Peak Bone Mass, Calcium, and Protein Intakes

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PEAK BONE MASS: ESSENTIAL CHARACTERISTICS

Definition

Peak bone mass can be defined as the amount of bony tissue present at the end of skeletal maturation (1). This biological variable is an important determinant of osteoporotic fracture risk because the mass of bony tissue present at any time during adult life is simply the difference between the amount achieved at maturity and that lost with aging (2,3). Hence the growing interest in investigations aimed at understanding how bone mass evolves during development and at identifying the most important genetic and environmental factors that influence its accumulation rate.

Bone Mass Measurement

The bone mass of a part of the skeleton is directly dependent on both its volume or size and the density of the mineralized tissue contained within the periosteal envelope. The techniques of single- and dual-energy photon or X-ray absorptiometry (DXA) measure the “areal” or “surface” bone mineral density (in g of hydroxyapatite/cm²), a variable which has been shown to be directly related to bone strength (4). Bone mineral content (in g of hydroxyapatite for a given region of interest) can also be used to assess bone mass gain, e.g., at the level of the lumbar vertebrae (1).

Bone Mass Gain Before and During Puberty

Before puberty, no consistent sex difference in bone mass of either the axial or the appendicular skeleton has been reported (1,5). There is no evidence of a gender
difference in bone mass at birth. Likewise, the volumetric bone mineral density appears also to be similar between female and male newborns (1,5). This absence of sex difference in bone mass is maintained until the onset of pubertal maturation.

During puberty, the gender difference in bone mass becomes expressed. This difference appears to be essentially due to a more prolonged bone maturation period in males than in females, with a larger increase in bone size and cortical thickness (1,6-8). Puberty affects bone size much more than volumetric mineral density. There is no significant sex difference in the volumetric trabecular density at the end of pubertal maturation (1). During puberty, the accumulation rate in areal bone mineral density at both the lumbar spine and femoral neck levels increases four- to sixfold over a 3- and 4-year period in females and males, respectively (1,8). The change in bone mass accumulation rate is less marked in long-bone diaphysis. There is an asynchrony between the gain in statural height and bone mass growth (1,8). This phenomenon may be responsible for the occurrence of a transient period of a relative increase in bone fragility that may account for the pattern of fracture incidence during adolescence (9).

Variance in Peak Bone Mass

At the beginning of the third decade, there is a large variability in the normal values of areal bone mineral density in axial and appendicular skeleton (1-3). This large variance, which is observed at sites particularly susceptible to osteoporotic fractures such as lumbar spine and femoral neck (10), is barely reduced after correction for statural height (11) and does not appear to increase substantially during adult life. The height-independent broad variance in bone mass develops during puberty at sites such as lumbar spine and femoral neck, where the accretion rate is markedly increased (7,8,12).

Time of Peak Bone Mass Attainment

Despite the fact that a majority of studies did not indicate that bone mass continues to accumulate significantly during the third and fourth decades, it was generally accepted that peak bone mass at any skeletal site was attained in both sexes during the mid-30s. However, recent studies indicate that in healthy Caucasian females with apparently adequate intakes of energy and calcium, bone mass accumulation can be virtually complete before the end of the second decade for both lumbar spine and femoral neck (7,8,13). Nevertheless, it is possible that both genetic and environmental factors could influence the time of peak bone mass achievement.

DETERMINANTS OF PEAK BONE MASS

Many factors, more or less independent, are supposed to influence bone mass accumulation during growth. The list of these determinants classically includes heredity, sex, dietary components (calcium, proteins), endocrine factors (sex steroids,
calcitriol, insulin-like growth factor–1), mechanical forces (physical activity, body weight), and exposure to risk factors (14–17). Quantitatively, the most prominent factor appears to be the genetic determinant.

Genetic Determinant

It is apparent from twin and family studies that genetic or inherited factors account for about 75% of the population variability in bone mineral density among age- and sex-matched normal individuals (14).

