bone density than those with disease onset in adulthood (34). These data are consistent with the hy-

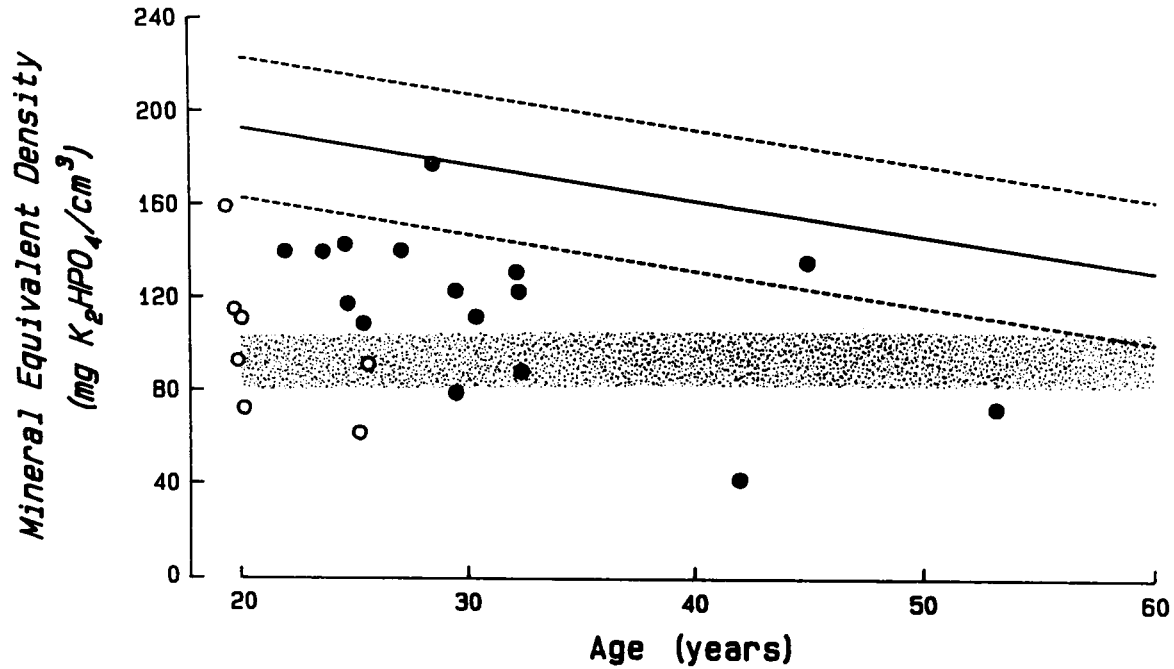


FIG. 2. Reduced bone density in idiopathic hypogonadotropic hypogonadism. Spinal trabecular bone density compared with age in 23 men with idiopathic hypogonadotropic hypogonadism. ●, Patients with fused epiphyses; ○, patients with open epiphyses. The solid line indicates the mean spinal bone density in normal adult men, whereas the dotted line indicates ± 1 SD from the mean. The stippled bar indicates the fracture threshold. (Reprinted with permission from *Annals of Internal Medicine*, 106:358, 1987. Copyright © 1987 American College of Physicians.)

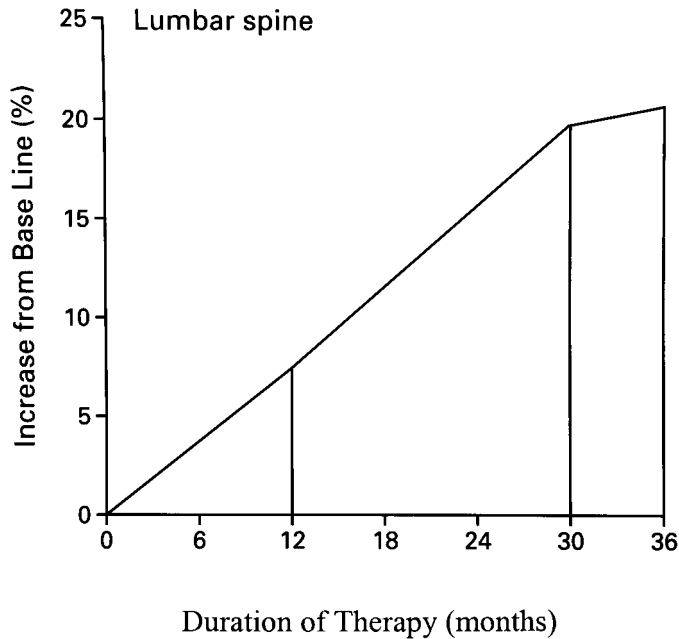


FIG. 3. Increased bone density in a man with aromatase deficiency during estrogen therapy. The percentage increase from baseline values is shown for the lumbar spine. Specific measurements were made at baseline, 12, 30, and 36 months. (Reprinted with permission from *New England Journal of Medicine*, 339:602, 1998. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

pothesis that there may be a narrow window in time during adolescence in which maximal bone mass accrues. Prolonged gonadal steroid deficiency during this time will probably have a permanent impact on adult bone mass.

Levels of GH and IGF-I increase dramatically during normal puberty, augmented by increasing levels of sex steroids. Much of the GH action on bone is mediated through IGF-I. IGF-I functions in an endocrine and autocrine/paracrine manner as a bone trophic hormone that positively affects bone growth and bone turnover by stimulating osteoblasts, collagen synthesis, and longitudinal bone growth (35–37). Therefore, in GH-deficient children, bone density and markers of bone formation are significantly reduced and improve with recombinant human GH treatment (38). Adult patients with untreated pubertal GH deficiency have reduced bone mass compared with treated patients (39). Therefore, GH deficiency during adolescence may lead to persistent osteopenia in adulthood.

