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Review

Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly

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ABSTRACT

Bone mass is a key determinant of fracture risk. Maximizing bone mineral mass during childhood and adolescence may contribute to fracture risk reduction during adolescence and possibly in the elderly. Although more than 60% of the variance of peak bone mass (PBM), the amount of bone present in the skeleton at the end of its maturation process, is genetically determined, the remainder is likely influenced by factors amenable to positive intervention, such as adequate dietary intake of dairy products as a natural source of calcium and proteins, vitamin D, and regular weight-bearing physical activity. Low calcium and vitamin D intakes are associated with negative effects on bone, including suboptimal PBM acquisition. As suggested by intervention studies, regular intake of dairy products may have positive and possibly sustained effects on bone mineral mass gain, contributing thereby to fracture risk reduction. Further evidence from intervention studies suggests that weight-bearing physical activities, such as jumping, may contribute to bone mineral mass gain in children. Optimizing PBM acquisition through dietary and physical exercise measures may represent a valuable primary method for the prevention of fractures.

Contents

Abbreviations: PBM, Peak Bone Mass; BMC, Bone Mineral Content (in grams); aBMD, areal Bone Mineral Density (in grams per square centimeter); vBMD, volumetric Bone Mineral Density (in grams per cubic centimeter); DXA, Dual energy X-ray Absorptiometry; IGF-I, Insulin-like Growth Factor I; RDA, Recommended Dietary Allowance; RDI, Recommended Dietary Intake.

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Introduction

Osteoporosis and fracture risk

Osteoporosis and its consequential fractures are among the leading causes of morbidity in industrialized countries, and are associated with considerable and growing individual, societal, and economical burden [1–3]. At the age of 50 years, the remaining lifetime probability of suffering any major osteoporotic (hip, distal forearm, proximal humerus, and spine) fracture is 20% for men and 50% for women [4,5]. The key determinants of bone strength and, conversely, of bone fragility are areal bone mineral density (aBMD) and bone structure [6,7]. This is reflected in the World Health Organization (WHO) definition of osteoporosis as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [6].

At any given age, the key determinants of fracture risk, bone mineral mass and bone structure, result from the difference between the amounts of bone gained and lost [1,8]. Following menopause and in the elderly, the amount of bone resorbed usually exceeds the amount of bone formed, leading to a net loss of bone mineral mass. Areal BMD measured by dual energy X-ray absorptiometry (DXA) is an important predictor of fracture risk in women and men after the age of 50 years [9]. Fracture risk approximately doubles with each standard deviation of bone lost from mean PBM [9,10]. According to a computer simulation of the bone remodeling process, the onset of osteoporosis is predicted to be delayed by 13 years if young adult aBMD is 10% higher than the mean [11] (Fig. 1).

PBM acquisition

Childhood is a period characterized by growth, development and maturation of the various body systems, including the skeletal tissue. Bone modeling begins with the development of the skeleton during fetal life and continues until the end of the second decade, when the epiphyseal growth plates are closed and longitudinal growth of the skeleton is completed. During this phase bones are modeled by bone formation and resorption occurring in distinct locations, leading to the various bone shapes in adults [12]. While bone remodeling also starts during fetal life, the highest level of remodeling is achieved during adolescence. Remodeling replaces old bone with new without changing the shape of the bone. This process allows for the preservation of skeletal mechanical integrity (e.g. through (micro-) fracture repair) and the control of calcium homeostasis by releasing calcium into the circulation when necessary [12]. PBM, which is defined as the amount of bone present in the skeleton at the end of its maturation process, is considered to be achieved by the end of the second decade of life [13]. Indeed, prospective observational studies suggest that more than 95% of the adult skeleton is formed by the end of adolescence [14,15]. However, some consolidation could take place during the 3rd decade, particularly in peripheral skeleton in males.

BMD and fractures during childhood and adolescence

Up to half of all children experience a fracture between the age of 5 and 18 years, i.e. throughout growth during which PBM is acquired [16]. The risk of sustaining a fracture is higher in boys than in girls. The most common site affected in both sexes is the distal end of the radius/ulna [17,18]. Children and adolescents with fractures have been shown to have lower BMC, bone size, and bone accrual than nonfractured controls, with low aBMD being a predictor of new fracture(s) [19,20]. Furthermore, the association between bone mineral mass and fracture risk in childhood was shown in a prospective study of a cohort of 6213 children, with an average age of 9.9 years, followed for 24 months [21], and by the findings of a recent meta-analysis [22]. Interestingly, reduced bone size relative to body size and low humeral vBMD in children with fracture compared to nonfractured matched controls were shown to contribute to fracture risk, following either slight, moderate or severe trauma [23], suggesting that fractures in childhood are related not only to the common falls and injuries of that age group, but also to underlying skeletal fragility [21].