Examination of bone mineral density at critical sites such as the lumbar spine and femoral neck, as well as the distal forearm, indicated that monozygotic (identical) twins were much more similar in bone mineral density than dizygotic (nonidentical) twins (14). The strength of this relationship was such that 75–80% of the population variation in bone mineral density could be explained by inherited/genetic factors. Of interest, it was also shown in these studies that the genetic contribution to bone mass was slightly less in the proximal femur and in the forearm than in the lumbar spine, suggesting that the impact of environmental factors could vary according to the skeletal site (14). Recent studies have shown that common allelic differences in the vitamin D receptor (VDR) gene could account for a part of bone mass or areal bone mineral density (bone mineral density) variability (18). Although the VDR gene appears to play a role in some aspects of bone development, it is not clear as to how this genetic effect is mediated. However, a rather large variability in either lumbar spine or femoral neck bone mineral density values remains in subjects sharing the same allelic variant of the VDR encoding gene (18).

That heredity is not the only determinant of peak bone mass is of practical interest because environmental factors can be modified. With respect to mechanical factors, the impact of various degrees of physical activity on those parts of the skeleton where the osteoporotic process can have dramatic clinical consequences in the last decades of the adult life, remains to be clearly determined.

Nutritional Factors

In healthy, apparently well-nourished children and adolescents, the extent to which variations in the intakes of some nutrients, not only calcium but also proteins, can affect bone mass accumulation, particularly at sites susceptible to osteoporotic fractures, remains to be clarified.

Over the last few years, our research team in Geneva has investigated the correlation between the intakes of several nutrients and bone mass accretion during pubertal maturation. There were two reasons for concentrating our attention on subjects at various stages of pubertal maturation. First, and as mentioned above, the height-independent broad variability in bone mass develops during puberty both in the spine and in the proximal femur, two skeletal sites where a marked acceleration in accretion
rate takes place. Second, puberty is considered to be a period characterized by major behavioral changes and alterations in lifestyle.

**Macronutrient Intakes During Pubertal Maturation**

It is assumed that important modifications in food habits would occur during pubertal maturation, particularly in affluent societies. However, there is still a lack of quantitative and qualitative information on the evolution of the macronutrient intakes in relation to pubertal maturation.

In a prospective survey carried out in about 200 female and male adolescents aged 9–19 years, food intake was assessed twice, with a 1-year interval, using a 5-day dietary diary method with weighing of all consumed foods. Diaries were analyzed for macronutrient consumption (lipids, carbohydrates, and proteins) with nutrition determination software that integrated food composition tables and 103 local food items. The stage of puberty or sexual maturity was rated from stage P1 (prepubertal) to P5 (adult).

With respect to macronutrients, the results indicated that total energy intake—which remained within the recommended dietary allowances (RDAs)—was significantly influenced by both pubertal maturation and sex when expressed in absolute terms, but by pubertal stage only when adjusted per kg body weight. As compared to RDA, the macronutrient distribution within the overall energy intake showed an excessive quantity of fat (especially saturated fatty acids) and an insufficient intake of glucid-rich fiber. The intakes of protein, two thirds of which was from animal sources, were above the RDA. Overall, the inadequacies in macronutrient intake distribution were remarkably constant throughout pubertal maturation. Thus, this survey did not suggest that adolescence was a period when bad food habits are particularly acquired. Rather, it indicates that the “affluent” type of diet which has been linked with several chronic diseases in adults from developed countries already prevails before pubertal maturation, with very mild changes during adolescence.