Nutritional factors

Body weight is a major determinant of bone density in children and adolescents. Studies in healthy normal weight and obese children and adolescents demonstrate that lean body mass correlates with total and lumbar bone mineral content (40). Adolescents with nutritional disorders are often also hypogonadal, making it difficult to determine the impact of these individual factors on bone density. In adolescents with nutritional disorders such as anorexia nervosa, the relationship between body mass and bone density is not present (41, 42), suggesting that multiple factors probably interact. In adolescent anorexia nervosa patients there is an imbalance in bone metabolism, with low bone formation uncoupled with resorption, in association with low bone density (42). IGF-I levels are reduced in these patients, probably due to combined effects of GH resistance (43) in addition to reduced liver IGF-I gene expression with undernutrition (37). Low bone formation in adoles-

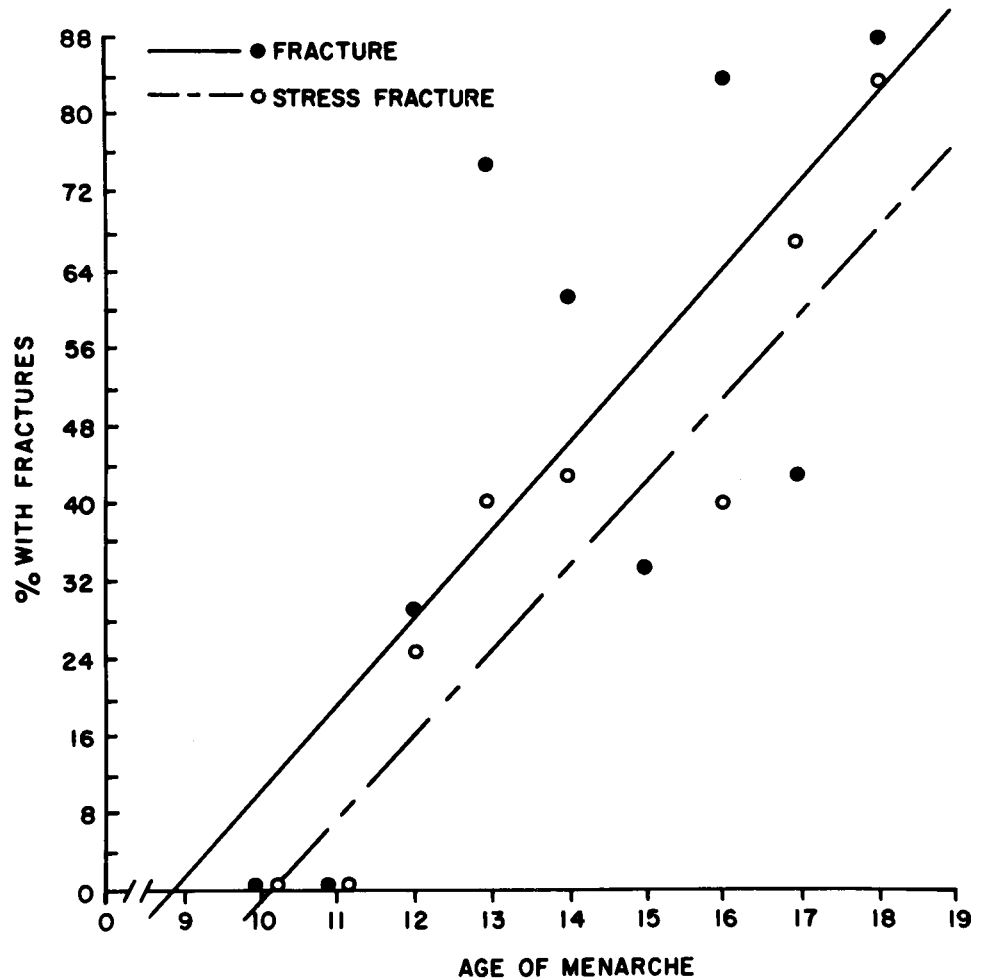


FIG. 4. Relationship between age at menarche and the percentage of young dancers ($n = 75$) with fractures and stress fractures. (Reprinted with permission from *New England Journal of Medicine*, 314:1351, 1986. Copyright © 1986 Massachusetts Medical Society. All rights reserved.)

cent girls with anorexia nervosa has been found to correlate strongly with levels of IGF-I (42).

Calcium intake has been shown to correlate with bone density in healthy children and adolescents. In a group of 151 healthy girls and boys, 7–15 yr old, Ruiz *et al.* reported that dietary calcium intake was the most significant determinant of spinal bone density, and that the majority of children with low spinal and femoral neck bone density had low dietary calcium intake (44). Other studies have found a small or negligible effect of dietary calcium on regional bone density (3, 45). Dietary calcium requirements increase substantially around the time of peak growth velocity and bone mineral accrual (46). Dietary calcium supplementation has been shown to improve bone density, but it is unclear whether the effect is sustained once supplementation is stopped. A long-term (3-yr), double blind, placebo-controlled trial of calcium supplementation in identical twin pairs, 6–14 yr old, showed that there was a significant effect of supplementation on radial and spinal bone density in prepubertal subjects, but not in pubertal subjects (47). A shorter term (18-month) trial did find a positive effect of increasing calcium intake from below to above the recommended daily allowance of calcium on bone density of the spine, but not of the peripheral sites in adolescent girls (48). Whether calcium or other micronutrient supplementation can lead to improvement in peak

bone mass remains unknown. Little is known regarding the definitive role of these factors in younger patients. There is probably an age-specific effect of many of these factors in the developing skeleton; therefore, it is important to define the impact of these variables on the development of bone density during childhood and adolescence.

