Osteoporosis: Is Primary Prevention Possible?

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Osteoporosis is a major and increasing cause of morbidity and mortality in developed countries, and set to become so worldwide in the next few decades. Health-care costs are high, principally due to associated hip fractures which often result in loss of independence. An individual’s risk of developing osteoporosis is determined by the peak bone mass reached at skeletal maturity, and the rate of bone loss later in adult life. Historically, strategies to prevent osteoporosis concentrated on reducing bone loss, particularly after the menopause in women. However, over the past decade there has been a greater focus on maximizing peak bone mass as an alternative or additional potential strategy. Although peak bone mass is to a great extent (70–80%) genetically determined, it is clear that events during fetal life, infancy and childhood are also important. This chapter will discuss the evidence that osteoporosis may be a disease that is amenable to primary prevention during early life, and the potential role of nutritional interventions.

It is important to appreciate that a number of factors have been shown to result in increased bone mass in the short-term, during the period of intervention. This may in itself have immediate outcome benefits for the individual, for example reducing short-term fracture risk. However, to represent a potential preventative strategy against osteoporosis, any such effect must be shown to persist after the intervention has stopped, resulting in higher peak bone mass and/or favorable effects on bone structure or bone turnover. This has received much less attention, and is the principle focus here.

Studies in Animal Models

The concept that early life events might program later bone health and risk of osteoporosis in humans is supported to some extent by animal data. For
example, malnutrition during the growth period has been shown to result in a slowing and eventually cessation of bone growth in a number of species. Bone histology typically shows an almost complete cessation of osteoblastic activity and the growth plate effectively becomes dormant, but these abnormalities are largely reversible after nutritional rehabilitation [1]. Most such studies did not involve malnutrition during prenatal or very early postnatal life. Consequently, they were potentially beyond the critical period during which permanent programming effects on the skeleton might occur. However, more recent animal experiments have demonstrated permanent effects of manipulating maternal nutrition during either pregnancy or lactation on offspring bone size and histology, including alterations in growth plate morphology [2, 3].

**Studies in Humans**

The remainder of this chapter reviews the relevant epidemiological and experimental data for long-term effects of early life events on bone health in humans, in whom investigations are necessarily more difficult and limited. Conceptually, when considering such data it is helpful to distinguish between effects on (i) skeletal (frame) size; (ii) mineral mass, and (iii) bone structure and strength. In practice, most studies include anthropometric measurements (for example, height) which are related to skeletal size, and a measure of bone mass, generally obtained using dual-energy X-ray absorptiometry (DXA). DXA provides a two-dimensional measurement of bone area (BA) and bone mineral content (BMC); BMC is then divided by BA to provide bone mineral density (BMD), but this is not a true ‘density’. Both BMC and, to a lesser extent, BMD remain influenced by body size. It is therefore important when interpreting the results of studies using DXA to attempt to disentangle effects on body (and hence skeletal) size and those on mineral mass per se. A further limitation is that DXA measures bone mass, but does not provide information on bone structure or strength which might be at least as important (if not more so) in terms of outcome. This issue is attracting increasing attention but has only really been addressed in more recent studies examining the long-term effects of exercise on the skeleton.

**In Utero Effects on Offspring Bone Mass**

Neonatal bone mass is clearly influenced by genetic factors, but also by factors associated with the intrauterine environment. Most studies have been observational, although a randomized trial of maternal calcium supplementation during the second and third trimesters reported higher size-adjusted neonatal bone mass in the offspring of supplemented mothers who were
themselves in the lowest quintile for baseline calcium intake [4]. Studies of vitamin D supplementation during pregnancy collectively suggest that the effects are minimal in mothers with adequate vitamin D status, but that in mothers with poor vitamin D status, supplementation may result in improved fetal growth and mineral accretion, and, possibly, improved postnatal weight and length gain [5].

Data from the Southampton Women’s study, in which detailed dietary intake data were collected during pregnancy from 145 women, and the infant’s bone mass was measured by DXA shortly after birth, suggest that parental birth weight, paternal height and maternal smoking have effects predominantly on skeletal size, whereas maternal skin-fold thickness, and exercise during late pregnancy may influence bone mass independent of size [6]. In a 9-year follow-up of 211 children from the same cohort, whole body BMC was positively associated with both maternal 25-OH vitamin D status during the last trimester and with umbilical venous calcium concentrations [7]. It has been proposed that maternal calcium stress may result in increased fetal and placental parathyroid hormone (PTH) and PTH-related protein (PTH-rP) leading to higher fetal trabecular bone formation (which, due to its greater surface area, provides a better calcium reservoir), and a decrease in cortical bone. After birth, trabecular bone is rapidly remodeled but the effects on the cortical ‘envelope’ may be more permanent, representing a potential mechanism for permanent effects on skeletal size [8].

