Growth and Bone Development

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Abstract

Osteoporosis is a major cause of morbidity and mortality through its association with age-related fractures. Although most effort in fracture prevention has been directed at retarding the rate of age-related bone loss, and reducing the frequency and severity of trauma among elderly people, evidence is growing that peak bone mass is an important contributor to bone strength during later life. The normal patterns of skeletal growth have been well characterized in cross-sectional and longitudinal studies. It has been confirmed that boys have higher bone mineral content, but not volumetric bone density, than girls. Furthermore, there is a dissociation between the peak velocities for height gain and bone mineral accrual, in both genders. Puberty is the period during which volumetric density appears to increase in both axial and appendicular sites. Many factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, endocrine status, and sporadic risk factors such as cigarette smoking. In addition to these modifiable factors during childhood, evidence has also accrued that fracture risk might be programmed during intrauterine life. Epidemiological studies have demonstrated a relationship between birthweight, weight in infancy, and adult bone mass. This appears to be mediated through modulation of the set-point for basal activity of pituitary-dependent endocrine systems such as the hypothalamic-pituitary-adrenal and growth hormone/insulin-like growth factor-1 axes. Maternal smoking, diet (particularly vitamin D deficiency), and physical activity also appear to modulate bone mineral acquisition during intrauterine life; furthermore, both low birth size and poor childhood growth are directly linked to the later risk of hip fracture. The optimization of maternal nutrition and intrauterine growth should also be included within preventive strategies against osteoporotic fracture, albeit for future generations.
Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1, 2]. The risk of osteoporotic fracture ultimately depends on two factors: the mechanical strength of bone and the forces applied to it. Bone mass (a composite measure including contributions from bone size and its volumetric mineral density) is an established determinant of bone strength, and the bone mass of an individual in later life depends upon the peak attained during skeletal growth and the subsequent rate of bone loss. Several longitudinal studies attest to the tracking of bone mass through childhood and adolescence, and mathematical models suggest that modifying peak bone mass will have biologically relevant effects on skeletal fragility in old age. There is evidence to suggest that peak bone mass is inherited, but current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk [3]. Environmental influences during childhood and puberty have been shown to benefit bone mineral accrual, but the relatively rapid rate of mineral gain during intrauterine and early postnatal life, coupled with the plasticity of skeletal development in utero, offer the possibility of profound interactions between the genome and early environment at this stage in the life course. There is a strong biological basis for such a model of disease pathogenesis. Experimentalists have repeatedly demonstrated that minor alterations to the diet of pregnant animals can produce lasting changes in the body build, physiology and metabolism of the offspring [4]. This is one example of a ubiquitous phenomenon (phenotypic or developmental plasticity) which enables one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development. Its essence lies in the critical period during which a system is plastic and sensitive to the environment, followed by a loss of that plasticity and a fixed functional capacity. The evolutionary benefit of the phenomenon is that in a changing environment, it maximizes phenotypic diversity and enables the production of phenotypes that are better matched to their environment than would be possible with the production of the same phenotype in all environments. This review will address the role played by influences during intrauterine or early postnatal life, in establishing the risk of osteoporosis in later years. It will cover the patterns of normal skeletal growth during intrauterine life, infancy and childhood; the epidemiological evidence linking the risk of low bone density and fracture to environmental influences during early development; the impact of maternal nutrition and lifestyle on intrauterine bone mineral accrual, and the mechanisms underlying the relationship between developmental plasticity and osteoporosis.
Normal Skeletal Growth