Several epidemiological studies have suggested a site- and sex-specific distribution of lifetime fracture incidence with peaks at both puberty and old age [24–27]. A population-based British cohort study showed that the peak incidence of fractures during childhood (boys, 3%; girls, 1.5%) was only surpassed at 85 years of age among women

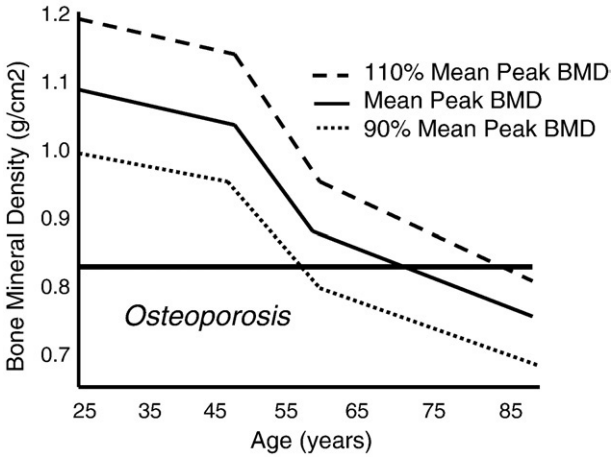

Fig. 1. Simulation of the influence of peak bone mineral mass on the age at which bone mineral density may reach the diagnostic threshold for osteoporosis. Adapted from Hernandez et al. [11], with permission from the publisher.

but never among men [17]. As the relationship between bone mineral mass and bone strength remains valid throughout life [28,29], maximizing PBM may be an important contributor to fracture risk reduction in children as well as in the elderly. There is growing evidence that the consequences of age-related or postmenopausal bone loss on fracture risk will depend on the level of PBM achieved during childhood and adolescence, as well as on the rate of bone loss [11,13,28–30]. Some experimental studies, however, indicate that gains in bone mineral accretion during childhood may only be transient and have triggered the argument that surmises bone mass is ultimately governed by a homeostatic system which tends to return towards a yet-to-be defined set point [31,32]. As acknowledged by the authors themselves, the sustainability of the effects on PBM may depend on the type of intervention as well as its magnitude, timing, and duration. In any case, and although most of today's efforts in fracture prevention have been directed at slowing the rate or postponing the time of onset of bone loss among elderly people, maximizing PBM is a potential primary strategy to prevent osteoporotic fractures later in life [33,34]. In addition, maximizing bone mass during growth may have immediate beneficial consequences by reducing fracture incidence during puberty.

The aim of this review is to discuss those determinants of bone health that are amenable to intervention during childhood, and that may contribute to the primary prevention of osteoporosis and thus to the reduction of fracture risk.

Peak bone mass

Quantitative assessment of bone mineral mass

Bone mineral mass is the only surrogate of bone strength accessible to measurement [35]. Bone mineral content (BMC) and bone mineral density (BMD) are measured by DXA, the method of choice due to the low radiation exposure and its high precision and accuracy [36]. BMC measures the amount of bone mineral in grams. Areal BMD (aBMD) expresses bone mineral content as a function of the projected bone scanned area in grams per square centimeter, while volumetric BMD (vBMD) measures bone mineral content as a function of bone volume in grams per cubic centimeter. vBMD is best assessed by quantitative computerized tomography. An increase in BMC will imply an increase in aBMD if bone mineral mass increases proportionally more than the projected bone area. These elements are important for interpreting data on bone mass changes during childhood when i) bones are growing in length and width, ii) cortical thickness increases as a result of endosteal bone resorption and periosteal bone apposition (increasing bone surface and volume), and iii) bone mineral mass itself increases steadily with a dramatic acceleration during adolescence. For mathematical reasons, aBMD measured by DXA overestimates the "true" vBMD in larger bones, and conversely underestimates it in smaller bones [37]. While BMC increases during growth, vBMD remains stable, suggesting that the increase in BMC is due to an increase in bone size and not primarily to an increase in volumetric bone density [38]. On the other hand, aBMD increases during growth reflecting the increase in bone size so that males and females have similar vBMD values but males have higher aBMD values, mainly due to the larger size of their bones [39]. This suggests that BMC may be a useful measure for assessing bone acquisition, particularly for pre-pubertal children and those in early stages of sexual development [38].

Kinetics of PBM acquisition

The patterns and dynamics of skeletal growth have been well characterized in cross-sectional and longitudinal studies [14,40–45]. In a cross-sectional study, bone mineral mass was higher after puberty than before, with differences observed across sexes and skeletal sites. In males, higher BMC and aBMD at both the lumbar spine and the femoral neck were achieved at an older age than in females [42]. Similar observations were made in the longitudinal Saskatchewan Bone Mineral Accrual Study in which maximal peak BMC velocity was reported at 14 years of age in boys and 12.5 years in girls [45] (Fig. 2). During the 2 years of peak skeletal growth, adolescents acquired over 25% of their future PBM [14,45]. The acquisition of PBM is normally considered to be completed by the end of the second decade of life [14,42,45,46], although a very small proportion of bone consolidation may occur during the third decade, particularly in males [41].

