Early Life Nutrition and Bone Development in Children

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Abstract

Fetal and early life may be a critical period for the development and/or programming of metabolic systems, including the skeleton. There are increasing human data from cohort studies on the association between early life nutrition and bone development in children. Breastfed children initially have lower bone mass than bottle-fed children, but longer-term studies suggest that they have higher bone mass (size adjusted) by age 8 years, especially in children born at term. By the time of peak bone mass, both preterm and term children have higher bone mass indicating a different bone accrual trajectory curve. These children also have lower fracture risk. Diet in utero has also been associated with subsequent bone mass from ages 6 to 16 years (but not fracture). Positive associations include milk, phosphorus, magnesium, potassium, protein, folate, calcium and vitamin D, while fat intake is negative. Smoking also interferes with bone mineralization possibly due to impaired placental function, but this deleterious effect on bone mass appears to diminish over time. All of these associations are statistically significant and independent of important confounders and later environmental exposures, suggesting that osteoporosis prevention programs need to start very early in the life cycle.

Introduction

Fractures are a major public health problem in males as well as females [1]. Bone density is one of the major predictors of these osteoporotic fractures in both the elderly [2] and children [3], and is the result of the amount of bone gained in early life (i.e. peak bone mass) and subsequent bone loss [4]. Physical activity and, to a lesser extent, diet (particularly calcium intake) during adolescence and early adulthood have been implicated as determinants of peak bone mass [5, 6]. However, the vast majority of adult bone mass
Jones

is attained before the age of 14 years [7]. In recent years, evidence has accumulated in support of the Barker hypothesis [8] for bone development for in utero diet and breastfeeding among other factors. The aim of the review is to summarize this literature relating to later effects of in utero and early life exposures for in utero diet, breastfeeding and smoking (as this may impair nutrition).

**Diet in Pregnancy**

Nutritional influences on childhood bone development may begin in utero, and because of in utero programming, such influences may affect both early skeletal development and the acquisition of bone mass throughout childhood. Studies examining this are few but there seems to be a consistency of results. In an early exploratory study from my group, maternal dietary intake of magnesium, phosphorus, potassium and protein during the third trimester of pregnancy was positively associated, and maternal fat intake negatively associated, with bone density in their children at age 8 [9]. In an English cohort [10] reporting associations between maternal diet at 32 weeks gestation and bone mineral content (BMC) and bone mineral density (BMD) at age 9 years, maternal magnesium intake was positively associated with total body BMC and BMD, but this did not persist when they adjusted for height. Furthermore, maternal intake of potassium was positively associated with spinal BMC and BMD, but this decreased after adjustment for weight. Both of these suggested an effect mediated through body size which differs from the Tasmanian data where the effect was independent of body size. Maternal folate intake was positively associated with spinal BMC adjusted for BA in the English cohort after adjusting for both weight and height of the children. The effect sizes in this study were smaller than those observed in the initial Tasmanian study [9]. In an Indian study [11], 6-year-old children of mothers who had a higher frequency of intake of calcium-rich foods during pregnancy (milk, milk products, pulses, nonvegetarian foods, green leafy vegetables, fruit) had higher total and spine BMC and BMD, and children of mothers with higher folate status at 28 weeks’ gestation had higher total and spine BMD, independent of parental size and DXA measurements. These children were smaller and lighter than norms, suggesting they were less well nourished, and the authors state that the results may reflect protein intake as well as micronutrients.

To date, studies have followed children up to age 6–9 years but not through puberty, so it is unclear if these associations are short- or long-term. Our recent report in 16-year-old children provides evidence in a well-nourished population that milk, fat and magnesium intake during pregnancy can independently influence bone mass for at least 16 years [12], and is thus likely to impact on peak bone mass. These results were similar (but smaller in magnitude) to
the results at age 8 years (table 1). Given the very small amount of bone laid down during pregnancy, this association most likely reflects early programming of later bone responses. Maternal magnesium density was positively associated with BMD at the femoral neck of 16-year-old adolescents, which is partially consistent with our previous report where it had strong associations in adjusted analysis that did not persist after adjustment for other dietary factors and the report of Tobias et al. [10]. Although the precise mechanism of maternal magnesium intake affecting bone health of offspring is currently unclear, it might be involved in changes of fetal calcium homeostasis and calcitropic hormones. Because magnesium is known to compete with calcium for binding to the calcium-sensing receptor, leading to a reduction in parathyroid hormone secretion, increased maternal magnesium intake has the potential to lower maternal serum calcium concentration. Another possible explanation is that magnesium intake is also positively associated with birth weight. However, adjustment for body size and/or birth weight did not alter our findings. Maternal milk intake density during pregnancy was positively associated with BMD of 16-year-old adolescents in this study, which is again consistent with our previous report [9]. Milk contains many potentially growth-promoting factors and is associated with higher birthweight for gestational age. Furthermore, a study in a group of pregnant African-American adolescents found that nutrition was significantly related to fetal femur growth during pregnancy, such that dairy intakes of 2 servings per day were associated with lower fetal bone development than were greater intakes of dairy [13]. Phosphorus density was associated with BMD of 8-year-old children but not of 16-year-olds, whereas calcium density was not associated with bone health in either 8- or 16-year-old children (possibly due to their high average intake). Tobias et al. [10] found that maternal phosphorus intake was positively related to total body BMC and BMD of 9-year-old children, but there are no other reports in adolescent children. It may be that phosphorus has a short-term effect rather than a long-term effect. In all of these studies apart