Fetal, Infant and Childhood Growth and Later Bone Mass

Size in Early Life

Data from a number of studies have shown positive associations between birth weight, birth length and/or weight at 1 year of age, and bone mass during later childhood [9], early adult life [10], and at 60–75 years of age [11]. In each case, associations were strongest for BMC and weakest for size-corrected bone mass, suggesting a predominant association between early size and later bone size rather than bone density per se. In one cohort there was evidence for an environment-gene interaction between vitamin D receptor (VDR) genotype and birth weight, suggesting that environmental factors may modify genetic influences on bone size [12].

Childhood Growth

One study in children born at term [9] and two studies in populations born preterm [13, 14] reported higher bone mass (after adjusting for current size) in individuals with either the greatest absolute length or weight gain, or with upward centile crossing during infancy and childhood. Consistent with these findings, data from a cohort of around 7,000 Finnish men and women born between 1924 and 1933 [15] showed that the risk of hip fracture was
significantly higher in those with a low rate of childhood growth between 7 and 15 years. This study is important since childhood growth was found to predict the clinically meaningful endpoint – osteoporotic fracture. All these studies emphasize that linear growth may be more influential than weight gain – an important observation since this represents a potential mechanism for maximizing bone mass, especially in populations who experience stunting of growth.

Nutrition and Bone Mass in Term Infants

Few studies have evaluated the long-term effects of infant diet on bone health in term infants. Jones et al. [16] reported that infants who were breast-fed had higher size-adjusted lumbar spine, hip and whole body BMD than formula-fed infants at 8 years of age. The effect remained after adjusting for confounding factors, and was most significant for infants breastfed for at least 3 months, although a greater duration of breastfeeding was not associated with further benefits for childhood bone mass. The frequency of night feeds during the first month of life (arguably a more reliable indicator of the ‘amount’ of breastfeeding than the number of day feeds) was significantly and positively related to later BMD, providing some evidence of a dose-response effect. Moreover, a mother’s intention to breastfeed at delivery (as opposed to her actual breastfeeding behavior) showed no relationship with later BMD. Collectively, these data suggest that the observations reflect a genuine biological effect of breast milk on later bone mass rather than confounding.

Two studies in term infants have demonstrated short-term effects of manipulating calcium intake, via changes to the fat blend used in infant formulas, on bone mass. Infants randomized to receive a formula containing a modified fat blend designed to improve calcium absorption had significantly higher size-adjusted whole body BMC than those who received a standard formula [17]; their BMC was also more similar to that of a group of breastfed term infants. Long-term follow-up of this cohort is underway to determine whether these early effects have persisted. Using an alternative strategy to improve calcium absorption, Koo et al. [18] reported higher bone mass in infants receiving a low palmitate versus a standard infant formula; long-term effects have not yet been evaluated.

Prospective Studies in Preterm Infants

Preterm infants are an interesting group in which to examine the influence of early factors on later bone health. They are born at a time of normally rapid mineral accretion and bone growth, and are thus at risk of mineral deficiency, as well as more general nutrient deficiencies, during the neonatal period.
They frequently have under-mineralized bones and may develop metabolic bone disease of prematurity. A large number of studies have examined the consequences of early diet on short-term bone health but data on longer-term bone outcomes are generally lacking. Backstrom et al. [19] studied a small group of infants randomized to vitamin D (500 or 1,000 IU/day) and either unsupplemented or mineral-supplemented breast milk. Bone mass measured at age 9–11 years was not influenced by early diet or by the dose of vitamin D. However, the duration of breastfeeding was positively associated with size-adjusted lumbar spine bone mass in mineral-supplemented subjects.

Bone mass was measured by DXA at 10–12 years in 230 children from our large prospective randomized trial of diet during the neonatal period. Subjects with evidence of metabolic bone disease during the neonatal period were significantly shorter at aged 10–12 years [20], suggesting a long-term effect of suboptimal early nutrition on skeletal growth. Compared to children born at term, the preterm group had reduced bone mass in association with their smaller body size, but there was no specific effect of early diet on bone mass. However, children randomized to receive the lowest nutrient diets during infancy had significantly higher plasma osteocalcin, suggestive of increased bone formation rates [21]. Follow-up of this cohort in early adult life is nearing completion and will provide the first experimental data in humans on the effects of early nutrition on peak bone mass and turnover.