Relationship between aBMD, vBMD, and fracture risk

Low bone mineral mass is already associated with increased fracture risk during childhood and adolescence. In a large prospective

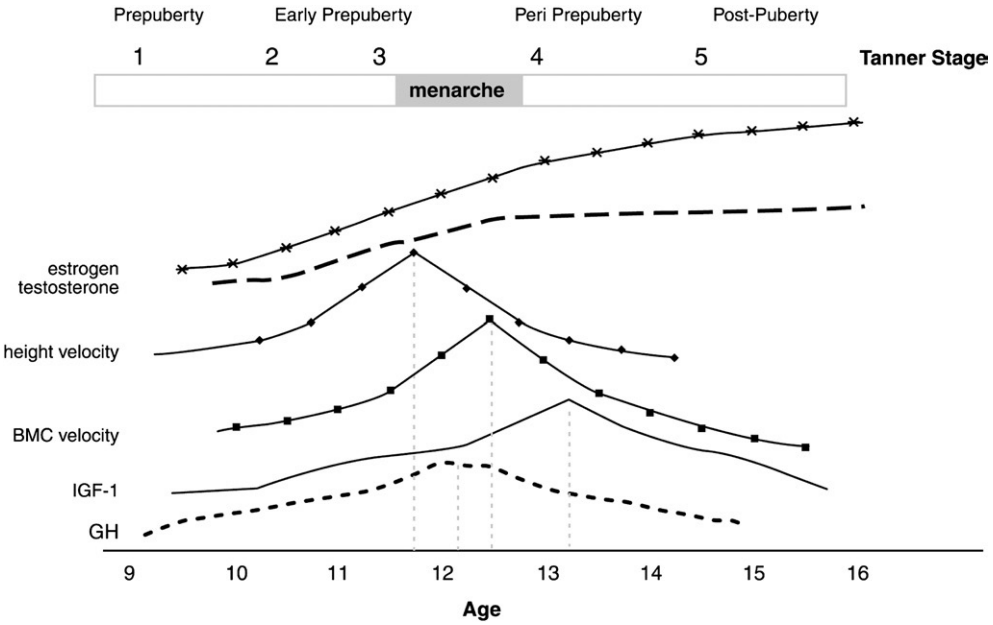

Fig. 2. Peaks for height velocity, BMC velocity, growth hormone amplitude and IGF-I amplitude in relation to age and pubertal stage in girls. Reproduced from MacKelvie et al., Br J Sports Med 2002;36:250–7, with permission from the publisher [172].

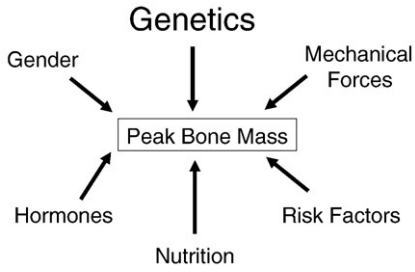

Fig. 3. Determinants of peak bone mass.Genetics account for 60% to 80% of the peak bone mass variance.

cohort study with 6213 children averaging 9.9 years of age and followed for 2 years, fracture risk was related to volumetric BMD, with one SD decrease in vBMD corresponding to a 89% increased risk of fracture [21]. These results were consistent with observations made in a cohort of girls followed over 8.5 years. Girls who experienced a fracture had decreased bone mineral mass gain in the axial and appendicular skeleton and reduced vertebral bone size upon reaching pubertal maturity, suggesting that childhood fractures may be indicative of low peak bone mass and persistent bone fragility [19]. This hypothesis was supported by another cohort study which showed that in girls with previous distal forearm fractures total body, lumbar spine, ultradistal radius, and hip trochanter BMC remained lower than in nonfractured controls 4 years postfracture [47]. As no spontaneous catch-up in BMC gain was observed in longitudinal studies, children who fractured may well develop into adults and elderly with increased risk for a fragility fracture.

Factors influencing bone mineral mass gain and PBM acquisition

Bone mineral mass gain during childhood and adolescence is influenced by many factors including heredity and ethnicity, gender, diet (calcium and protein intake), physical activity, endocrine status (such as sex hormones, vitamin D, growth hormone, and insulin-like growth factor (IGF-I), as well as exposure to risk factors such as cigarette smoking and alcohol intake [30,33,48] (Fig. 3). A 60% to 80% of the variance in PBM is explained by genetic factors [48–50] suggesting that the remainder may be amenable to interventions aimed at maximizing PBM within its genetically predefined variance [13,33,34] . As a 10% increase in PBM corresponds to a gain of one standard deviation in bone mineral density in adulthood, osteoporotic fracture risk may be reduced by up to 50% [48,51] by interventions aimed at maximizing PBM in a sustainable manner.