Peak Bone Mass
At any age, the amount and quality of an individual’s skeleton reflect their experiences from intrauterine life through the years of growth into young adulthood. The skeleton grows as the body grows, in length, breadth, mass and volumetric density. For men and women of normal bodyweight, total skeletal mass peaks a few years after fusion of the long bone epiphyses. The exact age at which bone mineral accumulation reaches a plateau varies with skeletal region and with how bone mass is measured. Areal density, the most commonly used measurement with dual energy X-ray absorptiometry, peaks earliest (prior to age 20 years) at the proximal femur, while total skeletal mass peaks 6–10 years later [5]. However, total skeletal mass does not reflect the considerable heterogeneity in mineral accrual at various skeletal sites [6, 7]. Thus, the growth velocity of total body length is high immediately after birth, but slows rapidly during infancy; it accelerates again at 12 months of age, due to more rapid longitudinal growth of the legs, but not the spine. The growth velocity of the legs continues to remain around twice that of the axial skeleton until puberty. Thus, there is a disassociation between the peak velocities for height gain and bone mineral accrual in both genders [8].

The importance of peak bone mass for bone strength during later life was initially suggested by cross-sectional observations that the dispersion of bone mass does not widen with age [9]. This led to the proposition that bone mass tracks throughout life and that an individual at the high end of the population distribution at age 30 years is likely to remain at that end at age 70 years. Recent longitudinal studies have confirmed this tracking, at least across the pubertal growth spurt [10].

Bone Growth in Utero
The fetal skeleton develops in two distinct components, intramembranous (the skull and facial bones) and endochondral (the remainder of the skeleton) ossification. The second is responsible for the formation of the bones which are the main sites of fragility fracture in later life. This form of ossification depends on a pre-existing cartilaginous model that undergoes invasion by osteoblasts and is only subsequently mineralized. The development of this cartilage model can be seen by 5 weeks gestation with the migration and condensation of mesenchymal cells in areas destined to form the bone [11]. These pre-cartilaginous anlagen reflect the shape, size, position and number of skeletal elements which will be present in the mature skeleton. There is then an ordered differentiation of mesenchymal stem cells into chondrocyte precursors, proliferative chondrocytes, pre-hypertrophic chondrocytes and hypertrophic chondrocytes. During these stages of differentiation there is expansion of the bony template and production of an extracellular matrix rich in cytokines which facilitate vascular invasion and mineralization. The major regulator of the proliferation of
chondrocytes is parathyroid hormone-related protein (PTHrP) [12], which is secreted by the perichondral cells; other proliferative stimuli include cytokines of the growth hormone (GH)/insulin-like growth factor (IGF) axis [13]. 1,25-(OH)2 vitamin D3 [14] and tri-iodothyronine [15] are stimuli for the differentiation of the chondrocytes through different stages. Once the cartilage model has been formed, vascular growth factors embedded in the matrix are released by chondrocyte metalloproteinases. This stimulates angiogenesis and, under the influence of Cbfa1 [16], osteoblasts from the perichondrium invade and lay down matrix which is then mineralized.

During the period of a normal human pregnancy the fetus accumulates approximately 30 g of calcium; the majority of this is accrued during the third trimester [17]. To supply this demand, there is a requirement for: (i) an adequate maternal supply of calcium to the placenta, and (ii) increased placental calcium transfer to maintain a higher fetal serum calcium concentration than the mother [18]. This materno–fetal gradient emerges as early as 20 weeks gestation [19]. It is mainly influenced by low levels of fetal parathyroid hormone activity; a lack of fetal parathyroids in mice leads to low fetal calcium levels and decreased mineralization [20]. The main effect of PTHrP seems to be on placental calcium transport [20]. Additionally there is evidence that PTH and PTHrP differentially affect the mineralization of cortical and trabecular bone [21, 22], and thus are attractive candidates for the physiological, mediation of intrauterine skeletal programming.

The rate of materno–fetal calcium transfer increases dramatically after 24 weeks, such that around two thirds of total body calcium, phosphorus and magnesium are accumulated in a healthy term human fetus during this period. Factors which increase placental calcium transport capacity as gestation proceeds are only partly genetically controlled, and are achieved through regulatory hormones including 1,25(OH)2 vitamin D3. As the majority of fetal bone is gained during the last trimester, one of the major variables affecting bone mass at birth is gestational age. Other factors known to influence neonatal bone mineral content (BMC) include environmental variables such as season of birth and maternal lifestyle. Newborn total body BMC has been demonstrated to be lower among winter births than among infants born during the summer [23]. This observation is concordant with lower cord serum 25(OH)2 vitamin D concentrations observed during the winter months, consequent upon maternal vitamin D deficiency. Other postulated contributors to impaired bone mineral acquisition during intrauterine life include maternal smoking, alcohol consumption, caffeine intake and diabetes mellitus [24].