**Calcium Intake During Pubertal Maturation**

In the same study, the calcium intake from dairy foods was assessed by two methods: first, and as mentioned above for macronutrients, by the use of a 5-day dietary diary made twice with a 1-year interval; and second, by using the more simple technique of the so-called frequency questionnaire. This frequency questionnaire for dairy calcium was added to the diary and completed with the help of a dietitian. The daily consumption of different dairy products and typical Swiss cheese dishes was evaluated. The results indicate that the mean calcium intakes according to pubertal stage ranged in females from 785 ± 51 (stage P1, mean ± SEM) to 1025 ± 108 mg/day (stage P4), and in males from 1007 ± 80 (stage P2) to 1415 ± 78 mg/day (stage P5). Overall, these values corresponded to the recommended daily allowance for age. Statistical analysis indicated that the total amount of calcium increased with the
stages of pubertal maturation \((p < 0.001)\), and that the mean intake of the adolescent females was less than that recorded in their male counterparts \((p < 0.001)\). In contrast, when related to body weight, the calcium intake decreased \((p < 0.001)\) with the stages of pubertal maturation and the gender difference was no longer statistically significant. Note that there was a positive correlation between the energy or protein intakes and the calcium consumption during adolescence. Nevertheless, these correlations were tighter in males than in females.

**Calcium Intake and Bone Mass Accumulation**

We found significant positive correlations between the absolute values of the total calcium intake and those of spinal and femoral bone mineral density for the whole cohort of either female or male subjects. Despite this significant positive correlation, there was an important variability for a given calcium intake in the bone mineral density values. Furthermore, our data suggest the existence of a threshold for the calcium intake above which the large variability in bone mass would be dependent on other factors that remain to be identified. In the female cohort, the significant positive relationship was observed in the pubertal subgroup P1–P4, but not in the P5 subgroup. Overall, the relations between the dairy calcium intake and the bone mineral density/bone mineral content values were very similar to those obtained with the recorded consumption for the total calcium. However, when the analysis of the results took into account the influence of age and pubertal maturation, the relations between the absolute values of the calcium intake and bone mineral density suggested that calcium may be more important before than during pubertal maturation. A recent study carried out in pairs of identical twins indicated that a calcium supplementation of 700 mg/day, given as calcium citrate malate above a mean daily calcium intake of about 950 mg, could significantly enhance the rate of bone mineral density gain in prepubertal children, but not after the onset of pubertal maturation (19). Furthermore, in prepubertal children, calcium supplementation appears to be more effective on cortical appendicular bone (radius) than on axial trabecular-rich bone (lumbar spine vertebral bodies) or on the hip (femoral neck, trochanter), as measured by dual-photon absorptiometry, a technique of lower precision than DXA. Therefore, there is a need to study the impact of calcium supplementation further, particularly at “critical osteoporotic” sites such as lumbar spine and femoral neck, using DXA technology, before making new general recommendation to public health institutions for osteoporosis prevention programs aimed at maximizing peak bone mass with calcium supplements.

In this context, we are currently studying the influence of calcium-fortified foods on bone mass accretion measured by DXA at several skeletal sites in prepubertal girls randomized in a double-blind placebo-controlled study.

As mentioned above, the association between VDR gene polymorphisms and concordance for bone mineral density in adult twins suggests that VDR alleles may be a genetic determinant of peak bone mass. We recently found a correlation between
VDR alleles and the rate of bone loss in calcium-supplemented vitamin D–replete elderly people. Therefore, it also appears to us of interest to investigate the relationship between VDR gene polymorphisms and bone mass accumulation in prepubertal girls.

Protein Intake and Bone Mass Accumulation

Various studies have found a relationship between the level of protein intake and either calcium phosphate metabolism or bone mass and the osteoporotic fracture risk (20–23). Nevertheless, a long-term influence of dietary proteins on bone mineral metabolism and skeletal mass has so far been difficult to prove. Apparently contradictory information suggests that either a deficient or an excessive protein supply could have a negative effect on the balance of calcium and the amount of bony tissue contained in the skeleton (20,23). With respect to nutritional recommendations, this means that either an increase or a reduction in protein intake could result in an increment in the calcium phosphate balance and bone mass, according to the prevailing physiologic or clinical conditions.