Other determinants of peak bone mass

Physical activity, particularly weight-bearing exercise, is known to have a positive effect on bone density in children and adolescents (3, 49). A study of 45 prepubertal gymnasts showed increased bone density compared with controls, and the duration of training correlated with bone density. Furthermore, the gymnasts had a 30–85% greater increase in areal bone density in the spine and legs over 12 months than bone age-matched prepubertal controls. In addition, a group of retired young adult female gymnasts had higher bone density at all sites (z -score, 0.5–1.5) compared with age-, height-, and weight-matched controls, suggesting a persistent beneficial effect of prior physical activity (49). However, excessive exercise during adolescence may lead to delayed puberty, amenorrhea, and low bone density (50). Therefore, the timing, intensity, and duration of the physical activity may determine whether it will have a positive or negative effect on bone density.

Disorders resulting in low peak bone mass

Turner syndrome. Low bone density is seen in children, adolescents, and adult patients with Turner syndrome, and an increased incidence of wrist fractures has been reported. Although abnormalities in gonadal steroids and GH secretion probably contribute to the osteopenia in this disorder, abnormalities have also been reported in prepubertal girls, suggesting an intrinsic bone defect. Bone metabolism studies using surrogate markers and histomorphometric analysis in children and adolescents with this disorder are consistent with a state of low bone turnover. Deficits in bone density have been shown in both cortical (radius) and trabecular (spine) bone. Data on bone density reduction at the lumbar spine vary depending on whether values are in reference to chronological or skeletal age, body mass index, or height and whether patients have received GH or estrogen treatment (51). In untreated young girls, 4–13 yr old, the largest study, in 78 patients, demonstrated normal spinal bone density when they were matched for bone age and height with prepubertal controls, and normal radial bone density when they were matched for height despite a significantly increased rate of wrist fractures (52). The investigators suggest that the increase in observed wrist fracture rate may be due to either an intrinsic structural defect or an increased rate of falling in these girls. Other studies have shown reduced bone density in these patients, but did not account for the variables (height, bone age, and body size) that may impact on bone density measurements. Of these factors, accounting for height is particularly important in this patient group due to their significant short stature and associated reduced bone size. Because the most commonly used method of bone density measurement, DEXA, provides an areal density measurement rather than a true volumetric density, individuals with bigger bones will have a greater reported bone density value. Methods to account for bone size when assessing bone density include the use of QCT or calculated volumetric bone density measurements (45) and are particularly useful in these patients.

Bone density and fracture risk in Turner patients are dependent upon treatment with GH and/or estrogen. In young Turner patients treated with GH, lumbar bone density or bone mineral apparent density is normal compared with that in healthy girls matched for bone age, height, and pubertal stage (53). In small, short-term studies, bone density increases with estrogen treatment (54), but there are no long term studies to determine whether estrogen therapy improves peak bone mass and, if so, what the timing and dosing requirements of estrogen administration are. The importance of estrogen deficiency is suggested by several studies in adult women with delayed exposure to estrogen. Radial bone density has been negatively correlated with age at initiation of estrogen replacement in adult Turner women (age, 20–50 yr) who did not enter puberty spontaneously (55). A significant reduction in spinal bone density has been shown in 40 women with Turner syndrome compared with healthy women of similar height and weight. The women with primary amenorrhea, indicating a longer duration of estrogen deficiency, had a significantly higher rate of fractures compared with women who had some spontaneous menses.

Approximately 50% of the women with Turner syndrome had sustained fractures at typical postmenopausal osteoporotic sites, including the vertebrae, femoral neck, and wrist (56). Adult women with Turner syndrome in whom estrogen therapy was delayed or insufficient had significantly lower lumbar bone density than women who had received estrogen replacement beginning at 16–18 yr of age. Both groups had significantly reduced bone density compared with normal women, but limitations of the study include lack of information on both height and bone age in the untreated patients (57). Overall, these data suggest that a prolonged duration of estrogen deficiency, particularly during adolescence, probably contributes to low bone density in women with Turner syndrome.

Klinefelter syndrome. It is not known whether the chromosomal defect in Klinefelter syndrome (XXY) has an effect on bone density independent of gonadal steroid deficiency. There are data to suggest, however, that the characteristic long bone abnormality, with increased lower body segment, is present before puberty and therefore is probably attributable to the underlying genetic defect rather than androgen deficiency (58). Young hypogonadal men with Klinefelter syndrome are at risk for low bone density, although bone density measurements in these patients have not been widely published. Horowitz *et al.* (59) reported significantly decreased forearm bone density in association with low bone formation and high resorption assessed by bone turnover markers in 22 adult men (19–68 yr old) with Klinefelter syndrome. There was no significant difference in forearm bone density between testosterone-treated or untreated patients; however, there was a significant relationship between bone density and serum testosterone levels. Sites composed of primarily trabecular bone, which are generally more affected in hypogonadal states, have not been examined in these studies. Therefore, although early diagnosis and treatment of androgen deficiency is recommended, site-specific data regarding testosterone administration on bone density are lacking.

Gonadal steroid insufficiency. Apart from known genetic syndromes, permanent or transient estrogen and testosterone deficiency during adolescence due to a number of causes (Table 1) can lead to reduced bone mass. Young adults with hypogonadotropic hypogonadism have both reduced cortical and trabecular bone density. Finkelstein *et al.* found that in 23 such young adult men, 70% had a radial bone density less than 2 SD below the normal mean, and 35% had spinal bone density below the fracture threshold (19). Patients had a similar reduction in bone density regardless of whether they had attained epiphyseal fusion, suggesting abnormal pubertal bone mineral accretion rather than accelerated bone loss alone. Treatment of patients with hypogonadotropic hypogonadism by maintenance of normal adult levels of testosterone resulted in an improvement in bone density. Patients with immature epiphyses had a greater response to treatment than those with mature epiphyses, but neither group attained normalization of bone density after an average of 2 yr (60).