**Developmental Origins of Osteoporosis**

Epidemiological studies of coronary heart disease performed over a decade ago demonstrated strong geographic associations between the death
rate from the disorder in 1968–1978 and infant mortality in 1901–1910 [25]. Subsequent research, based on individuals whose birth records had been preserved for seven decades, revealed that men and women who were undernourished during intrauterine life and therefore had low birthweight or were thin at birth, had an increased risk for coronary heart disease, hypertension, non-insulin-dependent diabetes, and hypercholesterolemia [26]. These associations are explained by a phenomenon known as programming [27]; this term describes persisting changes in structure and function caused by environmental stimuli acting at critical periods during early development. During embryonic life, the basic form of the human baby is laid down in miniature. However, the body does not increase greatly in size until the fetal period when a rapid growth phase commences, which continues until after birth. The main feature of fetal growth is cell division. Different tissues of the body grow during periods of rapid cell division, so-called ‘critical’ periods [28].

Evidence that the risk of osteoporosis might be modified by environmental influences during early life stems from four groups of studies: (a) bone mineral measurements undertaken in cohorts of adults whose detailed birth and/or childhood records have been preserved; (b) detailed physiological studies exploring the relationship between candidate endocrine systems which might be programmed (GH/IGF-1, hypothalamic-pituitary adrenal, gonadal steroid) and age-related bone loss; (c) studies characterizing the nutrition, body build and lifestyle of pregnant women and relating these to the bone mass of their newborn offspring, and (d) studies relating childhood growth rates to the later risk of hip fracture.

Population Studies

The first epidemiological evidence that osteoporosis risk might be programmed came from a study of 153 women born in Bath during 1968–1969 who were traced and studied at age 21 years [29]. Data on childhood growth were obtained from linked birth and school health records. There were statistically significant (p < 0.05) associations between weight at 1 year and BMC, but not density, at the lumbar spine and femoral neck; these relationships were independent of adult weight and body mass index. The data suggested a discordance between the processes which govern skeletal growth, and those which influence mineralization. They also provided direct evidence that the trajectory of bone growth might be modified in utero, an assertion previously only supported by inference from measurements of body height. The association between weight in infancy and adult bone mass was replicated in subsequent cohort studies of men and women aged 60–75 years, who were born and still lived in Hertfordshire [30, 31]. These studies showed highly significant relationships between weight at 1 year and adult bone area at the spine and hip (p < 0.005); the relationships with BMC at these two sites were weaker but remained statistically significant (p < 0.02). They also remained after adjustment for known genetic markers of osteoporosis risk, such as...
polymorphisms in the gene for the vitamin D receptor [32], and after adjustment for lifestyle characteristics in adulthood which might have influenced bone mass (physical activity, dietary calcium intake, cigarette smoking, and alcohol consumption). More detailed analyses of the interactions between polymorphism in the gene for the vitamin D receptor, birthweight, and bone mineral density (BMD) have been published from the same cohort study [33]. These suggest that genetic influences on adult bone size and mineral density may be modified by undernutrition in utero. Subsequent studies from the United States, Australia and Scandinavia have replicated these relationships between weight in infancy and adult bone mass. Finally, a recent twin study [34] evaluated the relationship between birthweight and bone mass among 4,008 white female twins aged 47.5 years. Statistically significant relationships were found between the intra-pair differences in birthweight and in BMC, after adjustment for height and weight, even among monozygous twin pairs. These data suggest that even in genetically identical subjects, a relationship can be detected between birthweight and adult bone mass.