Several reasons can be evoked to explain the present uncertainty about the effect of protein supplementation on calcium balance and bone mass. The outcome may differ because the protein supplementation was (a) prescribed either to well-nourished people or to subjects showing signs of malnutrition; (b) given in various forms—natural food products, i.e., ingested in complex forms, or given as purified extracts or even as mixtures of amino acids; (c) from either animal origin (casein, for instance) or vegetable origin (soya, for instance); (d) evaluated in either the short or the long term; or (e) assessed in the presence or absence of modifications to other nutritional factors such as energy or calcium.

Despite these uncertainties, several studies both in experimental animals and in human subjects strongly suggest that low protein intake per se could be particularly detrimental for both the acquisition of bone mass and the conservation of bone integrity with aging.

During growth, undernutrition, including inadequate supply of energy and proteins, can severely impair bone development. Studies in experimental animals indicate that isolated protein deficiency leads to reduced bone mass and strength, i.e., to osteoporosis, without histomorphometric evidence of osteomalacia (20,23). Thus, an inadequate supply of protein appears to play a central role in the pathogenesis of the delayed skeletal growth and reduced bone mass observed in undernourished children.

Low protein intake could be detrimental to skeletal integrity by lowering to an inadequate level the production of insulin growth factor–1 (IGF-1). The hepatic production and plasma concentrations of this growth factor, which exerts several positive effects on the skeleton, are under the influence of dietary proteins (24). Protein restriction has been shown to reduce the plasma level of IGF-1 by inducing a resistance to the action of growth hormone at the hepatic level (25). The effect of protein restriction could be mediated by a reduction in the hepatic supply of some essential amino
acids. Besides impairment in the hepatic IGF-1 production, results of other experiments suggest that protein restriction could still both increase the plasma clearance of IGF-1 and decrease its anabolic actions on some target cells. In this regard, it is important to note that in rats maintained under a low protein diet, IGF-1 when given in doses that normalize its plasma level, fails to restore carcass growth.

Variations in the production of IGF-1 could explain some of the changes in bone and calcium-phosphate metabolism that have been observed in relation to the intake of dietary proteins. Indeed, the plasma level of IGF-1 is closely related to the growth rate of the organism. In humans, the level of circulating IGF-1, of which the major source is the liver, rises progressively from 1 year of age to reach peak values during puberty. IGF-1 appears to play a key role in calcium phosphate metabolism during growth by stimulating both the renal transport of inorganic phosphate (Pi) and the renal production of calcitriol (17,26). This action could well explain the growth-related increase in the plasma levels of both Pi and calcitriol (17). Therefore, IGF-1 appears to play a key role in the adjustments of calcium phosphate metabolism required for normal skeletal development and bone mineralization during growth. During growth, a deficiency of IGF-1 or a resistance to its action that could be due to an inadequate protein supply could result in a diminution in the longitudinal skeletal growth. IGF-1 is considered to be an essential factor for longitudinal bone growth, as it stimulates proliferation and differentiation of chondrocytes in the epiphyseal plate (27). IGF-1 also plays a role in trabecular and cortical bone formation. In experimental animals, administration of IGF-1 can also affect positively bone mass (23).

In “well”-nourished children and adolescents, the question arises as to whether variations in the protein intake within the “normal” range can influence skeletal growth and thereby modulate the genetic potential in peak bone mass attainment. In the adolescent cohort described above, we have studied the relationship between the protein intake and bone mass gain at the lumbar and femoral levels. Since both bone mass and protein intake increased in both sexes during adolescence, it was not surprising to find a positive correlation between these two variables. However, the correlation was still statistically significant after correction for the influence of either age or pubertal stage. The association between bone mass gain and the protein intake was observed in both sexes at the level of the lumbar spine, the proximal femur and the mid-femoral shaft. The association appears to be particularly significant from pubertal stage P2 to P4. However, these results should not be interpreted as evidence for a causal relationship between protein intake and bone mass gain. Indeed, it is quite possible that the protein intake which overall was related to the amount of ingested energy in our cohort, is to a large extent determined by growth requirements during childhood and adolescence.