**Childhood Lifestyle Factors and Bone Health**

Although much of the research into the early origins of bone health has concentrated on events during fetal life or infancy, lifestyle factors later in childhood and adolescence have also received attention as potentially modifiable determinants of later bone health. Adolescence is potentially a particularly important period, since bone mass increases by 25–30% – equivalent to the amount of bone lost after the menopause. The two most studied lifestyle factors are calcium intake and exercise. However, whilst both interventions are generally associated with increased bone mass during the period of intervention, there is less evidence on the persistence of such effects.

**Childhood Diet**

**Calcium**

Epidemiological studies have shown associations between milk or calcium intake during childhood and both adult bone mass and fracture risk. Such associations are generally stronger at lower levels of calcium intakes. The results from cohort studies relating calcium intake recorded during adolescence and bone mass measured during the third decade are less consistent.

Several prospective randomized trials of calcium supplementation have now been conducted in children. Studies using calcium salts are generally
consistent in showing an increase in bone mass (rather than bone size) during the supplementation period. This is accompanied by biochemical evidence of decreased bone formation and reflects reduced bone remodeling. However, in all but one study, the effect reversed on stopping the calcium supplements [22, 23]. The exception, a study in Gambian children with very low baseline calcium intakes, reported a persistent increase in bone mass at the radius 24 months after stopping the supplements [24].

The study with the longest duration of calcium supplementation was conducted in girls starting at pubertal stage 2 and lasting up to 7 years [25]. The results suggested a beneficial effect of calcium supplementation during the period of maximum bone growth, and in subjects with the greatest requirements (those with larger skeletons, and with a low habitual calcium intake). However, once bone growth had largely ceased and consolidation was occurring, the beneficial effects were lost. Presumably, calcium requirements were lower during this period and were met in most girls by their habitual calcium intake.

In contrast to studies using calcium salts, two trials using either milk [26] or milk-based food supplements [27] as the calcium source have shown different effects, with increases in bone mass lasting up to 3 years after the intervention was stopped. Both studies were in girls, and the increased bone mass was associated either with increased height and bone size or with higher plasma IGF-1 concentrations. In one study, the beneficial effect of the intervention was greatest in subjects with the lowest habitual calcium intakes and was most apparent in the appendicular skeleton. It has been postulated that these observations reflect an anabolic effect of milk protein, possibly milk basic protein which is known to enhance bone strength by stimulating bone formation and collagen synthesis [28]. However, another randomized trial (this time in prepubertal boys and girls with high baseline calcium intakes) using a high calcium dairy drink found no effect on body size or bone mass either during an 18-month intervention or at the 12-month follow-up [29].

**Vitamin D**

Vitamin D in its active form plays a vital role in maintaining bone health, and deficiency states in children are associated with rickets which may have obvious permanent effects on bone structure. However, less is known about the effects of more subtle variations in vitamin D status, or vitamin D intake. In a non-randomized study, infants supplemented with vitamin D during the first year of life had significantly higher BMD at the radius and hip (but not spine) at 7–9 years than unsupplemented infants [30]. Supplemented infants received 400 IU/day of cholecalciferol, and both groups had similar breastfeeding durations. Vitamin D-supplemented subjects were also heavier and taller at the time of the bone measurements, suggesting the findings may reflect the effects of vitamin D predominantly on bone size rather than mineralization.
A study in Finnish girls reported a positive association between baseline concentrations of 25-OH vitamin D and gains in BMD over the subsequent 3 years. The association was present for girls in mid-puberty at enrolment but not for prepubertal subjects, and was also greater at the lumbar spine than the femoral neck [31].

Other Nutrients
Although there are theoretical reasons why other elements of the diet such as vitamin K, zinc, protein, sodium or fruit and vegetables might influence later bone health, no studies have yet been conducted on specific nutrients. Parsons et al. [32] studied Dutch children who had received a macrobiotic diet during infancy and early childhood. These children had very low dietary calcium intakes, marked vitamin D deficiency and demonstrated stunted growth between birth and 8 years of age. Despite subsequent catch-up in weight and height, significant deficits in bone mass were seen at all skeletal sites at 9–15 years. Although it is not possible to identify a specific etiological factor, these findings add to the evidence for long-term bone effects of early malnutrition and stunting.