\[ Table 1. \] Dietary factors and their association with spinal bone mass in Tasmanian children

<table>
<thead>
<tr>
<th>Dietary factor</th>
<th>Age</th>
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<tbody>
<tr>
<td></td>
<td>8 years</td>
</tr>
<tr>
<td>Calcium</td>
<td>no association</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>positive</td>
</tr>
<tr>
<td>Potassium</td>
<td>positive</td>
</tr>
<tr>
<td>Magnesium</td>
<td>positive</td>
</tr>
<tr>
<td>Fat</td>
<td>negative</td>
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from the original Tasmanian report, the proportion of variance explained by diet is small being in the order of 1–2%, and there has been no association with fracture to date. This may suggest a trivial effect, but there is substantial error with dietary questionnaires which is likely to weaken associations, and stronger results may be achieved using more comprehensive dietary assessment such as weighed food records.

Randomized controlled trials examining childhood bone outcomes from supplementation interventions in pregnancy are lacking. However, maternal vitamin D supplementation in pregnancy resulted in lower bone-specific alkaline phosphatase levels and smaller fontanelle size (suggesting improved skull ossification) [14] in infants, and in lower cord serum alkaline phosphatase [15] and greater crown-heel length [15] in neonates. Zinc supplementation in pregnancy in a poor area in a developing country resulted in increased fetal femur diaphysis length [16]. In a retrospective cohort study, maternal use of vitamin D supplements was associated with increased BMD at the distal radius and femoral neck, though not lumbar spine [17], and maternal vitamin D status during pregnancy also predicts bone mass in their children at age 9 years [18]. Though limited, these data provide support for further research into nutritional interventions in pregnancy.

**Breastfeeding**

There are limited data for mode of feeding in early postnatal life. There is controversy about short-term effects, with most studies showing a deficit in bone mass in breast milk versus formula-fed infants and one showing no effect with evidence suggestive of a catch-up phase by 2 years in one of these cohorts [reviewed in 19]. In a long-term study of preterm infants, those supplemented with banked donor breast milk for the first 4 weeks of life (regardless of type of infant feeding), had improved bone mineralization at the radius up to age 5 years [20] but this did not persist at age 20 years, although there was an association between the percentage of breast milk in the diet and whole-body BMD at age 20 years [21]. These studies have been restricted to preterm infants and cannot be generalized to term infants as unsupplemented breast milk may not fully meet the mineralization requirements of preterm infants [22]. There are less data in healthy children. Harvey et al. [23] reported no association at age 4 years, and we have previously reported a beneficial association of breastfeeding for both bone mass [24] and fractures [25] up to age 8 years in children, especially in those born at term. Other observational studies with bone measures at younger ages did not demonstrate associations between breastfeeding and bone density [19]. However, in a retrospective study, premenopausal women who had been breastfed for more than 3 months had greater cortical thickness at the radius and a trend towards greater cortical area and cortical BMC at the radius, but not at other sites [26].
Bone density tracks strongly from age 8 to 16 years, but a minority of children track deviate from tracking in either direction, i.e. up or down [27]. Children who were breastfed had a different trajectory to non-breastfed children being twice as likely to deviate upwards in terms of their bone accrual trajectory and half as likely to deviate downwards [27]. At age 16 years, the magnitude of effect from breastfeeding is greater than at age 8 (table 2), and there was also a reduction in incident fracture risk between age 8 years and age 16 years (table 2). This supports the concept of breastfeeding programming bone accrual (independent of linear growth). Breastfeeding is related to socioeconomic status; thus, it is possible that any association may be mediated by other factors. However, in our cohort, the associations persisted after adjustment for lifestyle and socioeconomic factors (apart from maternal education) and appear dependent on the duration of breastfeeding, frequency of night feeding and the percentage of breast milk in the diet suggesting a biologic association. Indeed, intention to breastfeed at birth was less strongly associated with bone mass than actual breastfeeding. Lastly, the reduction in fracture risk at both age 8 years and during puberty was largely mediated by higher bone mass, which is also most consistent with a biological association.