As for other nutrients such as calcium, only prospective interventional studies will ascertain whether variations in the protein intake within the range recorded in our Western “well-nourished” population can affect bone mass accumulation during growth. Such prospective intervention studies will delineate the crucial years during which modifications in nutrition would be particularly effective for bone mass accumulation in children and adolescents. This kind of information is important in order
to make credible and well-targeted recommendations in the perspective of setting up osteoporosis preventive programs aimed at maximizing peak bone mass.

REFERENCES


DISCUSSION

Dr. Guesry: You said you could not find any relationship between physical activity and bone mass. This is contrary to what I thought I knew about bone physiology. I wonder if this might be because of the way you express physical activity as per kg body weight. After all, in the denominator of this ratio, you have basically three compartments—fat, muscle mass, and bone mass—and the larger the muscle mass, the greater its traction on bone and so maybe the effect on calcium deposition. My question is, what is the relation between bone density and the total weight of bone of an individual? If there is not a close relationship, that be an explanation for your findings.

Dr. Bonjour: I would not like to give the impression that I am against the concept that physical activity does something good to your bones. There are many data to support that. What I am pointing out in this study is the fact that in normal children—moving around, going to school, some having more TV hours than others but all active—it is quite difficult to find a relation between bone mass gain and the recorded hours of physical activity. There could be various explanations for this. As I said, perhaps the methods are not adequate; however, there is an excellent correlation between energy intake and physical activity, so this gives us some confidence in the method used to assess physical activity. You suggest we should express the results differently; however, we also analyzed the data in terms of total hours and we did not find a positive correlation. We also tried expressing bone mass in several ways but we could not find a positive relationship. Our point is that when the World Health Organization asked us what kind of recommendations we could make at this stage for the prevention of osteoporosis in later life, we don’t think we have the data to support the imposition of 2 or 3 hours of physical exercise daily on children around the world in order to increase their bone mass. As to bone mineral density versus bone mass, the term “density” is misleading. What we measure is in fact an integration of volumetric bone mineral density within a skeletal piece and the size of this skeletal piece (1). So it is an integration of both. I don’t think it is a bad assessment of the risk of osteoporotic fracture because it is clear that not only is the volumetric bone mineral density taken into account, but also the bone size. In relation to the specific query about whether the bone mineral density we measure in the femoral neck or the lumbar spine is really related to the total bone mass, I have to say that the correlation is by no means perfect, but when you correct for height, which is related to overall bone mass, you slightly reduce the variability in the young adult (2).

Dr. Rey: When we discuss the relation between exercise and bone mass density, we usually discuss estrogen excretion as well, but you have chosen normal children from the Geneva
area who are not athletes, so we cannot suppose that exercise caused diminished estrogen secretion in these subjects. I think you have chosen a very crude way of expressing exercise, as hours per kg body weight. The effect of the exercise is probably completely different for swimming or for walking or for playing tennis, and the action on the bone will be different. And perhaps also the difference between children is too small to enable an effect on bone mass density to be seen. You have a very large variability in bone mass density—you said 20%; what was the variability of hours of exercise per kg body weight in your population?

Dr. Bonjour: We had a very large variability in the number of hours per week devoted to physical exercise (2–18 hours per week) and the range of bone mass gain was also very wide, particularly in subjects in Tanner stage P2–P4. We have expressed our results both in terms of absolute amount of hours and in terms of hours of exercise per kg body weight per week and we did not find a positive relationship with bone mass gain adjusted for either age or pubertal stage. I do not think there are any published prospective data showing a “dose-response” for exercise and bone mass gain during pubertal maturation in healthy subjects. Our results as well as those obtained by other investigators in similar longitudinal studies (for review, see ref. 3) strongly suggest that for many healthy children and adolescents, the physical activity threshold below which bone mass accrual is substantially impaired would be set at a rather low level. This of course does not exclude the existence of another threshold set in the upper portion of the normal range, explaining the positive effect of sustained and intensive physical exercise on bone mass observed in individuals involved in competitive sport.