Estrogen deficiency in female adolescents is associated

TABLE 1. Disorders resulting in reduced peak bone mass

Genetic syndromes (multifactorial)
Turner syndrome
Klinefelter syndrome
Hypogonadism during adolescence
Hypogonadotropic
Permanent, <i>i.e.</i> Kallman's syndrome, idiopathic
Delayed, <i>i.e.</i> constitutional delay, anorexia nervosa, hypothalamic amenorrhea
Hypergonadotropic
Gonadal dysgenesis
Gonadal failure, <i>i.e.</i> autoimmune, chemotherapy/radiation exposure
Aromatase deficiency
Estrogen receptor defect
Other endocrine disorders
GH deficiency
Cushing's disease
Hyperthyroidism
Diabetes mellitus
Rickets
Nutritional
Malnutrition
Chronic dietary calcium/vitamin D deficiency
Chronic diseases of childhood and adolescence (multifactorial)
Anorexia nervosa
Inflammatory bowel diseases
Cancer
Cystic fibrosis
Rheumatologic disorders
Osteopathies
Glucocorticoid-induced osteopenia
Osteogenesis imperfecta
Idiopathic juvenile osteoporosis
Neurogenic osteopenia
Metabolic diseases
Homocystinuria
Lysinuric protein intolerance
Menke's kinky hair syndrome

with reduced bone density. There are multiple possible causes of estrogen deficiency in female adolescents. Hypothalamic amenorrhea due to excessive exercise or stress is the most common cause in otherwise healthy adolescents, particularly athletes. Although weight-bearing activities during adolescence can have positive effects on increasing bone density, excess exercise can lead to low weight and amenorrhea. As estrogen deficiency and low weight often occur together, their independent effects on bone density are difficult to determine. Several investigators have reported that teenage and adult amenorrheic patients have reduced bone density compared with eumenorrheic controls. Warren *et al.* found that among a large group of professional ballet dancers, 13–29 yr old, the age at menarche highly correlated with the occurrence of stress fractures, and those with stress fractures had a significantly later age of menarche than those without fractures (31). However, when bone density measurements were controlled for weight, much of the difference between amenorrheic and eumenorrheic subjects became insignificant (30–32). In the young ballet dancers reported by Warren *et al.*, lumbar spine bone density was not significantly different between age- and weight-matched amenorrheic and eumenorrheic dancers when controlled for weight; however, metatarsal bone density remained significantly lower in the amenorrheic group. Therefore, nutritional status may mediate the site-specific effects of estrogen deficiency on

bone density. Estrogen/progesterone treatment has been shown in a prospective study of 24 young women runners (age, 14–28 yr) to significantly improve spinal and total bone density compared with that in medroxyprogesterone- and placebo-treated subjects (61). The effects of treatment with hormone replacement to improve bone formation in adolescent girls with estrogen deficiency has not been evaluated; therefore, it remains unknown what dose, timing, and duration of therapy may be beneficial.

A delayed timing of puberty may be an independent predisposing factor for reduced peak bone mass. Male patients with constitutional delay of growth and pubertal maturation have been reported to have significantly reduced bone mass during adulthood. Lumbar, femoral neck, and radial bone density has been found to be 2 SD or greater below the normal mean in one third of young adult men with a history of delayed puberty who were not given androgen treatment during adolescence (20). Significant differences in regional bone density were present even when bone size was accounted for with calculated volumetric bone density (62). Other investigators found a similar reduction in areal bone density in young adult men with a history of constitutional delay. However, there was no difference in calculated volumetric bone density between patients and controls, and there were no differences among those treated with testosterone, the nonaromatizable androgen oxandrolone, or untreated patients (21). Possible reasons for the discrepancy between these data include the inability to adequately account for bone size with calculated methods from DEXA measurements and the inclusion of patients with various etiologies and duration of abnormal growth and development. A further prospective study of this patient group throughout adolescence until peak bone mass is attained is needed to determine whether treatment with androgens in adolescent boys with constitutionally delayed puberty is required to achieve normal bone density. In female patients, data similarly suggest that a delay in the normal timing of pubertal development results in reduced bone mass. An increased fracture rate has been reported in young women with a history of delayed menarche (29, 31). Women with anorexia who had onset of the disorder during the teenage years have lower bone density than those in whom the disorder developed in adulthood (34) and, therefore, after the development of peak bone mass. However, it is not known whether estrogen deficiency alone or deficiency of other gonadal steroids (*i.e.* testosterone or progesterone) or nutritional variables is most important during development. Furthermore, the timing, dosage, and duration of estrogen therapy needed to maximize peak bone mass are unknown.

Other endocrine disorders

GH deficiency. Untreated GH deficiency during childhood and adolescence often leads to reduced peak bone mass. Adults with untreated pubertal GH deficiency have reduced bone density at the lumbar spine, femoral neck, and Ward's triangle compared with treated patients and normal controls (39). Kaufman *et al.* studied 30 adult men with childhood-onset GH deficiency and demonstrated a reduction of 20–39% in cortical bone density (forearm) and 9–19% in trabec-

ular bone density (spine) (63). In a larger study of 70 adult men with childhood-onset GH deficiency, one third of patients had lumbar bone density 2 SD or more below the normal mean (64). Low bone density measurements may reflect reduced height and bone size in these patients. Patients in whom volumetric bone density is measured by QCT or estimated by calculated methods from DEXA measurements to correct for bone size, however, also have been shown to have reduced spinal bone density compared with age- and sex-matched reference data (65, 66). Although a subset of patients studied had received prior treatment with GH, the adequacy of treatment dosage and timing has not been established. In children and adolescents with GH deficiency, bone density and markers of bone formation are significantly reduced and improve with recombinant GH treatment in short-term studies (37, 67, 68). A 2-yr study of 38 treated GH-deficient children, 4–16.9 yr old, demonstrated increased lumbar bone density by DEXA after 6 months of treatment but no significant change in calculated volumetric bone density until after 2 yr of treatment. These data indicate that early changes in bone density measurements may reflect changes in bone size, but prolonged treatment results in improvement in net bone formation (68). Longitudinal data in 32 GH-deficient children, 7.2–16.3 yr old, treated with GH for an average of 4 yr demonstrated a significant improvement in radial and lumbar bone density with therapy (Fig. 5) (69). The greatest improvement was observed with the longest treatment duration, and in this group, z-scores approached mean reference values. A group of 11 patients, 16–18.7 yr old, who had reached final height had significantly reduced lumbar bone density compared with short normal controls. Possible reasons for this include the interrupted and low dose GH treatment the patients received during the era of pituitary-derived GH. GH treatment appears to have a more pronounced effect on bone density in patients with childhood-onset GH deficiency than in those with adult-onset GH deficiency (70). Young adult men with childhood-onset GH deficiency who resumed GH treatment for 3–5 yr during adulthood demonstrated a significant (9.6–16.2%) improvement in lumbar, femoral neck,