**Physiological Studies**

To explore further the potential role of hypothalamic-pituitary function and its relevance to the pathogenesis of osteoporosis, profiles of circulating GH and cortisol were compared with bone density among groups of men and women whose birth records had been preserved. These studies revealed that birthweight and weight in infancy were predictors of basal levels of GH and cortisol during late adult life [34–36]. The levels of these two skeletally active hormones were also found to be determinants of prospectively determined bone loss rate. The data are compatible with the hypothesis that environmental stressors during intrauterine or early postnatal life alter the sensitivity of the growth plate to GH and cortisol. The consequence of such endocrine programming would be to reduce peak skeletal size, perhaps also to reduce mineralization, and to predispose to an accelerated rate of bone loss during later life [35–37]. Recent studies suggest that interactions between the genome and early environment might establish basal levels of circulating GH, and thereby contribute to accelerated bone loss [38]. Thus, a single nucleotide polymorphism has been discovered at locus GH1-A5157G in the promoter region of the human growth hormone (GH1) gene. This is associated with a significantly lower basal GH concentration, lower baseline delayed neuronal death and accelerated bone loss (fig. 1). As with polymorphism in the gene for the vitamin D receptor, a significant (p = 0.02) interaction was observed between weight at one year, allelic variation at this site and bone loss rate.

**Maternal Nutrition, Lifestyle and Neonatal Bone Mineral**

The third piece of epidemiological evidence that osteoporosis might arise in part through developmental maladaptation, stems from investigation of a
series of mothers through pregnancy; anthropometric and lifestyle maternal characteristics were related to the bone mineral of their newborn offspring [39]. After adjusting for sex and gestational age, neonatal bone mass was strongly, positively associated with birthweight, birth length and placental weight. Other determinants included maternal and paternal birthweight, and maternal triceps skinfold thickness at 28 weeks (fig. 2). Maternal smoking and maternal energy intake at 18 weeks gestation were negatively associated with neonatal BMC at both the spine and whole body (fig. 3). The independent effects of maternal and paternal birthweight on fetal skeletal development support the notion that paternal influences, for example through the imprinting of growth-promoting genes such as IGF-2, contribute strongly to the establishment of the early skeletal growth trajectory, while maternal nutrition and body build modify fetal nutrient supply and subsequent bone accretion, predominantly through influences on placenta.

In the most recent data from mother/offspring cohorts, body composition has been assessed by dual energy X-ray absorptiometry in 216 children at age 9 years [40]. They and their parents had previously been included in a population-based study of maternal nutrition and fetal growth. The nutrition, body build and lifestyle of the mothers had been characterized during early and late pregnancy, and samples of umbilical venous blood had been obtained at birth. Reduced maternal height, lower pre-conceptional maternal weight, reduced

**Fig. 1.** GH-1 genotype, 24-hour GH concentration, weight in infancy and adult bone loss: Hertfordshire Cohort Study. BMD = Bone mineral density. Data derived from Dennison et al. [38].
maternal fat stores during late pregnancy, a history of maternal smoking and lower maternal social class were all associated with reduced whole body BMC of the child at age 9 years. A lower ionized calcium concentration in umbilical venous serum also predicted reduced childhood bone mass ($r = 0.19$, $p = 0.02$); this association appeared to mediate the effect of maternal fat stores, smoking and socioeconomic status on the bone mass of the children.

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**Fig. 2.** Maternal triceps skinfold thickness in early pregnancy and neonatal bone mineral content (BMC) and density (BMD) among 144 term neonates. Values are mean ± SE. p values adjusted for sex and gestation. Data derived from Godfrey et al. [39].

