Prenatal Nutritional Influence on Skeletal Development

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Abstract

There is increasing evidence to suggest that prenatal nutritional factors may have long-term effects on the offspring. Osteoporosis is a worldwide public health problem leading to both morbidity and mortality, through associated bone fractures. Although in clinical practice most effort in fracture prevention is aimed at slowing the rate of age-related bone loss, there is accumulating evidence that peak bone mass, achieved in early adulthood, is an important factor in determining bone strength in later life. A variety of studies have shown that peak bone mass is influenced by early life events, including nutrition in the prenatal period. This chapter will use the example of bone development to consider the effects of maternal diet and nutritional status on the offspring.

Recent work has introduced the concept of developmental plasticity and ‘programming’, whereby ‘a stimulus or insult at a critical, sensitive period of early life has permanent effects on structure, physiology and metabolism’ [1]. Initially, this theory was developed through observations relating low birth weight to the development of high blood pressure, coronary artery disease, type two diabetes and obesity in later life, all current public health issues [2].

Another important public health issue is osteoporosis, ‘a skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and risk of fracture’ [3]. Osteoporotic fractures commonly occur at the spine, hip and wrist, with the estimated lifetime risk of a clinically apparent fracture at one of these sites in an individual aged 50 years totalling 50% amongst women and 20% amongst men [4]. The economic burden of osteoporosis amounts to USD 20 billion in the United States of America and GBP 1.7 billion in the UK annually and is set to increase with an increasingly aged population [5]. As peak bone mass appears to be a major determinant of osteoporosis risk in later

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life, research has focused on exploring the link between nutrition, growth in utero and postnatal bone health. The impact of ‘programming’ in determining adult risk of osteoporosis will be described in two categories: firstly, retrospective cohorts where bone assessment was undertaken in adulthood in those individuals whose maternal, birth and childhood records have been preserved, and, secondly, mother-offspring cohorts relating nutrition, lifestyle and body build of pregnant mothers to the bone mass of their offspring.

**Early Growth and Adult Bone Mass**

Early epidemiological evidence that the risk of osteoporosis might be programmed arose from a study of 153 women born in Bath, England, during 1968–1969, who were subsequently assessed at age 21 [6]. Data on childhood growth was obtained from birth and school records. Statistically significant associations (p < 0.05) were seen between weight at 1 year and lumbar spine and femoral neck bone mineral content (BMC), but not bone mineral density (BMD). Similar relationships were found in other cohorts [7, 8] with positive associations between adult BMC and either birthweight or weight at 1 year. A recent meta-analysis and systematic review has included these investigations, and others from around the world, to conclude that overall, each 1 kg increase in birthweight is associated with a 1.49 g increase in BMC at the lumbar spine and 1.41 g at the hip in adulthood [9]. These relationships have been shown to be independent of adult weight and BMI [7, 8], and the association between early growth and BMC rather than BMD (which is partly size-corrected) suggests that there may be discordance between the processes governing skeletal size and those regulating mineralization of bone; they also provide evidence that the trajectory of bone growth might be modified in utero. These findings are further supported by data demonstrating positive associations between birthweight and both radial and tibial size and strength assessed by pQCT in 313 men and 318 women from the Hertfordshire Cohort Study [10]. These associations persisted after adjustment for age, body mass index, social class, cigarette and alcohol consumption, physical activity, dietary calcium intake, hormone replacement therapy use and menopausal status. A perhaps more important outcome measure is fracture, and indeed, poor early growth, both in childhood and infancy, has been found to predict increased risk of hip fracture in adulthood. Thus, in a Finnish cohort of 3,639 men and 3,447 women born in a Helsinki hospital during 1924–1933, tall maternal height and low rate of childhood growth were associated with increased hip fracture risk in adulthood [11]. The effects of maternal height and childhood growth rate were statistically independent of each other, and remained after adjustment for socioeconomic status. Importantly, hip fracture risk was also elevated amongst babies with lower birth length. More recently, data from the same cohort has shown that risk of hip fracture is greater where increase in height outstrips increase in weight between 1 and 12 years.
Women in the lowest quartile of change in z-scores for body mass index had an 8.2-fold increase in hip fracture risk (95% CI 1.9–35) compared with those in the highest quartile. This suggests that thinness in childhood is a risk factor for hip fracture, perhaps because the growth of the skeletal envelope in these children is forced ahead of its capacity to mineralise.

Work from the UK has suggested that these associations might be mediated via an adverse effect of poor early growth on later proximal femoral geometry. Thus, in the Hertfordshire cohort, low weight at one year was associated with a narrower proximal femur with reduced bending strength [13]. Further work will be needed to investigate whether these associations might be already present in childhood and whether they might be amenable to modification during intrauterine or postnatal life.

**Maternal Diet, Lifestyle, Body Build and 25(OH)-Vitamin D Status**

Following the observations made from retrospective cohorts as detailed above, investigation has proceeded to prospective mother-offspring cohorts to further investigate the interplay between maternal nutrition, birth weight and subsequent childhood development.