Dr. Rey: You did not mention smoking as a negative factor on bone mass density. Can you make a comment about this?

Dr. Bonjour: We did not have enough data to establish a relationship in our adolescent cohort. There are published data showing a relation between smoking and bone mass in adults (4,5).

Dr. Haschke: You presented data from a study on calcium supplementation of children and adolescents, and you provided the supplements over periods of months at least, or over years. Has anybody looked at how the body handles all of this calcium? Has there been a study of calcium absorption, and of calcium and phosphorus balance in such children? Has anybody looked at whether this long-term supplementation may result in hypercalciuria? In premature infants, who of course are completely different, a high calcium intake results in hypercalciuria if you don’t provide enough phosphorus. There are so many studies going on that completely neglect possible adverse effects. Before calcium supplementation of children and adolescents starts to be advertised on TV, I think these matters should be examined.

Dr. Bonjour: We know from adult studies that calcium supplementation leads to hypercalciuria but if you do not have a stone-forming propensity, there is no harm in that; the “therapeutic” margin appears to be quite large. There are very few balance data in children, and when we analyze these data, we must also take into account that they are only short term; we don’t know what happens in the long term. It is clear that if you increase your calcium intake, you will increase your urinary excretion of calcium. In the calcium balance studies done by Matkovic and colleagues (6), there was no record of detrimental effect. Nevertheless, your remarks are well taken. Mainly based on short term studies, some people would like to recommend that all adolescents should consume around 1500 mg of calcium daily. In Geneva, the spontaneous calcium intake in girls is around 700–800 mg/day, so this means a doubling of intake. We must have more longitudinal data on the effect of calcium supplementation on bone mass gain to be sure about what level we need to increase to and at what age we have to do it.
Dr. Rodriguez Soriano: I would like to bring up another point which is the relationship between acid–base equilibrium and the bone mass. It has been shown that when you give potassium bicarbonate to postmenopausal women, they retain calcium because calcium balance becomes more positive (7). In an unpublished long-term double-blind study, it was found by the same authors that bone density, measured by densitometry, is improved in old ladies who are given potassium bicarbonate. How much do we know about the influence of small changes in acid–base equilibrium on the formation of bone?

Dr. Bonjour: We don’t know much. The acid–base story has been around for many years in adult osteoporosis. Some scientists have proposed that an acid diet would tend to dissolve bone, as can be observed in vitro with bone mineral. But usually it is very difficult in adult pathology to separate the part due to acidosis per se from the part due to other associated factors related to the underlying disease which maintain the acidotic state. As for the environmental determinants of bone mass accumulation during adolescence, I think we know very little. This is why I wanted to emphasize that neither calcium nor physical exercise alone can explain the large variability in bone mass gain; whether some other dietary factor(s) than calcium could play a role in this variability is a very open possibility.

Dr. Ballabriga: You have said that calcium is probably not the whole story. My question is, what is the role of saturated fat intake in the increase in bone density? Adolescent girls who fear obesity tend to limit their intake of saturated fat, and in boys, there may be the same problem because of fear of hypercholesterolemia. Can saturated fat alone increase bone density or is dietary fat a contributor to other micronutrients or vitamin D that could enhance intestinal calcium absorption?

Dr. Bonjour: At the same time as we recorded the calcium intake, we also recorded the intake of macronutrients including total lipids, saturated and unsaturated fats, and glucids. I have played with the data, trying to correct calcium intake for protein and for fat, but as far as I remember, we didn’t find anything that would make the calcium story any more convincing. But still I will go back to the data again since you raised the question.

Dr. Guesry: The intake of phosphate in toddlers and adolescents has about doubled during the last 30 years and you now have a calcium-to-phosphorus ratio of 0.5, which is certainly much lower than recommended. I wonder if you have data relating peak bone mass in adolescents and their previous phosphate intake.