and trochanter bone density, with the most significant effects observed in those with lower baseline bone density z-scores (71). These data suggest that GH treatment leads to improved bone density, which is a function of the dose and duration of treatment, and that patients may require prolonged GH treatment beyond the time of growth to improve peak bone mass.

Cushing's disease. Patients with Cushing's disease may have reduced bone mass due to the direct effect of hypercortisolemia on bone and the secondary hypogonadal state. The presence of osteopenia and vertebral collapse in a prepubertal child with Cushing's disease (72) suggests that cortisol excess is causative. Due to the rarity of this disorder in children, limited data on bone density are available. In the two largest published series of pediatric patients with Cushing's disease (n = 101 patients total, 4–20 yr old), bone density measurements were performed at diagnosis in only three patients, and only one patient had a fracture at diagnosis (73, 74). The patients in whom densitometry was performed had severe osteopenia (z-score = -3.9 to -7.0), which improved, but remained reduced, after treatment (73). Leong and colleagues described marked lumbar osteopenia (-3.2 SD) in a 15-yr-old girl with long-standing Cushing's disease during adolescence. Serum osteocalcin was markedly reduced pretreatment, suggesting low bone formation. After more than 2 yr of follow-up, bone density increased considerably, but remained reduced compared with that in her normal twin (75). These data suggest that reduced peak bone mass is a complication of Cushing's syndrome in childhood and adolescence, and relates to the duration of increased cortisol secretion. Specific hormonal or other therapeutic strategies to improve bone mass in this patient group have not been investigated.

Hyperthyroidism. Reduced bone mineral density in adult patients with untreated hyperthyroidism is common; however, data on the effects of hyperthyroidism on peak bone mass are limited. A study of 13 girls with hyperthyroidism, 5–14.9 yr old, demonstrated significantly reduced whole body and

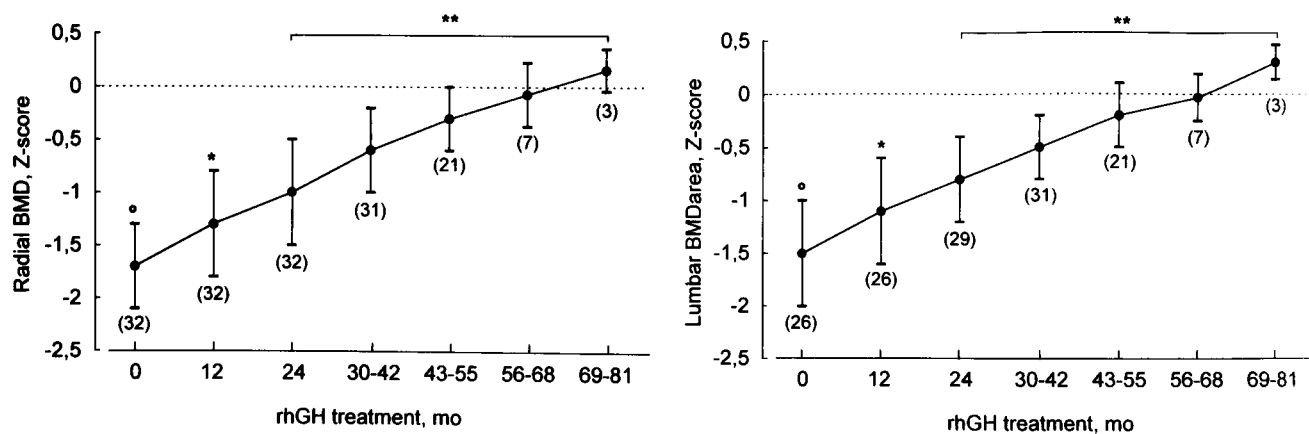


FIG. 5. Increase in bone density in children with GH deficiency receiving rhGH treatment. Mean radial BMD Z-score (left) and mean lumbar BMDarea Z-score (right) corrected for bone age in children with GH deficiency receiving rhGH treatment. Parentheses enclose the number of examined children. o, $P < 0.001$ vs. reference values; *, $P < 0.01$; **, $P < 0.001$ vs. 0. (Reprinted with permission from *The Journal of Clinical Endocrinology & Metabolism*, 81:3080, 1996. Copyright © 1996 The Endocrine Society. All rights reserved.)

spinal bone density at diagnosis compared with healthy girls matched for age and body size. The low bone density in untreated hyperthyroid girls occurred in association with elevated bone resorption as assessed by urinary N-telopeptide (76). However, bone formation was not assessed. Thyroid hormone levels correlated negatively with bone density and positively with N-telopeptide in these patients. Both bone density and bone resorption were no longer significantly different from control values at 12 and 24 months of follow-up in patients receiving successful medical treatment. These data suggest that untreated hyperthyroidism negatively affects bone metabolism and bone density in youths, but that the effects can be corrected with treatment and are therefore unlikely to affect peak bone mass in adequately treated patients.