The Princess Anne Cohort study followed a consecutive group of pregnant women attending antenatal services at one organisation. Analysis of the women and 145 subsequent births revealed maternal factors which were associated with decreased offspring whole body BMC included low maternal birth weight, and smoking, low triceps skinfold thickness (a surrogate marker of fat stores), and high levels of vigorous physical activity in late pregnancy [14]. Results from the larger Southampton Women's Survey confirmed these findings and additionally demonstrated that maternal parity, fat stores and walking speed were associated with neonatal bone width [15].

The maternal factor associated with the greatest individual influence on intrauterine bone development appears to be 25(OH)-vitamin D concentration during pregnancy. Thus, in a cohort of 198 white Caucasian women from Southampton, UK, 31% of whom had circulating 25(OH)-vitamin D concentrations less than 50 nmol/l and 18% less than 25nmol/l, low maternal vitamin D status during pregnancy was associated with reduced offspring BMC and BMD at 9 years old [16]. Similar results for neonatal BMC were observed in the Southampton Women's Survey [17]. Further evidence comes from a Korean study, in which maternal vitamin D levels were positively correlated with newborn vitamin D levels, which were positively correlated with whole body BMC [18], and a recent Finnish cohort where greater maternal vitamin D levels were positively correlated with neonatal BMC [19]. In the UK ALSPAC cohort, ambient UVB radiation (the predominant determinant of circulating 25(OH)-vitamin D levels) during pregnancy was positively associated with offspring bone size at 9 years old, independent of childhood body size.
[20]. An indication that vitamin D related changes might manifest early in gestation was gained from the Southampton Women’s Survey, in which the distal femoral metaphysis of the fetus at 19 weeks’ gestation was widened relative to its length in offspring of mothers who had low levels of circulating 25(OH)-vitamin D [21]. This metaphyseal ‘splaying’ is reminiscent of the more overt changes associated with postnatal infantile rickets. A randomised controlled trial of vitamin D supplementation in pregnancy aimed at optimising offspring bone mass is currently underway in Southampton, UK [22]. In contrast to these findings in white Caucasian populations where low levels of 25(OH)-vitamin D are relatively common, in developing populations maternal calcium intake may be the predominant influence on intrauterine bone development. Thus, in an Indian cohort higher maternal calcium intake during pregnancy was associated with higher lumbar spine and areal BMD in the offspring at birth [23].

Other studies have suggested that maternal fatty acid status and overall dietary intake might be important. Thus a positive correlation was observed between maternal n–3 long chain polyunsaturated fatty acid concentrations and offspring whole body areal BMD and lumbar spine BMC and areal BMD at 4 years of age. Furthermore, although specific individual minerals have been shown to affect bone mineral accrual, overall maternal dietary pattern during pregnancy is also important; thus a diet high in fruit and vegetables, while low in processed foods, was associated with greater whole body and lumbar spine BMC and areal BMD in the offspring at 9 years [24].

The mechanisms by which these nutritional aspects of the maternal diet might influence skeletal development in the offspring have not yet been elucidated. However, in one study the relationships between maternal 25(OH)-vitamin D levels and offspring bone mass appeared to be mediated, at least in part, by venous concentrations of umbilical cord calcium [16]. Additionally, mRNA expression of the PMCA3 plasma calcium ATPase transporter gene [25] was positively associated with neonatal BA and BMC in the offspring in a further study. Animal investigations have suggested that other PMCA forms may be regulated by 1,25(OH)2-vitamin D [26], but there are currently few data in humans. More recently, PHLDA2, a gene previously linked to low birthweight has been shown to be associated with lower foetal femur growth velocity between 19 and 34 weeks’ gestation as well as lower BMC at 4 years of age [27].

It is becoming apparent that the mechanisms underlying associations between early environmental factors, such as maternal diet, and later offspring health, might involve epigenetic modulation of gene expression. Animal studies confirm that alteration of maternal diet leads to modified epigenetic marking in the offspring, and human studies have confirmed a role of epigenetics in some diseases [28]. Few human bone-specific data exist as yet, but increased understanding of epigenetic processes is likely to help elucidate both mechanisms and potential early biomarkers of later adverse health outcomes.
Conclusion

With an ageing population, the burden of osteoporosis is set to increase. This review has demonstrated some of the recent work elucidating the influence of the early environment on the skeleton in utero and beyond to the attainment of peak bone mass. Novel interventions, aimed at optimising peak bone mass through interventions early in life, such as prenatal maternal vitamin D supplementation, clearly merit further investigation. Such strategies should help inform public health policy and reduce the burden of osteoporosis related fractures in future generations.

Acknowledgements

We would like to thank Medical Research Council (UK), Arthritis Research UK, National Osteoporosis Society (UK) and International Osteoporosis Foundation for funding this work.

References