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**Fig. 3.** Maternal smoking during pregnancy and neonatal bone mineral content (BMC) and density (BMD) among 144 term neonates. Values are mean ± SE. p values adjusted for sex and gestation. Data derived from Godfrey et al. [39].
age 9 years. Around 25% of the mothers had suboptimal vitamin D status as assessed by the serum 25-hydroxyvitamin D concentration (fig. 4). The children born to these mothers had significantly (p < 0.01) reduced whole body BMC at age 9 years. This deficit in skeletal growth remained significant even after adjustment for childhood weight and bone area [40]. These data suggest that the placental capacity to maintain the materno–fetal calcium gradient is important in optimizing the trajectory of postnatal skeletal growth. They are in accord with the results of follow-up studies relating vitamin D supplementation in infancy to BMD in later childhood. In one such study, prepubertal Caucasian girls aged 7–9 years, who had received vitamin D supplementation during infancy, had greater areal BMD at the radius and proximal femur than a group of female controls of similar age [41].

**Childhood Growth and Hip Fracture**

Most evidence relating the intrauterine environment to later osteoporosis stems from studies utilizing noninvasive assessment of bone mineral. The clinically important consequence of reduced bone mass is fracture, and data are now available which directly link growth rates in childhood with the risk of later hip fracture [42]. Studies of a unique Finnish cohort in whom birth and childhood growth data were linked to later hospital discharge records for hip fracture, have permitted follow-up of around 7,000 men and women who were born in Helsinki University Central Hospital during 1924–1933. Body size at birth was recorded and an average of 10 measurements were obtained of height and weight throughout childhood. Hip fracture incidence
was assessed in this cohort using the Finnish hospital discharge registration system. After adjustment for age and sex, there were two major determinants of hip fracture risk: tall maternal height ($p < 0.001$), and a low rate of childhood growth (height $p = 0.006$; weight $p = 0.01$). The effects of maternal height and childhood growth rate were statistically independent of each other, and remained after adjusting for socioeconomic status. More important, hip fracture risk was also elevated ($p = 0.05$) among babies born short. These data suggest that hip fracture risk might be particularly elevated among children in whom growth of the skeletal envelope is forced ahead of the capacity to mineralize, a phenomenon which is accelerated during pubertal growth.

**Developmental Plasticity and Osteoporosis**

The observed relationship between osteoporosis risk and size at birth or during infancy does not imply a causal role of being born small, but reflects the sensitivity of fetal growth to adverse intrauterine influences. The term ‘maternal constraint’ encapsulates those environmental factors that influence birth size even in healthy pregnancies, for example maternal size, age, parity and multiple pregnancy. Among modifiable mechanisms limiting nutrient supply to the fetus, maternal nutrition has received the most attention, but other early environmental factors such as smoking, infectious exposure, and season of birth, may have long-term effects.

Experimental evidence that the prenatal or perinatal environment can influence adult postnatal physiology is available in several mammalian species [43, 44]. These studies demonstrate that manipulation of the periconceptual, embryonic, fetal, or neonatal environment can lead to altered postnatal cardiovascular and/or metabolic function. Although the environmental triggering cues are not yet fully understood, most manipulations have been dietary and include maternal pan-undernutrition [45, 46], low protein diet [47], or high fat diet [48, 49]. Animal models for the developmental origins of osteoporosis replicate the observations made in humans. In the first such model, the feeding of a low protein diet to pregnant rats produced offspring that exhibited a reduction in bone area and BMC, with altered growth plate morphology in adulthood [50]. Maternal protein restriction also downregulated the proliferation and differentiation of bone marrow stromal cells [51] as assessed by fibroblast colony formation at 4 and 8 weeks.

‘Developmental plasticity’ provides organisms with the ability to change structure and function in response to environmental cues; these responses usually operate during critical time windows and then become irreversible. Such plasticity permits a range of phenotypes to develop from a single genotype in response to environmental cues. In *Daphnia*, helmet formation (a defensive, morphological change) is dependent on the early environment and
risk of predation. In the locust, *Locusta migratoria*, the wing shape and metabolic pathways are determined in the larval stage by pheromone signals indicating population density. In the axolotl, early environmental conditions determine whether the mature form will be purely aquatic or amphibious [52]. Developmental plasticity sets the template on which continued postnatal homeostatic and homeorhetic (maintaining a time-dependent process, e.g. growth trajectory) adaptation can occur.

