Bone mass acquisition in healthy children

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Although 80% of the variance in bone mass is determined genetically, there are many other factors which influence the accumulation of bone in early life and affect future risks of osteoporosis. This review considers the genetic, fetal, and environmental influences on bone mass acquisition in healthy children, and highlights important areas where paediatricians may have a role by counselling children and their families to adopt a healthy lifestyle which promotes bone health.

Even though the clinical consequences of adverse bone health are largely seen in old age, evidence is accumulating that many predisposing factors to osteoporosis arise in childhood. Given an ageing population, an increase in osteoporosis related fractures has enormous economic implications. For example, in the UK £280 million is spent annually treating osteoporotic hip fractures alone. In children as in adults, fracture rates have been shown to be higher in individuals with a lower bone mineral density (BMD). Therefore, an understanding of the many influences on BMD is important for deciding rational strategies for optimising bone health during childhood.

There are two functionally distinct phases of bone development. The first is skeletal patterning which occurs during the embryonic period, when the position and shape of the various skeletal elements is determined by the expression of numerous regulatory genes and by local growth factors. The second phase begins with mineralisation, the location of which is influenced by mechanical strain. A view is emerging (the mechanostat theory) that rather than just being a passive recipient to external stimuli, bone tissue regulates itself with the aim of maintaining its structural integrity and strength.

Supporting evidence has come from recent developments in genetic and molecular studies which have identified new local and central homoeostatic mechanisms controlling bone mass.

This article will review the genetic, fetal, and environmental influences on bone mass acquisition during childhood and will highlight recent discoveries that have shed light on how bone mass is maintained. Reference is made to the terms bone mass and BMD. Bone mass refers to the weight of bone and may be influenced by bone size. By contrast, BMD refers to bone mass adjusted for bone volume.

CHANGES IN BONE MASS DURING CHILDHOOD

During skeletal growth, the balance of cellular activity is in favour of net bone formation, and at peak bone mass the amount of osteoclastic bone resorption is exactly matched by the amount of osteoblastic new bone formation. Peak bone mass is the maximal amount of bone mineral accrued within bone during childhood and adolescence plus the consolidation that continues beyond the attainment of final height.

Dual energy x-ray absorptiometry (DEXA) imaging indicates that there is an increase in bone mass throughout childhood with a marked acceleration in accumulation at puberty (fig 1). The increase in BMD that occurs following puberty is confirmed by quantitative computerised tomography (CT). This latter technique has the advantage of measuring volumetric BMD and is less influenced by bone size than DEXA which tends to underestimate BMD in small subjects and overestimate it in larger individuals.

Physiological adaptation of bone to the local muscle force is particularly important in prepubertal children as some of the age dependent increase in BMD in these individuals is attributable to an increase in local muscularity.

Longitudinal studies of changes in bone mass during growth have confirmed that in girls, the greatest increases in bone mass occur between the ages of 12–15 years, compared with 14–17 years in boys. Although the rate of change in bone mass slows dramatically by the age of 16–18 years in females and 17–20 years in males, uncertainty remains about the age at which accumulation of new bone stops and peak bone mass is attained. Some cross-sectional studies have suggested that in adult women, bone mass continues to increase during the third decade to reach a peak between 30 and 35 years. Others, however, have suggested that peak bone mass reaches a peak between the ages of 25 and 35 years.

Although optimising the genetic potential for peak bone mass is thought to delay the onset of osteoporosis and fractures in later life, longitudinal studies have yet to confirm this hypothesis.

GENETIC DETERMINANTS OF BONE MASS

Twin studies indicate that genetic predisposition determines up to 80% of peak bone mass, whereas the remaining 20% is modulated by environmental factors and sex hormone levels during puberty.

This genetic influence is consistent with the findings that BMD is reduced in the daughters of osteoporotic women and in
men and women with first degree relatives who have osteoporosis. A large number of genes are responsible for determining bone mass, and polymorphisms of many of these have been suggested to influence bone mass (table 1). However, the magnitude of the effects of most of these polymorphisms on bone density in childhood have not been evaluated.

**Vitamin D receptor gene polymorphisms**

Several studies have examined the influence of vitamin D receptor alleles on BMD in children. In adult women, vitamin D receptor polymorphisms contribute to a relatively small variation in BMD. By contrast, in children compared with adults, vitamin D receptor polymorphisms account for a greater difference when femoral and vertebral BMD are compared between those with homozygous recessive (bb) and those with dominant genotypes (BB), suggesting that these polymorphisms have a greater influence on BMD during childhood. In a study of prepubertal girls, dietary calcium intake also correlated with change in BMD in those with homozygous dominant and heterozygous vitamin D receptor (BB and Bb) genotypes but not in those with the homozygous (bb) genotype. These data provide an explanation for why there is a variation in response to calcium supplementation in terms of BMD accrual in children.