It is important to note that the infants selected to participate in the original Tasmanian study were not a random, representative sample of children from Southern Tasmania. Six ‘selection factors’ that increased the risk of cot death were used to identify children. These were: gender (males), birthweight (low ≤2,500 g), maternal age, month of birth, duration of second stage labor and intention to breastfeed. Twenty percent of children born each year from 1988 to 1996 were selected. This created a sample with some biases. They were more likely to have mothers who smoked during pregnancy and less likely to have been breastfed. This increased study power, and adjustment for study factors did not change results, suggesting they are generalizable to other western populations of well-nourished children using the guidelines suggested by Miettinen [28].

<table>
<thead>
<tr>
<th>Study factor</th>
<th>Spine</th>
<th>Hip</th>
<th>Total body</th>
<th>Fractures RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding (yes vs. no)</td>
<td>+1.03%</td>
<td>+1.02%</td>
<td>+1.02%</td>
<td>0.40</td>
</tr>
<tr>
<td>Age 8 (refs.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 16 [24]</td>
<td>+3.42%</td>
<td>+2.84%</td>
<td>+2.85%</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Bold denotes statistical significance.
Smoking in utero

Smoking during pregnancy has also been associated with lower bone mass but not fracture in many studies. One study suggested this was dependent on term of gestation and that the association disappeared after adjustment for placental weight [29]. Placental weight has been associated with bone measures in Indian children [11], suggesting smoking interferes with bone development through intrauterine placental function which is different to how it is thought to influence bone mass in adults. Interestingly, in the Tasmanian cohort, the effect of smoking was no longer evident at age 16 years, with virtually no difference (even though the children were shorter and weighed less), suggesting the bone effect is transient and recovers [Jones, unpubl. data].

Conclusion

There is increasing evidence that early life nutrition has independent associations with subsequent bone mass and fracture up to age 20 years in prospective studies. Only a small amount of bone is laid down during pregnancy, so it seems unlikely that these factors influence this to any major extent. Thus, the data as a whole are more strongly in support of programming, suggesting that osteoporosis prevention should start very early in the life cycle.

Acknowledgements

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References

Early Nutrition and Bone


Discussion

Dr. Kish: I would like to make a comment about DEXA measurements with regard to bone density. DEXA is based on the absorption of X-ray by the tissues it passes through. If you put fat in front of the bone you are going to absorb some X-ray before it gets to bone. That will give a different signal than in somebody who is lean. I know

233
there have been formulas developed to try to correct this problem and would like to know if you tried to correct for this.

**Dr. Jones:** There are a number of ways to deal with that issue. It’s particularly a problem for overweight children and BMC, but bone mineral density is much less affected by body fat. There is, however, a correlation between body fat and bone density which probably is a true association in terms of cause and effect. I prefer weight adjusted for height, which gives a very good measure of body fat in children and works better that BMI because BMI is age dependent. You can also measure abdominal fat quite well with DXA by positioning cursors. In children, this is a reasonable approach. In older adults it’s more difficult because you get fat within muscle as you get older.

**Dr. Agarwal:** We measure bone growth, bone mass and fracture rates at the age of 12, 16 and 20 years. What about the role of sexual development in these children? The sexual development in a child of 8 years will differ from that of a 16- and a 20-year-old.

**Dr. Jones:** That’s an excellent question and one that we have looked at extensively. We found pretty similar correlations between age, height, weight and/or Tanner stage and bone mass. So, you can adjust for Tanner stage or you can adjust for age, height and weight.

**Dr. Stathatos:** Have vitamin D levels been measured during the study?

**Dr. Jones:** In our population, roughly 50% of the population is vitamin D deficient with a level below 50 nm. The only group that isn’t is the 8-year-olds, and there are roughly 10% of them below 50 nm. Vitamin D is related to bone mass and bone turnover markers in our children, and we have been trying to get money to do a trial from our government, so what we did was a meta-analysis. This shows that vitamin D supplementation works for bone mass if your vitamin D level is below 35 nm, but above that it does nothing. So I am a bit concerned about the apparent epidemic of vitamin D deficiency at present. There is a lot of reverse causation in terms of vitamin D levels and diseases, e.g. if you have juvenile arthritis, your vitamin D will be lower because you spend less time outside. Further, if you look at the relationships, they are not linear, they tend to be logarithmic, so there is more to be gained between 10 and 25 (US 4 and 10) than there is between 25 and 50, than there is between 50 and 100. So you are getting progressively less benefit the higher you go up the scale. So, even in the bone area which has been very well studied it’s still very controversial in adults as to what level you should treat. Personally, I think treating 25–30 is mandated, I think there is good enough evidence for that, and I suppose I am most comfortable getting everyone above 50.