Effects of calcium, proteins, and dairy products on bone during childhood and adolescence

Calcium intake

Evidence from clinical studies

Numerous associations studies between bone mineral mass (or density) and calcium intakes have been performed in children and adolescents. Most, if not all, suggest a positive association across different populations such as Scandinavians [52,53], Chinese [54–57], UK and US [58–60]. The effect of calcium supplementation on height, BMC and aBMD gain at various skeletal sites (radius, lumbar spine and femoral neck) has also been studied in several prospective randomized placebo-controlled intervention trials (Table 1). Daily intake of calcium-enriched food products (milk-extracted calcium phosphate) during 1 year was compared to placebo with regard to its effects on BMC and aBMD measured by DXA at six sites in 149 healthy ~7.9-year-old girls [61]. Gains in BMC, aBMD and bone area were greater in the group taking calcium-enriched food. The effect of the supplements was greater in the appendicular skeleton (radial and femoral sites) than in the lumbar spine, and greater in girls with a spontaneous calcium intake below the median of 880 mg/day [61]. Similar results were observed in a 1-year study of similar design with 235 boys averaging 7.4 years of age in which supplementation favored aBMD gain at the appendicular skeleton sites, but not at the lumbar spine. Bone size did not differ between groups [43]. In another randomized controlled trial of 3 years duration comparing the effect of calcium supplementation (1000 mg of calcium citrate malate per day) vs. placebo on aBMD in 70 pairs of identical 10-year-old twins whose average dietary intake of calcium approximated the recommended dietary allowance, aBMD increases were significantly higher in the intervention group at the radius and the lumbar spine. The benefit was essentially seen in children who remained pre-pubertal throughout the study [62]. Similar results were reported in another study comparing the effect of 18 months of calcium supplementation (500 mg/day calcium as calcium citrate malate) vs. placebo on aBMD and BMC in 94 girls aged an average 11.9 years at study entry. The authors calculated that the observed increase in BMC translated into an additional 1.3% of skeletal mass per year during adolescent growth [63]. Finally, two recent meta-analyses confirm the beneficial impact

Table 1
Effect of calcium supplements on bone mineral mass accrual (randomized controlled trials).

Study	Calcium supplement	Dose (mg/day)	Duration (months)	Mean age (years)	Sex	Skeletal site*	Difference (%) between Ca-supplemented and placebo groups
Bonjour et al. [61]	Milk extract	850	12	7–9	F	Radius/femoral shaft	1.7/1.2
Cameron et al. [149]	$CaCO_3$	1200	24	10.3	F	Whole body#	3.7
Chevalley et al. [43]	Milk extract	850	12	7.4	M	Femoral shaft	1.3
Dibba et al. [150]	$CaCO_3$	1000	12	10.3	F/M	Radius	3.9
Iuliano-Burns et al. 2006] [151]	Milk mineral/$CaCO_3$	600–800	10	8.9	F/M	Whole body	NS
Johnston et al. [62]	Ca citrate-malate	1000	36	10.0	F/M	Radius/spine	5.1/2.8**
Lee et al. [152]	$CaCO_3$	300	18	7.2	F/M	Radius	2.5
Lee et al. [153]	$CaCO_3$	300	18	7.0	F/M	Radius/spine	1.7/4.6
Lloyd et al. [63]	Ca citrate-malate	500	24	11.9	F	Whole body	2.2
Matkovic et al. [59]	Ca citrate-malate	1000	24	14	F	Radius	NS
Matkovic et al. [88]	Ca citrate-malate	1000	48	10.8	F	Trochanter	3.0
Moyer-Mileur et al. [154]	$CaCO_3$	800	12	12	F	Distal tibia	5.7
Nowson et al. [155]	$CaCO_3$/Ca citrate-malate	1000	18	14	F	Spine	1.6
Prentice et al. [156]	$CaCO_3$	1000	13	16.8	M	Whole body/spine/hip	1.3/2.5/2.3
Rozen et al. [157]	$CaCO_3$	1000	12	14.8	F	Whole body/spine	0.73/0.66
Stear et al. [158]	$CaCO_3$	1000	15	17.3	F	Femoral neck	2.3

* BMD or BMC, assessed by SPA, DXA or pQCT.
\# A significant difference was detected at lumbar spine and total hip after 12 months.
** Only in those remaining prepubertal throughout the study.

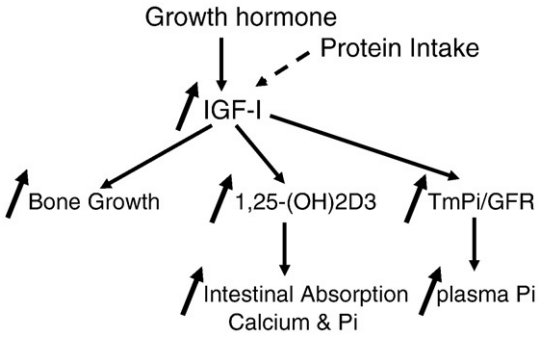

Fig. 4. Dietary protein intakes, IGF-I, and calcium-phosphate homeostasis. IGF-I influences bone growth, bone mass accumulation and mineral homeostasis.