**Type I collagen gene polymorphisms**

A polymorphism in the regulatory region of the type I collagen gene, COL1A1, affects the binding site for the transcription factor, Specificity protein 1 (Sp1). This polymorphism was shown to be associated with reduced BMD and osteoporotic fractures in pre- and postmenopausal women. The same polymorphism was associated with decreased vertebral BMD in prepubertal girls with the heterozygous and homozygous recessive genotypes. In adolescents, polymorphisms of the oestrogen receptor, interleukin-6 and osteocalcin genes have also been shown to be independent predictors of BMD.18–21

**Low density lipoprotein receptor related protein 5 (LRP5)**

Recent studies of heritable skeletal disorders have identified a new mechanism of bone mass maintenance. A kindred with an autosomal dominant inherited high bone mass phenotype, with typical features of a square jaw and torus palatinus (an exostosis in the midline of the hard palate), was found to be the result of a mutation of the gene encoding for low density lipoprotein receptor related protein 5 (LRP5).22 In affected individuals, serum markers of bone formation were increased whereas bone resorption markers were normal. The LRP5 protein normally mediates the binding of a growth factor, Wnt, to its receptor which allows activation of intracellular signalling to promote osteoblastic differentiation (fig 2, left). In vitro studies have shown that this LRP5 mutation prevented the binding of a natural inhibitor of Wnt signalling, Dickkopf-1 (DKK-1), thus leading to unopposed Wnt activity (fig 2, centre and right). Concordant with this finding was the discovery that in the osteoporosis-pseudoglioma syndrome, characterised by low bone mass with childhood fractures and abnormal eye development, the phenotype was the result of an inherited loss of function of the LRP5 gene leading to inhibition of Wnt signalling. Given that non-syndromic high bone mass maps to the region of 11q12–13, the region which encodes LRP5, it is possible that LRP5 polymorphisms are significant contributors to the natural variation in bone density in normal children. Furthermore, antagonism of DKK-1 action provides a novel therapeutic opportunity for the treatment of osteoporosis.

**FETAL INFLUENCES ON BONE MASS**

The association between low birth weight and a low BMD in adulthood suggests that intrauterine programming contributes to the subsequent risk of osteoporosis in later life. In longitudinal studies of adults, a significant association between weight at 1 year (a marker of intrauterine and early postnatal environment) and adult bone mineral content at the lumbar spine and femoral neck have been shown. These findings were significant even after adjusting for influences of adult body size and lifestyle. Furthermore, the genetic influences on adult bone size and BMD may be modified by undernutrition in infancy, as evidenced by the significant interaction between the vitamin D receptor genotype and birth weight, the interaction of which was a determinant of lumbar spine BMD in adulthood. A low childhood growth rate and tall maternal height are associated with an increased risk of hip fracture in late adulthood. The same study reported that the individuals who experienced fractures in later life, were short at birth but had normal height by 7 years of age, suggesting that the normal lag in bone mineralisation behind linear growth is exacerbated in these individuals.

Some studies suggest there maybe intrauterine programming of the hypothalamic-pituitary axis. For instance, there is an association between low birth weight and both low BMD and median stimulated growth hormone (GH) concentrations in adulthood. Others have found a significant relation between size at birth and cortisol secretion in adult life which may be a determinant of BMD in adulthood. Parental birth weight and maternal cigarette smoking, maternal thinness, and activity during pregnancy were found to independently influence skeletal growth and

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**Table 1** Gene polymorphisms that influence bone mass

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<tr>
<th>Receptors</th>
<th>Hormones/ cytokines</th>
<th>Enzymes</th>
<th>Bone matrix proteins</th>
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<tbody>
<tr>
<td>Vitamin D*</td>
<td>IL-6*</td>
<td>Aromatase</td>
<td>COL1A1*</td>
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<td>Oestrogen (ERα)*</td>
<td>IGF-1*</td>
<td>Collagenase</td>
<td>Osteocalcin</td>
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<td>LRP-5*</td>
<td>Leptin*</td>
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*Indicates influence on BMD shown during childhood.

BMP, bone morphogenetic protein; COL1A1, type I collagen; IGF-1, insulin-like growth factor 1; IL, interleukin; LRP-5, low density lipoprotein related protein 5; PTH, parathyroid hormone; TGF, transforming growth factor; TSH, thyroid stimulating hormone.
mineralisation in utero, as evidenced by correlation of these factors with neonatal BMD. This latter study shows the importance of the interplay between genetic and environmental factors in utero on prenatal skeletal development, although the mechanistic basis for these observations has yet to be established.