There are several mechanisms by which environmental cues can influence the developmental program. First, they can exert effects prior to implantation and affect gene expression, particularly by inducing epigenetic changes in the DNA. In the *agouti* mouse mutant, maternal dietary folate supplementation at conception alters the expression of the imprinted *agouti* gene by altering the capacity for methylation [53]. Non-imprinted genes can also undergo epigenetic change in response to the environment – the choice of exon usage in the glucocorticoid receptor gene is altered both by prenatal glucocorticoids and neonatal behavioral manipulation owing to changes in histone acetylation and DNA methylation in a transcriptional factor binding site [54]. These changes persist throughout life as manifested in altered hypothalamic-pituitary-adrenal axis activity. Second, tissue differentiation may be altered. Prolonged in vitro culture of the rodent or ruminant embryo affects the allocation of blastocyst stem cells to inner cell mass or trophectoderm lineages [55]. This influences the relative growth trajectories of the placenta and fetus, thus affecting fetal development in late gestation.

Developmental responses to environmental stimuli need not provide immediate advantages, but may alter the sensitivity of the organism to an anticipated future environment [44]. Such predictive adaptive responses are made during the phase of developmental plasticity to optimize the phenotype for the probable environment of the mature organism, and epigenetic change is likely to be the mechanistic basis. Where there is a match between the predicted and actual mature environment, these responses are appropriate and assist survival. In contrast, inappropriate predictions increase the risk of disease. A key issue thus becomes the relative importance of early life events in informing intervention strategies during human development, rather than during adult life. Increasing awareness of the need to promote the health and nutrition of women of reproductive age is one important element for the prevention of osteoporotic fracture in future generations across the globe.

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References


Discussion

**Dr. Thornburg:** Could you help us understand the trade off that you were discussing about increasing vitamin D sources from others?

**Dr. Cooper:** That's a very good question and one which taxed us enormously when we were going through the ethical approval for the vitamin D trial. If you look at the literature there is undoubtedly a high prevalence of vitamin D insufficiency in mothers in Western populations. Some of the estimates from northern Europe and the USA would reach 40%, being less than 20 ng/ml, and 25–30% being less than 10 ng/ml, so a high prevalence of low biochemical values. The data are very scanty on the relationship between vitamin D status and later cardiovascular health, cognitive function, the likelihood of allergy and a predisposition to infection. Broadly speaking, there is a possible role for vitamin D deficiency in diabetogenesis; a possible protective effect against respiratory infection, and an association with allergy and IgE-related hypersensitivity disorders. So in our cohort we studied those outcomes and basically there was no relationship between 25-OHD and adiposity or glucose tolerance; there was no relationship with cognitive function, there was a weak positive relationship with respiratory infection, and there was no relationship with pulse wave velocity.

**Dr. Barclay:** That was a beautiful presentation. I was very interested to see the results of this prudent diet study which are quite similar in fact to the results of the Dash study, the dietary interventions to stop hypertension in which the intakes of fruits, vegetables and dairy products was increased for adults. Not only was the blood pressure lower at the end of the study, after several months, but also the indicators of bone status had improved, which is going in the same way as your mother to infant relationship. In the Dash study one of the hypotheses was that it could be the calcium, magnesium and potassium versus sodium ratio. Do you think this is a valid hypothesis and do you think this has some value in nutrition during pregnancy and lactation?

**Dr. Cooper:** I am not in the least bit qualified to answer the relevance of those nutrients to blood pressure, but I think that there has been quite a lot of work on the two divalent cations and the monovalent cations and their relationships to bone health. I would have said that the best explanation of the data was actually linked to the ionized calcium itself rather than to the relative calcium/magnesium and sodium/potassium fluxes which would be involved in hypertension. There is some (circumstantial) evidence that urinary acidification modifies both calcium and magnesium balance and that this influences skeletal status through secondary hyperparathyroidism.