of calcium/dairy products on bone mineral mass during growth. Based on the meta-analysis of 21 randomized controlled trials, the authors of the first report conclude that increased dietary calcium/dairy products, with or without vitamin D, significantly increases total body and lumbar spine BMC in children with low baseline intakes [64]. Similarly, the second meta-analysis of 19 randomized controlled trials including 2859 children aged 3 to 18 years, shows a positive effect of calcium supplementation, with doses ranging between 300 and 1200 mg/day, on total body BMC and upper limb BMD with an effect-size of 0.14 standard deviation for both [65]. Although no fracture primary endpoint trial is available, this reported effect-size may be clinically relevant when considering that BMD is 1% to 5% lower in children with upper limb fractures vs. controls [19,66]. Persistence and compliance of calcium supplements may limit the efficacy of such a measure. The potential cardiovascular adverse events suggested in adults have never been reported in children and adolescents. On the contrary, a 65-year follow-up has shown that childhood diets rich in dairy or calcium were associated with lower all causes of mortality in adulthood, particularly a reduced risk of death from stroke [67].

Persistent benefits following cessation of the intervention

Follow-up studies of these randomized controlled trials have suggested that the effects of calcium supplementation may be sustained after cessation of the intervention. In one study mean BMC, aBMD and bone area remained significantly higher post-treatment in the calcium-supplemented group suggesting that milk-extracted calcium supplements taken during the pre-pubertal period may have sustained effects on PBM acquisition and maintenance in girls for at least another 3.5 years after discontinuation of calcium supplementation [68]. In another study, similar results were observed, however, 1 year after supplement discontinuation in boys [43]. Persistence was not observed 3 years after cessation of calcium supplementation in a cohort of Chinese adolescent girls [69]. It has been previously suggested that the effects of calcium may persist mainly in tall persons, due to their higher calcium demand during the pubertal growth spurt [70]. A recent meta-analysis reports some persistence of calcium effects at the upper limb following the discontinuation of supplementation [65]. These results suggest that pre-pubertal calcium supplementation is a determinant of bone remodeling and possibly of bone modeling. Increased calcium intake before and during puberty may contribute to maximizing PBM within its genetically predefined individual variance.

Protein intake

Role of proteins in PBM acquisition

Dietary proteins provide the body with the necessary amino acids for building the bone matrix. Dietary proteins are also influential factors for bone growth, as they alter the secretion and action of the osteotropic hormone IGF-I (Fig. 4). As such, dietary proteins may modulate the genetic potential of PBM attainment. Low protein intake was shown to have deleterious effects on bone mineral mass acquisition by impairing the production and effects of IGF-I [71,72]. IGF-I promotes bone growth by stimulating the proliferation and differentiation of chondrocytes in the epiphyseal growth plate and through direct effects on the bone forming cells, the osteoblasts. In addition, IGF-I increases the renal conversion of 25 hydroxy-vitamin D_3 into the active hormone 1,25 dihydroxy-vitamin D_3 and thereby contributes to increased calcium and phosphorus absorption in the gut. Furthermore, IGF-I directly increases the renal tubular reabsorption of phosphorus [71].

Evidence from association studies

A positive correlation was found between the level of spontaneous protein intake and BMC/aBMD in pre-pubertal boys [73] (Fig. 5). In the same study, increased physical activity was associated with greater BMC at both axial and appendicular sites under high but not

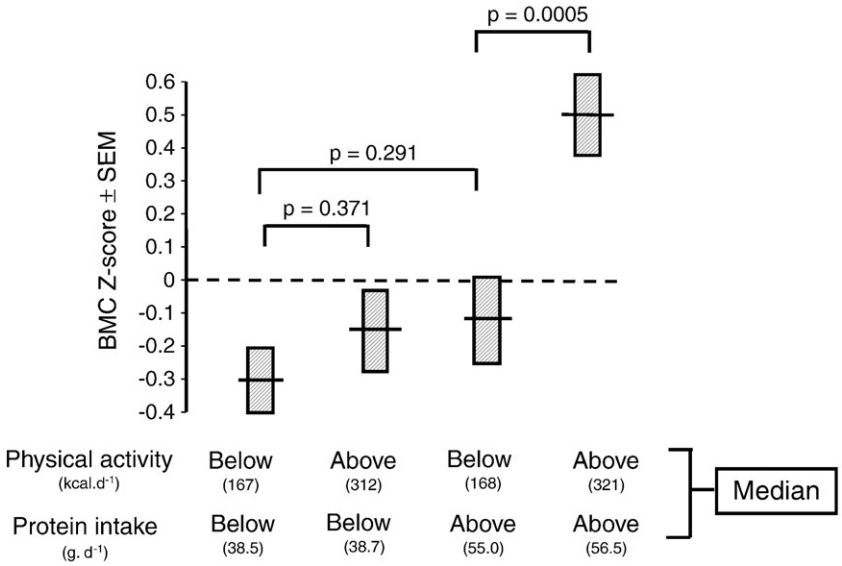

Fig. 5. Interaction between physical activity and protein intake in prepubertal boys. *Y*-axis is the mean of *Z*-scores for radial metaphysis and diaphysis, femoral neck, total hip and diaphysis, and lumbar spine. Reproduced from Chevalley et al. [73], with permission from the publisher.