Children Activity
Weight-bearing physical activity has attracted increasing interest as a potentially modifiable determinant of peak bone mass. Several studies have reported higher bone mass in elite pediatric gymnasts and athletes compared to matched controls, and a number of randomized intervention studies in children and adolescents have demonstrated increased bone mass in loaded bones during the period of increased activity. The interventions used vary in intensity and ease of application, but include programs designed to be implemented as part of the routine school day (for example, jumping activities for 10 min 3 times/week). Collectively, the results of these studies suggest that effects are site-specific, greatest for cortical bone, and that interventions may be most effective during puberty when bone growth is most rapid. Although the majority of studies have used DXA to measure bone mass, some studies using peripheral quantitative computed tomography (pQCT) have also reported higher cortical cross-sectional area, cortical thickness and increased parameters of bending strength, suggesting that weight-bearing exercise may have benefits for bone structure as well as bone mass.

Despite the generally positive results of short-term interventions, data demonstrating that the beneficial effects of exercise persist and are reflected in higher peak bone mass, improved bone strength or reduced fracture risk are more limited. Follow-up of ballet dancers, gymnasts and other athletes into adult life suggests that they do have higher bone mass than matched controls but such studies are limited by potential biases related to the self-selected nature of the athletes. A 6-year longitudinal study in normally active adolescents reported that those in the highest quartile for activity had significantly
greater gains in bone mass than those in the lowest quartile; the differences persisted for at least 1 year after peak bone mineral velocity was reached, but the cohort was not followed until they attained peak bone mass [33]. Lloyd et al. [34] reported that exercise (but not calcium intake) during adolescence positively influenced bone mass and bone-bending strength in the femur in a cohort of 80 young women followed prospectively for 10 years.

Follow-up of individuals who have participated in intervention trials is as yet limited. Fuchs and Snow [35] reported that the gains in hip BMC and BA (but not lumbar spine BMC and BA) seen during a randomized trial of high-impact training in prepubertal children were maintained for at least 7 months after the intervention ceased. The effect of the intervention appeared to operate by increasing bone size, rather than by increasing bone density per se. These results are consistent with those reported in a 12-month follow-up of 3- to 5-year-old children [36] who participated in a randomized trial of activity intervention. The intervention was associated with increased leg BMC and greater tibial periosteal circumference. At follow-up, although there were no persisting changes in leg BMC, the difference in periosteal circumference persisted.

**Interactions Between Activity and Calcium Intake**

In some studies, the effect of weight-bearing exercise was seen only in subjects with the highest calcium intakes. For example, Iuliano-Burns et al. [37] found a positive interaction between calcium supplementation and physical activity on femur bone mass in girls aged 7–11 years, whilst in 3- to 5-year-olds the effect of an activity intervention on leg BMC was seen only in those who were also supplemented with calcium [36]. Interestingly, 12 months after the intervention period, there was no persisting effect of calcium supplementation although the effect of activity was still apparent.

**Conclusions**

Available data are consistent with a predominant association between growth during fetal life, infancy and childhood on later skeletal size. The data suggest that optimizing growth, particularly linear growth, during infancy and childhood is likely to increase peak bone mass, which in turn might reduce the risk of osteoporotic fracture. Proposed mechanisms for these effects include programming of PTH/PTH-rP in utero leading to permanent effects on the size of the cortical envelope [8] and alterations in the set points of the GH-IGF-1 or hypothalamic-pituitary-adrenal axes [38]. Polymorphisms of the VDR are also associated with height and bone size [39] and may interact with environmental factors.

In contrast to the effects of early growth, there is some evidence that infant nutrition may influence bone mineralization and turnover more
directly. For example, breastfeeding may have benefits for later bone mass that are independent of effects on bone size, while suboptimal nutrition in preterm infants influences later bone turnover. This is a difficult area to investigate in children, generally relying on proxy measures of mineral mass (such as size-adjusted bone mass) and biochemical markers of bone turnover, with their limitations.

There are reasonably compelling data that weight-bearing exercise during childhood and adolescence may result in lasting benefits for bone health. Effects are usually region-specific and result predominantly from local responses to stress induced by loading. These studies emphasize the need to obtain measures of bone structure and parameters of bone strength, and not simply measure bone mass. In contrast, the evidence for a lasting effect of calcium supplementation on bone health is less convincing. The use of calcium salts results in a temporary reduction in bone remodeling but probably not in long-term benefit unless supplementation is maintained throughout the growth period. However, supplementation using calcium derived from milk products may have a more lasting but anabolic effect on bones. Furthermore, interactions between VDR genotype and calcium absorption have been demonstrated [40]. VDR genotype could therefore potentially modify the response of individuals to calcium supplementation. Suggested measures for maximizing peak bone mass and optimizing bone health based on current evidence are presented in table 1.