**Dr. Walker:** About mechanisms, you suggested that it is possibly an epigenetic process. Have you considered looking at polymorphisms? If you look at other micronutrients, folic acid is a classic example, there are polymorphisms in the metabolic pathways of these micronutrients, which could very well be the case in vitamin D or calcium, and could cause a much higher supplement to be given to prevent osteoporosis.
Dr. Cooper: Of course with the preface that Dr. Barker gave on the genome, the notion that fixed genetic variation would explain the observations is unlikely. However, we looked at candidate genes and we have actually published two papers: one looking at polymorphism in the vitamin D receptor [1], and the other looking at polymorphism in the promoter region of the growth hormone gene, the GH1 gene [2]. In both of those when you look at the adverse polymorphism, there is an interaction with birthweight in determining bone mass and the bone loss rate 70 years later. It is difficult to explain the rapidity of the secular trends that we are talking about in these diseases through altered frequencies of fixed genetic variation so that mathematically you would look at gene expression rather than fixed variation as the explanation.

Dr. K. Bergmann: In our childhood and adolescent health examination survey in Germany we found a very strong seasonal effect of low vitamin D, perhaps about 35% of the students have this problem between December and April and a very small percentage have the same problem during July to October. Do you think that matters and, as far as your results are concerned, are there any seasonal effects in what you observed?

Dr. Cooper: We have used broadband ultrasound attenuation (BUA) in the heel, which is a far less precise methodology than DXA, to look at what happens throughout pregnancy in women. When the 11–28 weeks of gestation occur in the summer months there is hardly any change in BUA. The pregnancy that has the 11–28 weeks of gestation in the winter months shows the steepest rates of BUA loss, with spring and autumn in between.

Dr. K. Bergmann: If we observe this in adolescents, do you think it matters? Should we do something about preventing low vitamin D values between December and April?

Dr. Cooper: My view is that the phenotypic expression of low circulating 25-OHD is not strong enough to treat, unless the calcium-phosphate product is low and the alkaline phosphatase is high.

Dr. K. Bergmann: In the United States there is no fortification. Does this change the picture?

Dr. Cooper: That is a very important question, and this needs to be evaluated in a randomized controlled trial.

Dr. Wilson: I would like to follow up on Dr. Walker’s question briefly. You suggested that the secular trend is incompatible with any sort of genetic basis, which is probably true, but might the secular trend be dependent on underlying genetic differences that may contribute and give rise to a future epidemic of osteoporosis because of aging? You also talked about some methylation data. Of course methylation data have the problem of what is the chicken and what is the egg. Do you have any chicken–egg experiments to suggest that there is a causal modification?

Dr. Cooper: When I was referring to the term, secular trend, I meant after adjustment for demographic changes in the population; so after adjustment for age changes, for cardiovascular disease and for osteoporotic fracture there has been a rise. If you look at the Rochester data, fracture incidence data for the 7th to 8th decades, there is a rise from about 19.30, then a plateau for 10–12 years and then the beginning of decline. Age period cohort modeling on these shows that there is clearly an age effect, clearly a period effect but, very interestingly for this discussion, clearly a residual birth cohort effect. So there is something going on not just in the current environment and in the late stage of life, but also some experience that is differentially undergone by different birth cohorts. Data exploring methylation of the acetylcholine receptor gene and vascular reactivity suggest that alteration in folate intake might modulate gene expression.

Dr. Shaalan: During the last 3 years I have implemented a multidisciplinary project for osteoporosis in Egypt and the results will be available by the end of this year.
The preliminary results show that we have a very high incidence of osteoporosis in Egypt, although it’s a sunny country. During the next 3 years we will study nutritional intervention with micronutrients and one of the main domains of this intervention will be vitamin D supplementation. You said that you are interested in new future studies on micronutrient supplementation before and after pregnancy. I am also interested in the peak bone mass attainment. Do you think it would be feasible and beneficial to unify our research to see the differences between our two countries, especially with regard to the different environmental and genetic pools?

Dr. Cooper: Yes, of course.

References