Type 1 diabetes mellitus. There are conflicting data regarding whether reduced bone density is a complication of type 1 diabetes mellitus. The majority of studies in adults demonstrate osteopenia of cortical and trabecular sites, which is generally correlated with the level of blood glucose control and duration of diabetes, and the incidence is increased in patients with other chronic complications of diabetes (77–79). Although an increased fracture risk has not been found in this patient group, increased calcaneal fractures have been reported in patients with long-term vascular complications and in those receiving steroid treatment (80, 81). Osteopenia appears to be minimally progressive in adulthood (77, 82), suggesting that the low bone density seen in adult patients may result from a reduction in peak bone mass. Studies in children and adolescents with a short duration of diabetes, however, have shown no differences in spinal and peripheral bone density assessed by DEXA between patients and age- and sex-matched controls (83–85). Using QCT, which allows selective measurement of trabecular and cortical bone, the largest study (86) of 48 diabetic children and adolescents, 5.2–19.6 yr old, found a small significant decrease (3.5%) in cortical bone density and no difference in trabecular bone density in patients compared with controls matched for age, sex, skeletal and pubertal maturation, and anthropometric measurements. The reduction in cortical bone density did not correlate with the duration of diabetes or the level of control, as assessed by glycosylated hemoglobin. In contrast, Lettgen *et al.* (87) studied a smaller group ($n = 21$) of diabetic children and adolescents, 6.2–19.9 yr old, of variable disease duration (0.8–18. yr) using forearm QCT and demonstrated significantly decreased trabecular bone density (–18.9%) and a smaller (–5.1%), nonsignificant decrease in cortical bone density compared with age-, pubertal stage-, and sex-matched controls. The duration of diabetes and glycosylated hemoglobin was significantly inversely correlated with trabecular bone density in these patients. Therefore, the majority of data demonstrate a small or negligible reduction in bone density in children and adolescents with diabetes mellitus; however, data are limited to cross-sectional studies. Longitudinal data on bone mineral accretion during childhood and adolescence are needed to identify those patients who may be at risk for low peak bone mass. Osteopenia may develop over the long term, with patients in poor control and with other diabetic complications at highest risk.

Glucocorticoid therapy. Osteopenia and growth retardation are common complications of glucocorticoid therapy in pediatric patients. The rate of bone loss is related to glucocorticoid dose, but osteopenia occurs in children receiving less than 0.16 mg prednisone/kg·day (88). Loss of bone occurs most rapidly in the first 6 months of glucocorticoid therapy (89) predominantly in trabecular bone (90–92). Glucocorticoid-induced osteopenia and failure to achieve peak bone mass are thought to result from multiple factors, including direct effects of glucocorticoids on bone, impaired calcium absorption, abnormal renal calcium handling, reduced gonadal steroid secretion, and changes in the GH/IGF-I axis (89).

Bone undergoes constant remodeling, and any factor causing bone resorption to exceed bone formation will result in bone loss. Several lines of evidence suggest that glucocorticoids impair bone formation (93–95). Glucocorticoid administration may also increase bone resorption, although the evidence of a direct effect of glucocorticoids on bone resorption is less extensive (95, 96).

Glucocorticoid effects on mineral metabolism represent a partial explanation for glucocorticoid-induced alterations in bone formation and resorption. Glucocorticoids impair calcium absorption in the duodenum (97) and result in secondary hyperparathyroidism, stimulating osteoclastic activity and bone resorption (98). Glucocorticoid-induced alterations in vitamin D metabolism are also postulated, but are controversial (99, 100).

Glucocorticoids may impair the attainment of peak bone mass through alterations in gonadal function at the level of the pituitary and through direct effects on the gonads (101–103). Although hypogonadism may be a contributing factor to glucocorticoid-induced osteoporosis in adolescents, bone loss still occurs in the presence of clinically normal gonadal function (89).

Glucocorticoids may also impair the attainment of peak bone mass via effects on the GH/IGF-I axis. High dose, long-term glucocorticoid therapy markedly attenuates GH secretion (104). The impact of short-term glucocorticoid exposure on skeletal development in children varies from study to study depending upon the dose and timing of glucocorticoid therapy and the method used to assess GH secretion. However, regardless of the effects on circulating IGF-I, IGF-I activity appears to fall within hours of glucocorticoid administration in children whose peripheral IGF-I levels remain unchanged (105).

Bone loss in children receiving glucocorticoids is dose related, and therefore it is prudent to prescribe the lowest effective dose. Although preserving the normal function of the hypothalamic-pituitary-adrenal axis, alternate-day glucocorticoid regimens do not prevent bone loss (106). Therefore, children and adolescents receiving glucocorticoid therapy may be at risk for effects on attainment of peak bone mass and bone loss. Specific interventions to protect bone mass in glucocorticoid-treated children have not been assessed, although maintaining normal calcium and vitamin D intake is recommended. In addition, postpubertal adolescents receiving chronic glucocorticoid therapy should be monitored for development of hypogonadism.

Nutritional disorders. Multiple disorders resulting in deficient caloric and micronutrient (calcium and vitamin D) intake during childhood may affect peak bone mass. Specific nutritional disorders associated with reduced bone density include inflammatory bowel disease (IBD), celiac disease, and anorexia nervosa.

Inflammatory bowel disease. Both types of IBD are associated with an increased prevalence of osteopenia (107), although among patients with IBD, those with Crohn's disease have been noted to have a higher risk of osteopenia than those with ulcerative colitis (108). Semeao *et al.* (109) found that of 119 children and young adults with Crohn's disease, 70% of patients' had bone mineral density z-scores at least 1 SD below the normal mean, and 32% had scores at least 2 SD below the normal mean. Nutritional factors such as the use of hyperalimentation, vitamin D deficiency, and calcium malabsorption may contribute to bone loss in adolescents with IBD (110). In the above-mentioned cross-sectional study of 119 children and young adults with Crohn's disease, low bone density was associated with the use of nasogastric tube feeds and total parenteral nutrition independent of glucocorticoid use (109). Although alterations in vitamin D metabolism as well as calcium/mineral metabolism are thought to contribute to bone loss in IBD, this has not been demonstrated in some clinical studies (111).