It is relevant to consider the likely practical relevance of the effect sizes observed in intervention studies. The effects of weight-bearing exercise interventions on BMD are in the order of 3–5% (depending on the loading applied), whilst reported effect sizes in follow-up milk supplementation trials vary from 1 to 5%. Whilst there are difficulties and uncertainties inherent in extrapolating bone mass data from children to adults, it has been calculated that a 2–3% increase in peak bone mass could reduce later fracture risk by 10–20%.

Table 1. An ‘evidence-based’ approach to optimizing later bone health

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<th>In utero</th>
<th>Infancy</th>
<th>Childhood</th>
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<td>Adequate maternal vitamin D status</td>
<td>Breastfeeding</td>
<td>Weight-bearing exercise</td>
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<tr>
<td>Adequate maternal calcium intake</td>
<td>Adequate calcium/ phosphorus intake (especially for preterm infants)</td>
<td>Adequate calcium intake (particularly during pubertal growth spurt)</td>
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<tr>
<td>Adequate vitamin D intake</td>
<td>Milk/milk-based products</td>
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<tr>
<td>Maximize linear (bone) growth</td>
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Osteoporosis: Is Primary Prevention Possible?
In conclusion, whilst further research is clearly required (table 2), there is evidence that osteoporosis may be at least partly preventable by interventions during early life designed to optimize linear growth, nutrition and weight-bearing activity. Furthermore, available data suggest that the effect sizes observed with such interventions are of a magnitude which could be potentially significant in public health terms in reducing the burden of osteoporosis.

### Table 2. Suggested areas for future research

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<tbody>
<tr>
<td>1</td>
<td>Long-term follow-up of existing intervention trials (nutrition, exercise) to determine which interventions affect adult outcome, identify sensitive periods and site specificity of interventions</td>
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<tr>
<td>2</td>
<td>Use of additional techniques for assessing bone structure and strength (e.g. peripheral quantitative computed tomography, pQCT) as well as bone mass</td>
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<tr>
<td>3</td>
<td>Identification of environment–gene interactions which might allow targeting of interventions for vulnerable groups</td>
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<td>4</td>
<td>Investigation of potential mechanisms – e.g. effects on hormonal axes, bone structure</td>
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In conclusion, whilst further research is clearly required (table 2), there is evidence that osteoporosis may be at least partly preventable by interventions during early life designed to optimize linear growth, nutrition and weight-bearing activity. Furthermore, available data suggest that the effect sizes observed with such interventions are of a magnitude which could be potentially significant in public health terms in reducing the burden of osteoporosis.

### References

Osteoporosis: Is Primary Prevention Possible?


Discussion (Also refer to the Presentation “Nutrition and Cancer Prevention: Targets, Strategies, and the Importance of Early Life Interventions” by S.D. Hursting et al)

Dr. Laron: I have 3 questions for Dr. Fewtrell. One, which norms do you propose for BMD for young children, and which norms for DXA? The second question is with regard to volumetric DXA; you mentioned it but didn’t discuss it further. We know that short children may have a below normal DXA which normalizes when bone volume is calculated, so that somebody who may seemingly need treatment may actually not need it. What is your opinion? The last question is what do you think about the new approach of passive exercise in small babies which Eliakim and Nemet [1] recently described and which improves bone density as measured by the ultrasonography method?

Dr. Fewtrell: With regard to the norms for DXA BMD, there are now pediatric reference data incorporated into most machines, and databases are being improved and updated. For example, there is the new large Hologic pediatric database from the US that is just becoming available. I think the problem of size issues with DXA is very important, and applies both to research and clinical settings, although in different ways. Essentially, many patients have stunted growth and appear to have low areal bone density, although this may simply reflect their small size rather than indicating that they have undermineralized bones. A number of approaches have been suggested to adjust for the effect of size, including the use of so-called ‘volumetric’ bone density such as BMAD, or adjusting for weight and height. In fact we have recently done some work showing that different size correction approaches actually produce similar results in terms of categorizing groups of patients as having normal or abnormal bone mineralization [2], so it probably doesn’t matter which correction you use as long as size is considered. But I think there is actually another issue here because once you have done your size correction and come to the conclusion that a child is small and has an appropriate amount of mineral for their size, that still doesn’t tell you whether they are at increased risk. That is where techniques that measure other parameters of bone geometry or strength might be important. We need to know more about the distribution of the bone mineral, and the shape and geometry of the bones because these factors may determine things like fracture risk.