**Dr. Puri:** Our studies [1] have shown that diet really had no relationship with the vitamin D status, that it was mainly lifestyle factors. In a country like India, it is mainly exposure to sunlight. These factors are very important, especially when we are talking about school children. Were these factors built into the study to see the effect on BMD?

**Dr. Jones:** Yes, and our results are essentially the same as yours. There was no association between vitamin D assessed by the diet and vitamin D levels, so the children mainly get it from outdoor physical activity. That’s true at both 8 and 16 years; however, by age 16 the outdoor activities become trivial, and what we need is UV-emitting computers because that’s the only way they are going to get their vitamin D. We have done intervention trials with big doses, and we can find that 300,000 U every 6 months prevents everyone dropping below 50 nm.

**Dr. Guandalini:** Somehow related to vitamin D, I have a question related to dietetic needs of calcium later in life. We have recommendations in western societies of very high intake of calcium. The recommended intake has in fact been recently revised up to 1,200 and even 1,600 mg per day during adolescence. Now, the general
assumption is that such intakes can only be fulfilled by drinking large amounts of milk. So my question is purely conceptual. Cow's milk is for the young of the cows, it's not intended by mother nature for human consumption, and cows have only been domesticated as recently as 10,000 years ago. Hence, how could we be dependent on milk? Is it possible that there are no other sources of calcium? Are green leaves not enough to accommodate for our calcium need? If not, then is it conceivable that our need has been a bit overestimated?

**Dr. Jones:** I gave a debate in Sydney a month ago on why not to give calcium supplementation. With the meta-analysis in children, we showed that moving average intake from 700 mg a day (which is average in the population) to 1,200 did nothing. When you go back and look at the balance studies, they put people on a very high fixed intake of 1,200–1,500 mg a day. Intake is the main determinant of calcium balance. More recent balance studies have shown that most people can balance their calcium around to 600–700 mg a day. So, I personally think the IDRs are incredibly high and inflated. It is hard to get enough from non-dairy sources. You can get it from can fish, but it has to be fish with the bones in the can so sardines and salmon but not tuna, you can get it from sesame and figs as well. But the body has the ability to vary calcium absorption from 10 to 50% of the diet, so we can actually vary it a great deal and you have got to get down extremely low before you get hypocalcemia or osteomalacia from calcium deficiency probably in the order of 200–300 mg a day.

**Dr. Guandalini:** So, our huge dependence on milk from another mammal species seems awkward, and I take it you would agree that these recommendations are on the excessive side.

**Dr. Van Goudoever:** A technological question again. We were talking about the DXA scans, and there are new machines now on speed of sound, and scattering of ultrasound measuring bone density. What are your thoughts about that?

**Dr. Jones:** I will send you my paper on ultrasound in fractures. In these children, I measured bone in multiple ways. Calcaneal ultrasound was a good predictor of fractures in teenagers. However, it doesn't work in young children because the heels largely have a couple of bits of bone floating in fibrocartilage. I think the most promising is high-resolution CT, which is low radiation and can image down to 80 nm, and that can actually give you a picture of bone structure in vivo.

**Dr. Fasano:** Another philosophical question related to the main topic you covered concerns the biology of the bone as a result of the balance between osteoclasts that destroy your bones and osteoblasts that build them up. Of course, osteoblasts need vitamin D, but physical activity is a tremendously important aspect of the story. Are there any data in the literature explaining how the health of bones of our kids is changing with the change in the habit of their physical activity?

**Dr. Jones:** Good data from the US were published in *JAMA* a couple of years ago showing that forearm fracture rates have been increasing in the US over the last 40 years, and there are probably two reasons for that. One is children are getting less active, and secondly they are getting fatter, and the bigger you are the harder you fall. Coca Cola and television watching also increase fracture risk. So, the worry is hip fractures in the elderly might be going down because people are getting more obese, but fractures during puberty are going up.

**Dr. Stathatos:** Any comment on vitamin K to help the synthesis of connective tissue in bones?

**Dr. Jones:** Vitamin K is important for osteocalcin, which is an enzyme produced by osteocytes. In bone, there is about 100 million of these cells, but we are not totally sure what they do. In children, there are no data that I am aware of for vitamin K and bone. In adults, meta-analyses show that vitamin K supplements decrease fracture risk, but this has mainly been taken up in Japan.
Reference