The reduction in bone density in children with IBD is probably multifactorial. In addition to nutritional factors, other complicating factors include poor linear growth, delayed puberty, and therapies used to treat IBD. Although several studies have found glucocorticoid treatment to have the strongest correlation with bone density in these patients (112, 113), IBD is a risk factor for accelerated bone loss independent of the use of glucocorticoids (114, 115). In addition to glucocorticoid therapy, accelerated bone loss may occur due to the use of cyclosporin and 6-mercaptopurine (109, 110). Bone loss associated with IBD may also result from the production of inflammatory cytokines (110). Cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor, released during the inflammatory state, are thought to recruit and activate osteoclasts, perhaps contributing to bone loss and failure to attain peak bone mass (116).

Therapy for the prevention of bone loss in children with

IBD is limited. There are no studies directly comparing calcitonin with vitamin D and calcium supplementation in this population. Bisphosphonates have been shown to prevent glucocorticoid-induced osteoporosis in a multicenter study of 477 corticosteroid treated adults (24 with IBD) (117) and in a small series of corticosteroid-treated children (118). However, the long-term impact of bisphosphonate therapy upon skeletal development in children is unknown, and the use of bisphosphonates in children remains experimental at the present time (119).

Celiac disease. Children with the common pediatric enteropathy celiac disease, in which nutrient absorption is impaired, are also at risk for reduced bone density. Mora *et al.* demonstrated significantly reduced lumbar and total bone density at diagnosis of celiac disease in 44 patients, 2.6–20.4 yr old, after controlling for anthropometric measurements (120). Follow-up studies of these patients on a gluten-free diet demonstrated normalization of bone density.

Anorexia nervosa. Anorexia nervosa is another important nutritional cause of osteopenia commonly seen in adolescent girls, with spinal (trabecular) bone density most commonly affected. Lumbar bone density is reduced more than 1 SD below the normal mean in nearly half of height- and bone age-matched adolescent girls (42) and correlates with the duration of anorexia (41, 42). Adult women with anorexia nervosa who had onset of the disorder during adolescence have more severe osteopenia than those who developed the disorder during adulthood (34), indicating that abnormal bone mineral accrual occurs in adolescent patients. Surrogate markers of bone turnover demonstrate reduced bone formation uncoupled to bone resorption in adolescent girls with anorexia nervosa (Fig. 6), with the majority of the variation in bone formation due to the nutritionally dependent bone trophic hormone IGF-I (42). Therefore, nutritional status, in addition to gonadal steroid deficiency, is an important factor in the development of osteopenia in adolescents with anorexia nervosa. Improvement in bone density is seen with weight recovery before resumption of menses, suggesting the importance of nutritional status; however, significant osteopenia may persist (33). Potential negative effects on bone density from excessive exercise, increased cortisol se-

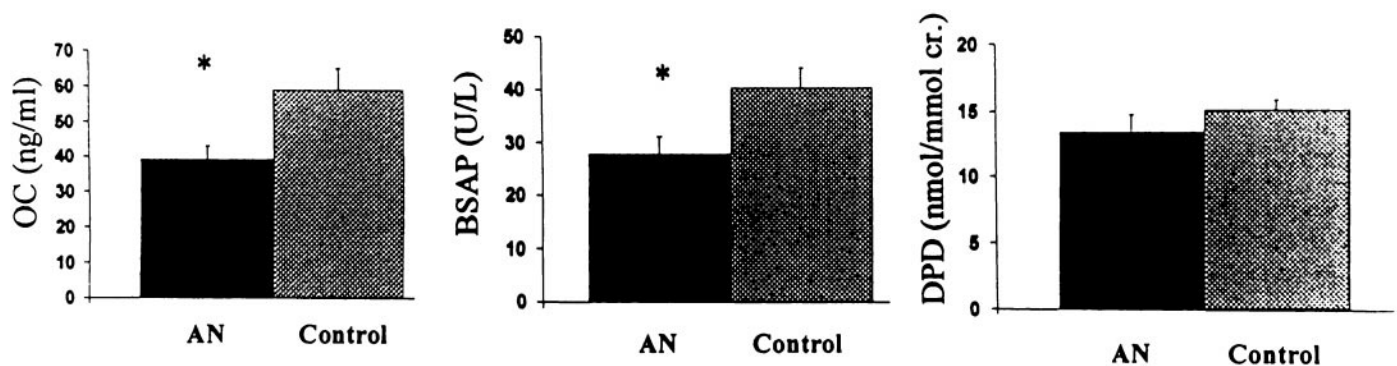


FIG. 6. Reduced bone formation uncoupled from bone resorption in adolescent girls with anorexia nervosa. Comparison of bone turnover markers in subjects with anorexia nervosa (AN; n = 11) and controls (n = 15). OC, Osteocalcin; BSAP, bone-specific alkaline phosphatase; DPD, deoxypyridinoline. *, $P = 0.02$ for AN subjects vs. bone age-matched controls. (Reprinted with permission from *The Journal of Clinical Endocrinology & Metabolism*, 84:4494, 1999. Copyright © 1999 The Endocrine Society. All rights reserved.)

cretion, and reduced calcium and vitamin D intake in these patients have not been proven. These data emphasize the importance of early diagnosis and treatment of underlying nutritional disorders in childhood to acquire normal peak bone mass.