Dr. Laron: I asked this question because of IGF1 and growth hormone. In patients who have growth hormone or IGF1 deficiency, when a simple DXA is used they are found to be osteoporotic [3] but if the volumetric BMD is calculated they become normal [4], and the same might be true for the children who are short by other causes.
Dr. Fewtrell: That is true, I think we should not be using the term ‘osteoporosis’ in children based on DXA measurements with the criteria established for adults. I know that in the US this has resulted in problems where children who are small and consequently have a low areal BMD Z score have been erroneously diagnosed as having osteoporosis. This is why it is so important to apply some form of size correction. In the UK we are currently compiling our own reference database from which we will be able to get a size-adjusted BMD Z score and not just the areal BMD Z score, to get around this problem.

Dr. Laron: What was the respective machine?

Dr. Fewtrell: Our reference data come from different GE Lunar machines that have been cross-calibrated. Cross-calibration could also be performed with other machine makes as well.

With regard to your earlier question about the use of passive exercise in preterm infants, I am not aware of the ultrasound study you mentioned, but I know Moyer-Mileur et al. [5] have done some work previously suggesting that passive exercise in preterm infants improves their bone mass in the short-term, and that makes sense. Whether the effect persists in the long-term is another matter – this has not been investigated.

Dr. Roma: Since most hypoallergenic diets and formulas, elemental and semi-elemental, are lactose-free, is there any influence on calcium absorption? Do you recommend calcium and vitamin D when children are on steroids for a long time?

Dr. Fewtrell: There is certainly some evidence that children who are on a milk-free diet have a greater risk of fracture during childhood, but I don’t know specifically about hypoallergenic diets. With regards to calcium and vitamin D when children are on steroids, we know there is an increased risk of low bone mass and fractures associated with steroid treatment, but whether that is reduced or prevented by giving additional calcium or vitamin D is not clear, although it is presumably important to make sure they have at least an adequate intake. I know in practice that most patients in our own hospital who have a low bone mass are put on calcium and vitamin D supplements, although the hard evidence that this has benefits is perhaps not there.

Dr. Abrams: I have a brief comment about lactose-free formulas and calcium absorption. We looked at that and did not find a very large effect. Most of the non-whole milk-based formulas do have additional calcium in them, so we don’t think that this probably has a big effect on the overall calcium absorption. The total amount was greater than what would be achieved from breast milk, so I don’t think that is a big issue.

Dr. Lucas: Dr. Hursting that was really a wonderful presentation, I really enjoyed it. When you restrict animals or humans for that matter with food, they are less obese, live longer and get less cancer. But specifically how do we understand what elements you are actually reducing in the diet that have cancer protection, because theoretically you could just be reducing the carcinogens in the diet by reducing food intake?

Dr. Hursting: In the animal model system we used purified diets, so I think the carcinogen exposure was reduced. We would measure that in our diets, and they were getting equal, basically no amounts of carcinogen. We have done some studies in terms of the type of calories, where one sees the most effect, and so you can restrict carbohydrate calories, fat calories, protein calories, and the bottom line is that the effect is obesity prevention. Now the sharpest effect is with carbohydrate calorie restriction, and we think that is because the sharpest effect is seen with an IGF drop, and some of the other factors that we are looking at are seen primarily with carbohydrate restriction. But it has been done with a total diet or with fat restriction, protein restriction, and protection from cancer is seen. So it appears that the obesity prevention component is the critical step to this. One should think about the exercise that when we have done the head studies with that we don’t see the degree of protection, even though we can achieve a body weight to a similar degree we don’t see the degree of protection.
that we do with that carbohydrate calorie restriction. We don’t see the drop in IGF1. So we are trying to move a little beyond but we do think that that is a part of the story.

**Dr. Lucas:** But that would be the link between nutritional protection from both cancer and cardiovascular disease.

**Dr. Hursting:** Yes, that is right. The downside is that when we do DXA on our mice and try to look at any effects of our energy restriction approaches, the only one that we come up with is that their bones are less dense. We found that if we do a combination of calorie restriction with the running wheel for example we can reverse that. Obviously that is the recommendation for humans. Part of the answer to this obesity issue is watching caloric intake and increasing physical activity, and that combination, at least based on our mouse data, is sufficient to raise any IGF drop related to a decrease in bone.

**Dr. Hamburger:** At the bottom of your list of inflammatory responses that lead to cancer you had asthma, and I recall that throughout 30 years, in 1970s, 1980s and 1990s, allergy and elevated IgE was said to cause cancer, then it was said to protect against cancer, asthma was associated with cancer, asthma was associated with less cancer, and finally after 30 years of studies it was decided that there was no relationship between allergy, asthma and cancer. Would you comment on that?