low protein intake [73]. Anabolic effects on diaphyseal bone were shown with long-term (4 years) dietary protein intake during growth, suggesting that proteins may have positive effects on bone modeling during childhood and adolescence [74]. Two recent studies suggest that the effects of protein intake on bone may depend on the type of proteins [75,76]. Increased dietary intakes of aromatic amino acids, as found in soy, cereals, and dairy products, were shown to lead to higher serum IGF-I levels than were found with increased intake of branched chain amino acids [76]. The increase in urinary calcium excretion observed with aromatic amino acids appears to be related to an increase in intestinal calcium absorption, without any change in bone turnover markers. Based on results from observational studies, we can hypothesize that the dietary intake of particular proteins plays a greater role in bone modeling and in the acquisition of PBM than others.

Evidence from randomized controlled intervention trials

In one randomized study in 8-year-old boys, high milk intake (1.5 l/day) but not high meat intake (250 g/day), and identical protein amounts included in the normal diet for 7 days, reduced bone turnover as assessed by biochemical markers of bone resorption (C-terminal telopeptides of type I collagen, CTx) and formation (serum osteocalcin and bone-specific alkaline phosphatase) versus baseline. After 7 days, the average daily protein intake increased in both groups by 47.5 g, yet the milk group had higher ($P<0.0001$) calcium intake, suggesting that calcium and/or some milk-derived compounds, rather than the total protein intake accounted for the decrease in bone turnover [75].

Dairy products

Role of dairy products in PBM acquisition

Milk and dairy products provide large amounts of calcium and phosphorus, and other components such as proteins, particularly casein, which may enhance calcium absorption and mineral retention [77]. In a balanced diet, about 70% of dietary calcium should come from milk and dairy products, 16% from the few vegetables and dried fruits that are considered as good sources of calcium and the remainder from minerals and drinking water or other discrete sources [77].

Evidence from association studies

There is broad and consistent evidence that long-term milk avoidance is associated with smaller body height as well as lower BMC, aBMD and/or vBMD in growing children [78–85]. Furthermore, pre-pubertal children with low milk intake were shown to be more prone to fractures, mainly of the distal radius, generally occuring after a low energy trauma such as a fall from standing height. In those children who had avoided drinking cows' milk for prolonged periods, fracture risk was 2.7-fold higher than in a matched birth cohort [66,86]. In contrast to widespread preconception, milk consumption was not associated with excessive weight gain or increased body fat but was associated with increased body height [80,85,87]. A positive association between aBMD at the hip and the spine was reported in an observational study of 7 years duration which compared the affects of dairy products, calcium supplementation and no intervention [88]. Regular intake of dairy products throughout adolescence increased aBMD at the hip and the spine, while calcium supplements had no effect at the spine. In addition, dairy products were associated with a significantly greater total and cortical area at the proximal radius suggesting that calcium supplementation essentially effects bone remodeling while dairy products are likely to exert an additional effect on bone modeling, resulting in increased bone growth and periosteal bone apposition [88]. These observations are consistent with earlier reports indicating that children who did not consume any dairy products had smaller stature due to short bones [83]. After menarche, girls with milk intakes below 55 ml/day had significantly lower BMD, BMC, and IGF-I as well as higher PTH compared to girls consuming over 260 ml/day of milk alongside other dairy products [89]. Finally, consuming less than a glass of milk per week during childhood and/or adolescence was associated with a 3% reduction in hip BMC and aBMD and with a 2-fold increase in fracture risk during adulthood [90].

Evidence from randomized controlled intervention studies

The earliest controlled intervention trials were published more than 80 years ago by Lord Orr [91], and by Leighton and Clark [92]. They reported that a daily intake of 400 to 600 ml of milk, in addition to a normal diet, had a positive effect on height gain in Scottish school children over a 7 month observation period. In a randomized controlled trial conducted in 581 children, 190 ml milk daily was associated with a 3% higher height gain by 22 months [93].

Three more recent intervention trials confirmed the beneficial effect of milk/dairy products on bone mineral mass during growth (Table 2). In the first study, the effect of milk supplementation on total body bone mineral acquisition in adolescent girls, with a mean age 12.2 years, was evaluated in an open randomized intervention trial. The intervention group received 568 ml (one pint) of whole or reduced fat milk per day for 18 months, the control group did not. The intervention group had significantly greater increases of aBMD/BMC and serum levels of IGF-I were significantly higher than in the control group [94]. In another open randomized controlled study with healthy 10–12-year-old girls with low dietary calcium intakes at inclusion, increasing calcium intake by consuming cheese (1000 mg calcium daily) appeared to be more beneficial for cortical bone mineral mass accrual than was tablet form supplementation of the same amount of calcium [95]. The largest randomized controlled intervention trial with dairy products was conducted in 10-year-old Chinese girls in nine primary schools. In the first and the second group, the subjects received 330 ml milk fortified with calcium, and with or without vitamin D supplementation, on school days for 2 years. A third group served as control. Significantly higher gains in height, body weight, BMC and aBMD were observed in the groups receiving milk, with or without vitamin D, indicating that school-milk programs during childhood may improve bone growth [96]. In addition, greater

Table 2
Effect of dairy product on bone mineral mass accrual (randomized controlled trials).