Chronic diseases of childhood and adolescence

Cancer. Children and adolescents who undergo treatment for malignancy are at risk for poor bone mineral accrual due to the combined effects of the disease and treatment with glucocorticoids, chemotherapeutic agents, and cranial irradiation. The endocrine effects of treatment that contribute to osteopenia include GH deficiency and hypogonadism. In addition, these patients may have poor nutritional intake, reduced vitamin D levels, and low levels of physical activity, which may impact bone development. In a study of 28 children with leukemia or solid tumors, 2.9–16 yr old, calculated volumetric femoral and lumbar bone density was normal at diagnosis, but femoral bone density decreased by 11.3% over 1 yr. A small decrease (2.4%) in lumbar bone density in patients older than 7 yr was seen, but was not significant (121). Bone markers demonstrated reduced bone formation at diagnosis, with bone formation normalizing and resorption increasing with treatment, suggesting that the disease and its treatment may have differing effects on bone turnover. Patients with acute lymphoblastic leukemia (ALL) appear to be at a higher risk for osteopenia than those with other malignancies. Warner *et al.* found that in 35 child and adolescent survivors of ALL (7–19 yr of age, minimum of 18 months after completion of therapy), the percentage of predicted bone mineral content was reduced at the hip compared with 20 age-matched survivors of other malignancies and 31 sibling controls. In addition, although there was an improvement in the percentage of predicted bone mineral content at the spine with increasing duration of time off therapy, there was significantly less improvement in the ALL group compared with the group with other malignancies (122). In some studies, regional bone density has been correlated with previous exposure to specific chemotherapeutic agents as well as cumulative dosing (121, 122).

Among the long-term consequences of treatment of childhood malignancy, GH deficiency due to hypothalamic-pituitary damage from intracranial radiation therapy is common. In a study of 21 young adults who were treated for intracranial malignancy during childhood, all developed GH deficiency by the end of puberty. Those who did not receive GH treatment were osteopenic at the femoral neck, lumbar spine, and Ward's triangle compared with the GH-treated patients (123). However, other published data indicate that osteopenia may be present despite GH replacement in childhood brain tumor survivors (124). Therefore, the etiology of osteopenia in this patient group is probably multifactorial. What specific interventions may improve bone density in this patient population remain unknown; however, maximizing nutritional status, including calcium and vitamin D intake; minimizing immobilization; and replacing hormonal deficiencies when present should be part of the standard treatment.

Cystic fibrosis. Osteopenia is a common complication of cystic fibrosis in children and adults, which will probably significantly impact the quality of life in these patients as they continue to live longer. In adults, fracture rates have been reported to be 2 times greater in young women and men with cystic fibrosis than in the general population, with a particularly high risk for rib and vertebral compression fractures (10- to 100-fold risk) (125). Analysis of surrogate markers of bone turnover demonstrates an imbalance, with low bone formation and increased resorption in pubertal and young adult patients (126). Both poor bone mineral accrual and accelerated bone loss are implicated in the pathogenesis of osteopenia in these patients (126–128); however, few longitudinal data are available. One longitudinal study of 41 youths and adults with cystic fibrosis (9–50 yr of age) evaluated interval change in bone density over an average follow-up period of 17 months. Although spinal hip and whole body bone density were reduced at baseline in all subjects, continued decreases were seen only in subjects less than 18 yr old. These data are consistent with poor bone mineral accretion in young patients with cystic fibrosis (128). The cause of the low bone density in this population appears to be multifactorial, being variably correlated with low body mass, vitamin D insufficiency, glucocorticoid therapy, severity of illness, decreased physical activity, and hypogonadism (127, 129–132). There are no published therapeutic trials of treatment of low bone density in cystic fibrosis; however, one randomized controlled study in adults reported severe bone pain after iv pamidronate therapy, possibly related to increased production of inflammatory cytokines (133, 134).

Rheumatological disorders. Rheumatological disorders such as juvenile rheumatoid arthritis (JRA) have been associated with growth retardation (135) and low bone mineral density even in the absence of therapy with glucocorticoids (136–138). Osteoporosis associated with pathological long bone fractures as well as vertebral compression fractures have been reported in 20% of children with JRA (139). In one cross-sectional study, 30% of children with mild to moderate JRA had low total body bone mineral density (137). JRA appears to be associated with a low bone turnover state, as determined by reductions in both markers of bone formation as well as markers of bone resorption (138). The etiology of bone loss in JRA is probably multifactorial, with possible contributions from inflammatory cytokine production, diminished physical activity, alterations in nutritional factors, and the use of immunomodulatory agents (137, 138).

Other systemic rheumatological diseases, such as systemic lupus erythematosus and juvenile dermatomyositis, have been associated with reductions in bone mineral density. However, given the widespread therapeutic use of corticosteroids, it is difficult to demonstrate independent effects of these diseases on bone density. One prospective study of 113 children with chronic rheumatological diseases (including systemic lupus erythematosus, juvenile dermatomyositis, and JRA) demonstrated a reduction in osteocalcin, which was greatest in children with active disease before any treatment with corticosteroids (140). The precise mechanisms by

which these chronic inflammatory diseases result in osteopenia remain unclear and are likely to be multifactorial.

Conclusions

Normal bone mineral accretion during childhood and adolescence is a complex process involving genetic determinants, gonadal steroids, GH/IGF-I effects, and nutritional and other environmental factors. Assessing the normality of bone density measurements in childhood by the current methods is complicated by the lack of normative data in large populations of children who are well characterized in terms of anthropometric measurements and pubertal and skeletal maturation. Nevertheless, data identify numerous hormonal disorders that predispose young patients to reduced peak bone mass and thereby increased risk of life-long osteoporosis. These data support the importance of the awareness of risk factors for osteopenia in adolescents at risk and of correcting hormonal and nutritional disorders when present. The cause of many osteopenic disorders in childhood is multifactorial; therefore, there is a need for further elucidating the pathogenesis of poor bone mineral development. Future research is clearly needed in this area to develop treatment strategies to preserve maximal bone mass in patients at the highest risk for reduced peak bone mass.

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