**Dr. Hursting:** That is the most mixed story of those conditions that I talked about. There are some recent data suggesting that perhaps there is a bit of risk for lung cancer. But you are right, historically that has been a more mixed bag. In other allergic situations, generally like an acute allergic response, it does not appear to be like these chronic long-term inflammatory conditions.

**Dr. Pereira-da-Silva:** Two questions for Dr. Fewtrell. It is well known that premature babies are prone to osteopenia. Two weeks after delivery of the preterm baby the mother’s milk may have insufficient calcium and phosphorus to fulfill the needs and demands of the growing premature baby. During the stay in the intensive care unit, it is easy to provide fortifiers to human milk but after discharge this is a problem in exclusively breastfed babies [6]. Would you suggest continuing supplementing these babies with calcium and phosphorus? At present we use hypophosphatemia to monitor early osteopenia, but recent studies suggest that this is a poor marker for bone mineral content in premature babies compared to DXA measurements [7]. Which biochemical marker would you suggest for early detection of osteopenia?

**Dr. Fewtrell:** I think there is potentially a problem of inadequate nutrient intake in preterm infants who go home exclusively breastfeeding – not just for calcium and phosphorus but for other nutrients as well. While these infants are in hospital, human milk is supplemented with phosphorus or with a multi-nutrient breast milk fortifier, but typically when the infant is discharged these supplements are stopped. This is certainly the case in the UK. The only potential source of additional minerals and other nutrients for these infants during this period is top-ups with infant formula – and it makes sense if a nutrient-rich post-discharge formula is used for this purpose. Whether a low mineral and nutrient intake during the post-discharge period in breastfed infants actually makes any difference to their longer-term bone health is not known. The evidence is that preterm infants who are breastfed do have lower bone mass during the neonatal period than those who receive formula, but that they eventually catch up in terms of their size and bone mass. What was your other question?

**Dr. Pereira-da-Silva:** Which biochemical marker would you suggest for the early diagnosis of osteopenia?

**Dr. Fewtrell:** I am not actually a neonatologist but I don’t think there is any available marker for osteopenia that performs better than monitoring the degree of hypophosphatemia together with alkaline phosphatase. We and others are looking at quantitative ultrasound as a potential monitoring tool, but I don’t think it looks particularly promising at the moment.
Dr. Chad: I would like Dr. Hursting to comment on the studies involving modulation by dietary manipulation of fatty acids n-3 and n-6 in cancer prevention. And the other comment would be the relationship between celiac disease and lymphoma later in life.

Dr. Hursting: I don't know the latter data so I can't comment on that. The n-3s are back, and I think primarily because of this inflammatory issue and the identification of this prostaglandin and the COX-2-related pathway, it is a great target for cancer prevention. Actually the n-3s were coming back even before that but it has accelerated the research on that pathway through fatty acid manipulation, e.g. the fish oils. It is definitely an important area and quite effective. It has expanded not only into the prostaglandin and cancer story but is a modulator of angiogenesis and other targets along the pathway. We are going to see a lot of work on that in the next few years.

Dr. Greef: Obviously from what you have said and I accept that there is a lack of evidence, should we now be recommending that our patients consume an ideal diet, which nobody does, and supplement with natural vitamins, possibly with the antioxidant mix, phytochemical mix, n-3 mix? Do you think we should recommend this? I often think we hide behind something for which there is no evidence-based medicine to support it. It is a sort of deck and dive issue, but at the rock face we have got to make decisions.

Dr. Hursting: I am not a big fan of supplementing mega doses, but I am a fan of a multivitamin approach. Particularly if we can work it and keep the caloric intake at a reasonable level, I think it is reasonable to recommend a multivitamin approach.

Dr. Hanson: We think of the inflammation, at least from the cancer side, as being a bad thing, but you are right, those inflammatory cells have to be present to fight infection and other things. I am intrigued by the fact that there are so many macrophages and other inflammations related to immune cells in adipose tissue. This is a fairly recent sort of finding and it has opened the eyes of a lot of us to start to look for those. Also the calorie restriction, for example, does seem to be knocking not only the COX-2 path down but IL-6, and we are trying to get in quickly and look whether we are in some way preventing such an influx of those macrophages in the adipose tissue for example. I think this is an important piece of it in the whole immune story and how it relates to inflammation. We are going to see a lot of good work on that, and it will become a topic in the cancer field.