Study	Intervention	Mean age (years)	Duration (months)	Sex	Skeletal site*	Difference (%) between intervention and control groups
Cadogan et al. [94]	Milk (568 ml)	12.2	18	F	Whole body	2.9
Chan et al. [80]	Dairy	11	12	F	Spine/whole body	9.9/6.6
Cheng et al. [95]	Cheese (equivalent to 1000 mg Ca)	11.3	24	F	Tibia shaft	4.4
Du et al. [96]	Milk (330 ml)	10.1	24	F	Whole body	4.2
Lau et al. [159]	Milk powder (equivalent to 650 mg Ca)	10.0	18	F/M	Spine/hip	1.4/1.1
Merrilees et al. [160]	Milk (equivalent to 1160 mg Ca)	16	24	F	Spine/femoral neck/trochanter	1.5/4.8/4.8
Zhu et al. [97]	Milk (330 ml)	10.1	24	F	Metacarpal cortical thickness, periosteal diameter	5.7/1.2

* BMC/BMD assessed by DXA, X-ray or pQCT.

increases in cortical thickness measured in metacarpal bone and higher IGF-I concentrations at 24 months were observed in both the milk groups [97].

Consequences of milk displacement from diet

Overall, increased dietary intake of dairy products enhances bone mineral acquisition in children and adolescents and could contribute to maximal PBM. In addition, milk intake at a younger age may instigate similar habits of milk intake later in life [87]. Calcium intakes do not currently meet recommended dietary intakes (RDI) in many countries. In France for example, where the RDI for calcium is 1200 mg/day for adolescents, 41–48% of the boys and 63–73% of the girls consumed less than two thirds of the RDI between 11 and 17 years [77,98]. One of the proposed explanations was that in western diet milk had been displaced by soft drinks and that the displacers were beverages containing caffeine and phosphoric acid, such as cola, which may have additional and direct deleterious effects on bone due to the relative metabolic acidosis [99,100] and high levels of phosphate they provide [101]. This hypothesis was tested in a short-term 10-day study and it showed that high intake of cola along with a low-calcium diet induced increased bone turnover compared to a high intake of milk with a low-calcium diet, suggesting that the current trend towards a replacement of milk with cola and other soft drinks may negatively affect bone health [102]. In 2004, the American Academy of Pediatrics Committee on School Health issued a preventive statement indicating that the displacement of milk consumption by soft drinks resulted in calcium deficiency with an increased risk of osteoporosis and fractures [103].

Effects of vitamin D on bone during childhood and adolescence

The role of vitamin D in bone mineralization

Vitamin D plays a key role in calcium-phosphate homeostasis. Dietary sources of vitamin D (vitamin D_2 or ergocalciferol and vitamin D_3 or cholecalciferol) are scarce and mainly limited to oily fish species; however, vitamin D also has an endogenous origin, as the ultraviolet B radiation from the sun catalyses the conversion of 7-dehydrocholesterol to cholecalciferol in the skin. Vitamin D_2 and D_3 are converted into 25-hydroxy-vitamin D (25-(OH)D) in the liver and subsequently to 1,25-dihydroxy-vitamin D (1,25-$(OH)_2D_3$) or calcitriol, in the kidney. Circulating levels of 25-(OH)D are the best marker of vitamin D status, with a long half life of approximately 30 days. The active vitamin D metabolite, 1,25-$(OH)_2D_3$, is the metabolic effector of vitamin D throughout the body, with a short half life of 4 to 6 h. 1,25-$(OH)_2D_3$ has many established or suspected direct and indirect effects [104], including those with a positive impact on bone mineralization. Indirect 1,25-$(OH)_2D_3$ actions participate to the effect on bone: predominantly increased intestinal calcium and phosphorus absorption, but also inhibition of parathyroid hormone synthesis and secretion, and control of calcium ion channels expression in the intestine and kidney cells. Local actions on bone include increased production of bone proteins, such as osteocalcin and type I collagen, increased production of FGF23, a regulator of phosphate homeostasis, enhanced osteoblast differentiation, and control of osteoclast activity, possibly via a local action on the RANKL-osteoprotegerin system.