Animal studies have focused on maternal undernutrition as a causal factor for how fetal programming leads to reduced BMD in later life. These studies have confirmed that intrauterine exposure to maternal protein deficiency lead to offspring with reduced bone mineral content and bone area in adulthood. Furthermore, the bone marrow mesenchymal stem cells (that is, osteoblast precursors) of these offspring were adversely affected as evidenced by a reduction in colony formation, proliferation and differentiation coupled with an impaired responsiveness to anabolic factors such as GH, IGF-1, and 1,25 dihydroxyvitamin D₃.

HORMONAL INFLUENCES
During childhood, GH is an important hormonal contributor to bone mass accrual before and after the attainment of final height. Levels of GH and insulin-like growth factor 1 (IGF-1) increase dramatically during puberty, augmented by the increasing levels of sex steroids. GH action on bone is mainly mediated through IGF-1, which positively effects bone turnover by stimulating osteoblast proliferation and differentiation. The prepubertal increase in adrenal androgens, specifically dehydroepiandrosterone metabolites, also have beneficial effects on the accretion of bone strength. New bone formation at puberty is likely to be the result of a further increase in muscularity and also the anabolic effects of the sex hormones on bone accretion. During the pubertal period, oestradiol has important effects, not just from increasing bone density but also by modulating bone remodelling by suppression of bone turnover at the endocortical surface leading to an increase in cortical thickness.

PHYSICAL ACTIVITY
Exercise exerts a positive effect on bone mass as young women involved in high impact or weight bearing activity (such as gymnastics) during both childhood and adolescence, have a higher bone mass than those not participating in such activity. The timing of an exercise intervention during childhood is also important. Exercise initiated during the prepubertal or early pubertal years appears to be the most beneficial to improving bone mass. A simple school based jumping programme given during the prepubertal years has been shown to significantly improve bone mass at the hip and spine. These advantageous effects were sustained for up to seven months after the exercise intervention had been discontinued. In peripubertal girls, a similar high impact, circuit based jumping programme also increased bone mineral content at the hip and spine and to a greater extent than that observed in prepubertal children. Furthermore, in a study of females that played racket sport to a national level, there was a twofold increase in bone mineral content in those that started playing at or before menarche when compared to those starting later.

Thus physical activity during early childhood and adolescence appears to be an important predictor of peak bone mass which may account for up to 17% of the variance in BMD between individuals in their late 20s. It is less clear however, whether physical activity in youth is translated into a reduced fracture risk in old age. A recent study has shown that fracture incidence in elderly former soccer players was no different from controls. Although BMD was higher in the years following retirement from soccer, cessation of exercise resulted in an accelerated loss of bone density, such that those who had been retired for over 35 years and aged over 60 years had no significant residual benefit in BMD. It can be hypothesised that the exercise induced benefits of optimising peak bone mass may only be short term and prospective longitudinal studies are needed to clarify this important issue.

NUTRITIONAL INFLUENCES
Nutritional sufficiency
Adolescent females who recover from anorexia nervosa have persistent osteopenia and a greater reduction in spinal BMD compared to those with the adult onset of the disease, suggesting that nutritional inadequacy predisposes to osteopenia. Reduced IGF-1 expression, GH resistance, and hypogonadism resulting from undernutrition are contributing factors in this disorder. Over-nutrition may also influence bone formation as overweight children have an increased predisposition to reduced BMD and fracture. There is increasing evidence that the hormone leptin, secreted by adipocytes, is involved in bone formation. Studies in normal children have shown a positive correlation between serum leptin levels and adiposity whereas leptin deficiency or resistance is associated with obesity. In children, cerebrospinal fluid (CSF) leptin

Figure 2 Left: in the absence of DKK-1, LRP5 interacts with the Wnt receptor and activates intracellular signalling leading to bone formation. Centre: DKK-1 prevents this interaction and an active signalling complex does not occur. Right: mutant LRP5 preferentially forms complexes with Wnt, leading to constitutive activation of Wnt signalling and bone formation.
concentrations are correlated with plasma leptin concentrations and only free (biologically active) leptin is detectable in CSF. These findings are interesting given that leptin has recently been shown in experimental studies to have a role in both the central and peripheral regulation of bone formation. Mice lacking either the functional leptin gene or the gene for its receptor have high bone densities, and intracerebroventricular administration of leptin to leptin deficient animals resulted in marked bone loss. Further animal studies indicated that the downstream mediator of leptin was the sympathetic nervous system, the activation of which lead to reduced bone mass. By contrast, in vitro studies suggest that leptin has direct beneficial effects on osteoblasts including stimulation of type I collagen synthesis, human osteoblastic differentiation, and matrix mineralisation.

