Establishing good bone health in children

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Abstract

Osteoporosis is a major public health concern, and is likely to increase in prevalence as the current population ages. One proposed benefit of establishing good bone health in children is the optimization of peak bone mass, which may have an effect on fracture risk in adulthood. Preventing childhood fractures is also desirable. Optimal skeletal health is not only influenced by bone mass but also bone size, shape and microarchitecture. Methods of assessing these properties of bone have improved over recent years, and therefore our understanding of the determinants of bone health has improved. Potential factors which influence bone health include genetics, hormones, nutrition, exercise and other lifestyle factors. These may interact with each other and they can vary in their impact at different times across the life cycle. This review will examine the effects of these factors in the foetus, infant, child and adolescent.

Keywords bone; exercise; fractures; genetics; nutrition; osteoporosis; vitamin D

Introduction

The proposed benefits of establishing good bone health in children includes a reduced likelihood of fractures and optimization of peak bone mass that may lead to a reduction in the risk of osteoporosis in adulthood. There are concerns that with life expectancy increasing that osteoporosis is likely to become an increased healthcare burden. Defining strategies to optimize peak bone mass may be the best preventative approach to osteoporosis. There are also current concerns about bone health in children, with a rise in childhood obesity and nutritional deficiencies like vitamin D deficiency not uncommon. There has been a steady rise in fracture rates in children and adolescents, with age-adjusted incidence rates 32% higher in boys and 56% higher in girls in the United States. Optimal skeletal health is not only influenced by bone mass but also bone size, shape and microarchitecture. Methods of assessing these properties of bone have improved over recent years, and therefore our understanding of the determinants of bone health has improved. Potential factors which influence bone health include genetics, hormones, nutrition, exercise and other lifestyle factors. These may interact with each other and they can vary in their impact at different times across the life cycle. This review will examine the effects of these factors in the foetus, infant, child and adolescent and serves as an update on the previous review (2009).

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Prenatal determinants

Programming & genetics

It is well established that the population variations in bone mineral density has a significant heritability estimated between 60 and 80%. There is an additional influence of gender with several mother–child studies showing that mother–daughter bone mineral density (BMD) are more closely correlated than mother–son BMD. Some 26 genes have been associated with BMD but individual genes on their own provide less than 1% of the variation in BMD. Meta-analysis of these data indicates that there are nine genes that are associated with clinically significant increases in osteoporotic fracture risk. Fracture risk has also been extensively investigated by genome-wide association studies but the heritability is somewhat less than that seen with BMD.

There is increasing evidence that in utero and early life events not only exert an immediate effect on neonatal bone health, but that this effect may also persist into infancy, childhood, and even adulthood. The rapid rate of mineral gain during intrauterine and early postnatal life coupled with skeletal cell differentiation and development is postulated to offer the possibility of unique interactions between the genome and the early environment which can enable a type of skeletal phenotypic or developmental plasticity. One of the fundamental mechanisms of foetal programming is epigenetic modification, that is, heritable changes in gene expression, without altering the underlying DNA sequence. These changes involve post-translational modification of amino acid histones, such as acetylation, methylation and phosphorylation, leading to altered expression of microRNAs. Epigenetic regulation of bones and osteoporosis is not wholly established, but is a topic of current research.

Placental transfer of nutrients appears to be partly under epigenetic control. Calcium and vitamin D are essential nutrients for foetal bone growth and most calcium is supplied to the foetus during the 3rd trimester via active transport across the placenta. The expression of a placental calcium transporter (PMCA3) gene has been found to predict neonatal whole body bone mineral content (BMC) assessed by DXA.

Several studies have described birthweight and postnatal growth as predictors of adult bone mass and skeletal size, and short birth length with slow childhood growth has been shown to predict adult hip fracture. In one twin study of 445 monozygotic twins and 966 dizygotic twins, birthweight was found to positively predict BMC and bone mineral density (BMD) at a mean age of 47 years. The effect of birthweight on BMC was quantified by a recent meta-analysis as a 1 kg increase in birthweight being associated with a 1.49 g increase in lumbar spine BMC (95% CI

0.77–2.21), and a 1.41 g increase in hip BMC (95% CI 0.91–1.91).

Another key protein that may be influenced by intra-uterine environment and play an important role in future bone health is Insulin-like growth factor 1 (IGF-1). It is known that umbilical cord blood levels of IGF-1 are correlated with BMC in infants. Interestingly it has been shown that umbilical cord blood levels of IGF-1 are positively correlated to maternal protein intake during the third trimester. This seems to indicate a direct influence of maternal nutrition on future bone development of offspring. Several other maternal factors have been shown to influence bone health in offspring. Season of birth and exposure to ultraviolet B light have been shown in several studies to have significant influence on bone development in childhood - with children at age 9 found to have significantly lower BMC if maternal UVB exposure during late pregnancy was low. Other maternal factors which have been shown to have a negative effect on newborn bone mass are smoking, exercise in late pregnancy, and women with lower fat stores.