Dr. Saavedra: Would you care to speculate on the potential effect of changes in bone mineral content or density in the first 2 years of life and later on? You showed some good relationships within what would be accomplished or prevented by improving bone density in adolescence, for example, and maybe even later. There has been a trend towards increasing calcium levels, because those are the few things we can manipulate, both in complementary foods as well as in breast milk substitutes. With some formulas the bone mineral content is even higher than breast milk controls. Do you see their benefits and how much are we influencing potential bone health in later in life?

Dr. Fewtrell: The short answer is that I don't think we know, because we don't have long-term data from populations in whom the short-term effects of early calcium intake on bone mass have been monitored. The data from the calcium supplementation trials which tend to be later in childhood or adolescence are not consistent, and it seems to me that the response probably depends on other factors such as genes and...
other elements of the diet. That is something that has perhaps been neglected. We have all tended to focus on calcium which I suppose is an obvious thing, but calcium requirements are likely to vary depending on what else you are eating. This may partly explain the low rates of osteoporosis seen in some populations with very low habitual calcium intakes but who also have low intakes of animal protein and salt. Overall, I'm not at all convinced that simply increasing calcium intake in healthy term infants is likely to have a long-term benefit. Obviously preterm infants have a mineral deficit so the situation is different.

Dr. Abrams: I would just like to make a comment that in infancy and early childhood we are trying to make sure that the children don't have fractures, and rickets is associated with very low vitamin D and extremely low calcium intakes as occur in parts of Africa. So there is minimal intake of calcium and vitamin D needed in early childhood to prevent fractures, but we have no reason to think that it has a long-term effect with the high levels of calcium that catch-up growth isn't entirely possible, and the data from breastfeeding would even suggest that perhaps some lower intakes are beneficial but a little balance must be found to make sure that rickets doesn't occur.

Dr. Schofer: I was a little surprised about your remarks on vitamin D and calcium supplementation that there are no efficacy data in children. Is that true also for chronic inflammatory conditions like chronic inflammatory bowel disease or hematic diseases, where it is a common practice to substitute these patients with vitamin D and calcium?

Dr. Fewtrell: I assume you are referring to my comments about the efficacy of calcium and vitamin D during my presentation. What I was saying was that there simply aren't a lot of randomized trials looking at the effects of vitamin D intake in childhood on later bone health, although obviously we need adequate intake to prevent rickets. With regard to the other part of your question about calcium and vitamin D supplements in various chronic diseases, I don't think this has been looked at systematically in randomized trials, although it is certainly common practice and is unlikely to do any harm. I am aware of a randomized trial of calcium and vitamin D supplementation in patients with cystic fibrosis that is being conducted by an Italian group at the moment, but I am not aware of trials in other chronic conditions.

Dr. Schofer: I have one more question for Dr. Hursting. Are there any data that you are aware of linking Helicobacter infections in children with lymphoma? We are very often in the situation that we find Helicobacter and then we need to think about whether eradication therapy should be used or not.

Dr. Hursting: I am not aware of anything with lymphoma; I mean childhood cancers specifically, although there are certainly animal data as well as human data on various Helicobacter species in adult cancer development. It appears again to be related to a chronic inflammation that perhaps requires 10 or more years to manifest, to cause trouble, but clearly in the animal systems there are a number of Helicobacter species that are linked over time and increased tumor development, and also some human data go on with it.

Dr. Arvanitakis: Considering the fact that peak bone mass is almost complete at 25 years of age, how effective do you think we shall be in treating the adult with cystic fibrosis and osteoporosis? Is there any evidence in the literature regarding the relationship between beef meat and the human colon cancer?

Dr. Fewtrell: It is increasingly recognized that young adults with cystic fibrosis have a low bone mass and are at an increased risk of fractures. The evidence is that most patients with cystic fibrosis probably don't attain a normal peak bone mass. They seem to have relatively normal bone mass until puberty but do not show the expected rapid gain in bone mass during puberty. The etiology is likely to be multifactorial, involving nutritional factors, chronic inflammation, delayed puberty and drug treatment. The recent consensus statement published by Aris et al. [8] suggests that all cystic
fibrosis patients should have calcium, vitamin D and probably vitamin K supplements, and they should be treated with bisphosphates if they also have low bone mass, bone pain or fractures.

Dr. Hursting: Regarding the beef question, there are mixed data on beef consumption that have sharpened in the last few years and that sharpening has to do with two components: cured meats, cured beef and other meat products are clearly linked to colon cancer risk. The second is charred meat that is also clearly emerging as a risk factor, not a very strong one but a consistent one. So beef in general doesn’t seem to be, but cured and charred meat are probably the two conditions you want to avoid.

References