Calcium
A high intake of milk during childhood and adolescence is associated with increased bone mass at maturity. The amount of dietary calcium consumption exerts a positive dose dependent effect on spinal bone mass in young women which is consistent with the known anabolic effect of calcium on the growing skeleton. Data such as these prompted studies of calcium supplementation in healthy children. In a study of identical twins of mean age 10 years, calcium citrate supplementation over three years significantly increased bone mass in the supplemented children when compared to their non-supplemented siblings. Others have shown in young children that calcium supplementation also augments the bone response to physical activity, resulting in greater cortical thickness and area. Milk extracted calcium phosphate, given for nearly one year, also significantly increased bone mass accrual in prepubertal girls. This beneficial effect was maintained three years after discontinuation of the supplementation, at a time when the subjects were pubertal or postpubertal. By contrast, following the completion of puberty in the calcium citrate supplemented twin studies, BMD was no different from sibling controls. It is possible that calcium phosphate extracted from milk may have additional anabolic properties over other calcium salts. If this is the case, a simple measure such as dietary supplementation with milk extracted calcium phosphate could favourably alter bone mass acquisition during childhood with lasting effects into early adulthood.

Vitamin D
Vitamin D is an essential dietary factor necessary for normal mineralisation of osteoid tissue. Evidence is accumulating of a resurgence of vitamin D deficiency in Western society, particularly in ethnic minorities. There is increasing support for this issue to be addressed by a renewed public health campaign to prevent the likely resultant adverse effects on children’s bone health. There are recent published guidelines for the amount of vitamin D required to prevent vitamin D deficiency. Vitamin D supplementation, even when given during infancy, has been associated with an increase in BMD in prepubertal children.

Other dietary factors
The consumption of vegetables such as onions is associated with inhibition of bone resorption leading to an increase in bone mass, although the pharmacologically active compound(s) leading to this effect remain unidentified. By contrast, a high consumption of carbonated beverages may lead to a reduction in BMD during adolescence. This effect is likely to be the result of milk displacement from the diet rather than from the direct effects on bone from the components of carbonated soft drinks such as caffeine, phosphorus, or glucose.

FRACTURES IN CHILDHOOD AND ADOLESCENCE
Fracture incidence in children peaks between the ages of 10–15 years. Fractures in this age group are related to bone strength which is a consequence of not just bone mass but also bone microarchitecture, biomechanics, and bone geometry such as cortical thickness.

Distal forearm fractures are the commonest childhood fracture and the incidence is increasing. It has been shown in healthy girls that each single standard deviation reduction in total body areal BMD, equivalent to a 6.4% change, approximately doubles the risk of new fractures at any site. Recent studies have elucidated factors that lead to upper limb fracture. In young girls, high body weight, a previous forearm fracture and low total bone areal BMD each independently increase the risk of fracture and similar risk factors have been shown in boys. Furthermore, those girls with forearm fractures did not show evidence of catch up of their bone mineral content up to four years following fracture. Girls with forearm fractures have also been shown to have a significantly smaller cross-sectional area at the distal radius, which coupled with increased body weight, may confer a biomechanical disadvantage and increase the predisposition to fracture following a fall. Time spent viewing television, computer, and video, as a measure of physical inactivity, also has a dose dependent association with wrist and forearm fractures. Taken together, these findings indicate that overweight children should be advised to take measures to reduce their weight while increasing physical activity levels in an attempt to optimise their bone health.

While exercise increases bone mass in children, the influence of physical activity levels on fractures in this age group is less clear. Sports participation, particularly contact sports, has been shown to increase upper limb fracture risk in boys, whereas the risk was decreased in girls. Moreover, the fracture risk was decreased in both sexes when undertaking light physical activity. These gender discordant effects may have been the result of the difference in attitude to sport between the sexes.

SUMMARY
Childhood growth represents a critical period for the acquisition of bone mass. Although genetic influences are the predominant determinant of bone mass, it is only environmental influences which may be modified to optimise bone mass in childhood. Promoting a healthy lifestyle, including regular high impact and/or weight bearing physical activity together with a healthy diet containing optimal calcium and vitamin D intake, may improve the best way to achieve maximal peak bone mass. The recognition by paediatricians of such factors which influence bone mass in childhood is important. They can advise children and their families accordingly and influence public health policies which may lead to an improvement in children’s diets and levels of habitual physical activity, thus reducing the risks of osteoporosis and fractures in later life.

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