Vitamin D

The topic of vitamin D deficiency is currently a focus for both clinical practice and research in paediatrics. There has been a recognized resurgence of symptomatic vitamin D deficiency in children across Europe. There is a possibility that maternal vitamin D status has an effect on infant and child bone status, and potential consequences thereafter on peak bone mass accrual. In addition, there is recognition that vitamin D has a role outwith its skeletal effects, such as in immune function or cardiovascular disease. All of these are still under debate in the scientific community, but it has also led to a change in the level of vitamin D required to achieve 'sufficiency' for health. Vitamin D is vitally important for growth and maintenance of healthy bone. It is produced in the skin following exposure to sunlight, and in addition, a small amount is obtained from the diet. Vitamin D undergoes hydroxylation in the liver to 25 hydroxyvitamin D which is then further hydroxylated in the kidney to 1,25 dihydroxyvitamin D which is the active metabolite. This active metabolite acts on the gut to stimulate calcium and phosphate absorption. It acts to maintain calcium homoeostasis, when dietary calcium is low, calcium stores are mobilized from bone via parathyroid hormone.

Vitamin D deficiency is common in non-Caucasian individuals residing at higher latitudes, and pregnant women and their offspring are at particularly high risk. Vitamin D status is so important during pregnancy as the mother is the sole source of vitamin D substrate for her developing foetus; infants born to mothers with vitamin D deficiency are born with low stores. Those infants subsequently breastfed are further at risk of vitamin D deficiency as there is very little vitamin D in breast milk, approximately 40 IU (1 μg) per litre. The consequences of vitamin D deficiency as an infant include seizures secondary to hypocalcaemia, osteopenia, and cardiomyopathy. There is some inconsistency in the results of studies examining the effect of maternal vitamin D deficiency on bone mass accrual in utero, and through later childhood. One study of 50 mother–infant pairs showed that mothers deficient in vitamin D had babies deficient in vitamin D, and that these infants had, relative to birthweight, a lower whole body and femur bone mineral content measured by DXA. Conversely, Abrams et al reported no effect of umbilical cord vitamin D levels on whole body BMC and areal BMD in their cohort of newborn infants, where umbilical cord serum 25 hydroxyvitamin D was <50 nmol/litre in approximately 60%, and <12.5 nmol/litre in 20% infants. Javaid et al found reduced maternal vitamin D levels in late pregnancy to be associated with reduced bone mineral content and bone mass in the offspring at age 9 years. However, another recent study found no association between maternal vitamin D status in pregnancy and offspring BMC at age 10 years. In agreement with this van Eisjden et al, found no effect of maternal vitamin D deficiency in early pregnancy on linear growth of children up to the age of 6 years. There is still some controversy surrounding the optimal timing and dosage of vitamin D in pregnancy. Evidence is accruing that a pregnant woman's vitamin D requirements are closer to 4000 IU/day rather than the 400 IU/day which is the standard amount in over the counter prenatal vitamins. Hollis et al. randomized pregnant women to receive 400 IU, 2000 IU, or 4000 IU per day of vitamin D, and found that achieving 'sufficiency'(serum vitamin D >80 nmol/litre) was better with 2000 IU or 4000 IU, and that 4000 IU was the only effective dose in African American women. This dose was not associated with any adverse events. Women who are breastfeeding require extra vitamin D, and more vitamin D is transferred into breast milk when the lactating mother is replete. Doses of 6400 IU/day have recently been shown to be effective and safe in achieving vitamin D sufficiency in mother and her infant. Further randomized controlled trials of vitamin D supplementation in pregnancy, with serial bone assessments through to adolescence are needed to accurately address the current gaps in knowledge. Two such trials are in progress and the results awaited with interest. Public health interventions should reflect the latest research findings, so that pregnant women are directed clearly during this important time in the life cycle. Pregnant women with dark skin, those who keep their body extensively covered or with low dietary intake of vitamin D should have the correct supplementation as a priority. Robust data detailing the prevalence of symptomatic vitamin D deficiency in infants, such as the Scottish Paediatric Surveillance Programme, is crucial to assess the effectiveness of public health interventions.

Calcium

Interventional studies of calcium supplementation have demonstrated a benefit on maternal health during pregnancy, by reducing the frequency of pregnancy induced hypertension. This has implications for foetal growth, primarily by prolonging gestation and reducing intrauterine growth restriction. It also seems likely that a low maternal calcium supply may limit foetal mineral accretion. However there are still conflicting results on the effect of calcium supplementation on foetal growth and mineral accretion. Abalos et al. supplemented a large cohort of Argentinian calcium deficient women with 1500 mg of calcium per day, and found no effect on foetal growth parameters. This was similar to Abdel-Aleem et al., who also supplemented pregnant mothers with 1500 mg of calcium per day, and found no effect on the infants size at birth or at 12 months of age. However Koo et al. reported that supplementing maternal calcium intake had a positive effect on foetal bone accretion, in mothers whose calcium intake was low. Conversely, other studies have shown