Dr. Bonjour: Yes, we also analyzed the data with respect to phosphate but we didn’t find a coherent relationship between bone mass gain and phosphate intake, which was sufficient in all these children. The calcium-to-phosphorus ratio was also calculated, but we didn’t find a positive relationship with that either. But I agree with you that one reason for difficulty in obtaining a positive correlation between bone density and calcium in the diet is the presence of a nutrient exerting a negative effect. One candidate might be phosphate, but I think the only way to make some progress in our knowledge in this field is to do an intervention study where we test one nutrient and exclude the others.

Dr. Van Staveren: We did a longitudinal study of school children in the Netherlands over 10 years and we also did not find a good relationship between calcium intake and bone mass. But when you look into these data, you can see that although there is a large range in calcium intake, the intake is almost always above the 500 mg per day. I think that some of the factors that inhibit calcium uptake are much more important in the lower range of intakes, below 500 mg per day.

Dr. Bonjour: I am pleased to hear what you have found in the Netherlands. I know data from many other places around the world where a positive correlation between calcium intake
and bone mass gain was not found. I agree with the concept of a threshold which could indeed be around 500 mg.

**Dr. Whitehead:** I think if one is looking for a response to growth or a response to bone density from calcium supplementation, it is in the developing countries that one is likely to find the best response, because of their low calcium intakes.

**Dr. Bonjour:** I will not disagree with you.

**Dr. Leis:** Have you got any experience with ultrasound to estimate bone density in children?

**Dr. Bonjour:** We have just started to evaluate this technique in our unit, studying ultrasound measurements of the calcaneum and also a technique which measures "quality of bone" in the tibia. I have no data personally, but there are data showing that there is a correlation between ultrasound measurements and bone mass determination measured by dual X-ray absorptiometry. There are also some data indicating that ultrasound determinations can predict the prevalence of fracture in a large population. It may be that ultrasound can give a dimension of bone assessment relating to bone strength separately from bone mass.

**Dr. Gruskin:** Recently, Dr. Michael Norman has reported on follow-up in people with X-linked hypophosphatemic rickets who had received equivalent doses of vitamin D and larger doses of phosphate for years, compared to untreated individuals. With ultrasound measurements, he found that a significant proportion of the patients receiving larger doses of phosphate had nephrocalcinosis which was not apparent on conventional X ray. This observation suggests that one ought to look for toxicity in calcium supplementation studies using renal ultrasonography.

**Dr. Bonjour:** There is no evidence that high calcium intake alone, up to 2.5 g per day in an adult, could lead to nephrocalcinosis because you shut off parathyroid hormone, which shifts the calcium from the extracellular to the intracellular compartment. This is why phosphate supplementation, as given to these patients with congenital hypophosphatemic rickets, can be dangerous; it stimulates parathyroid hormone and you can get nephrocalcinosis.

**Dr. Goulet:** During the last 5 years, we have had the opportunity to study some patients on very long-term parenteral nutrition, i.e., for more than 5 years. This has been a longitudinal study using dual X-ray absorptiometry. We have shown that in patients with normal growth velocity there is a cumulative bone mass retardation, without correlation between growth velocity and calcium and bone mass accretion. This means that after many years, there is a very low peak bone mass, and our current explanation for this, after controlling for the vitamin D intake and other factors, is that it could be due to the cyclic nocturnal infusions of calcium and phosphorus which these patients receive. I would like to have your comment on that and on what could be the long-term risk in those patients in terms of early osteoporosis.

**Dr. Bonjour:** There is evidence that the way meals are distributed and the amount of calcium and phosphate in the diet can trigger a greater or lesser degree of parathyroid activity and this could influence bone mass.

**Dr. Goulet:** We assessed for parathyroid status and it was normal, as was the vitamin D status and the metabolism of the vitamin.

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