Evidence from association studies

Severe vitamin D deficiency (serum level of 25-(OH)D below 15 nmol/l or 6 ng/ml) leads to rickets in children and osteomalacia in adults. The bone deformities and high risk of fractures that characterize these disorders result from impaired intestinal absorption of calcium and phosphorus and secondary hyperparathyroidism, contributing to defective mineralization of bones and cartilage growth plates. Less severe vitamin D deficiency is very seldom associated with rickets, but may be found to be associated with secondary hyperparathyroidism. In a cross-sectional study performed in Finland, 62% of the adolescents had serum 25-(OH)D levels below or equal to 40 nmol/l, which was determined to be the cut-off level below which intact PTH increased [105]. These subjects had significantly lower mean forearm aBMD values, indicating an impact of secondary hyperparathyroidism due to low serum 25-(OH)D levels on bone [105]. Similarly, low 25-(OH)D ($\leq$25 nmol/l) levels have been found to be associated with lower forearm and/or tibial BMD in two other studies of 10–16-year-old Irish and Finnish girls [106,107]. More discordant data, however, have been obtained in association studies considering the BMD or BMC at trabecular bone sites (hip, lumbar spine, femoral neck). So far, one study has shown an association between severe hypovitaminosis D during winter (25-(OH)D levels <20 nmol/l) and a smaller aBMD gain at the lumbar spine and the femoral neck in girls around menarche [108]. But two other studies have failed to show an influence of low vitamin D status on bone mineral density and/or content at the total body, hip, upper femur, and lumbar spine sites in 10–12-year-old Finnish girls and in 16–22-year-old Californian girls [107,109].

Thus, low vitamin D status (below 25–40 nmol/l) may impair bone growth and mineralization at appendicular sites and increase the risk for reduced bone gain at the lumbar spine in girls in a peri-menarcheal stage. To be noticed, such low vitamin D status is far from being rare in Europe, as 25-(OH)D levels below 30 nmol/l have been observed during winter and spring in 30% to 50% of the nonimmigrant children living in Denmark, Finland, Poland, and Russia [107,110–112], and in 17% to 35% of those living in European countries located at lower latitudes, namely France and Moldova (unpublished results), Greece [113], Germany [114], and Switzerland [115].

Evidence from epidemiological and randomized controlled intervention studies

Systematic vitamin D supplementation during infancy has led to a dramatic decrease in the incidence of rickets during the two first years of life. For example, this incidence fell from 20% to 0.03% between 1938 and 1962 in the USA, and from 15–26% to 0.06% between 1950–1960 and 1990 in France. Vitamin D supplementation during infancy may also lead to higher BMC and aBMD at the radial and femoral sites later in life, as shown in 106 Caucasian girls seen at the age of 7–9 years [116]. The daily vitamin D dose recommended to prevent the occurrence of rickets during infancy varies with the country. For example, 10 μg is the RDI in the USA [117], whereas 25–37.5 μg is the RDI for rickets prevention in France [118]. Of interest, both recommendations appear to maintain 25-(OH)D levels in a similar range, 50–100 nmol/l, as shown in French infants with vitamin D doses between 18 and 33 μg/day [119], and in US breast-fed infants receiving 10 μg/day [117].

In older children and adolescents, the recommended daily dose is still a matter of debate, as are the optimal levels of circulating 25-(OH)D that should be maintained throughout the year [120]. Based on the reported increased risk of impaired bone mineralization in children and adolescents with 25-(OH)D levels below 30–40 nmol/l, and on the high incidence of such low levels in temperate countries during winter–spring, one may propose that recommended vitamin D intakes should at least maintain 25-(OH)D levels above this threshold. Using a decision-making abacus with two input variables: summer UV exposure (duration, skin surface exposed, and geographical localization) and vitamin D intake (supplements, diet), it appears that children and adolescents with insufficient sun exposure during summer require vitamin D intakes higher than 8 μg/day to maintain their 25-(OH)D levels above 25 nmol/l [121,122]. In addition, 5–10 μg/day of vitamin D_3 have been shown to be sufficient to maintain the 25-(OH)D levels of Finnish adolescent girls in the summer range [123].

Such supplementation is in the range of the10 μg/day proposed in the USA [116], and results from the few randomized placebo-controlled studies published so far are consistent with these proposals. Indeed, subtotal body lean mass, hip BMC, and lumbar spine BMD in Lebanese premenarcheal girls were enhanced by weekly vitamin D_3 supplements corresponding to a daily intake of 5 or 50 μg/day during 1 year [122]. Similarly, BMC accrual at the lumbar spine and hip was 12–17% higher in mid-pubertal Finnish girls after 1 year of supplementation with 5 or 10 μg/day of vitamin D_3, compared to the placebo group [123].

Whether vitamin D_2 has similar potency on bone health as vitamin D_3 remains unclear, as no intervention study has yet been reported on bone mass accrual in children and adolescents receiving vitamin D_2. The only available data suggest that higher daily doses of vitamin D_2 (10–20 μg) are necessary to prevent the winter occurrence of severe hypovitaminosis D (25-(OH)D below 20 nmol/l) in Finnish adolescent girls [124]. However, comparisons of the relative potencies of vitamin D_2 and D_3 to increase serum 25-(OH)D levels in other populations have shown either lower or equal potency [125]. Differences in the 25-(OH)D used may in part explain the discordant results. Some of the currently used assays insufficiently recognize the D_2 form and therefore underestimate the vitamin D status of subjects receiving vitamin D_2. Thus, more studies using accurate assays are needed to compare the relative potency of vitamin D_2 and D_3 on the vitamin D status and studies are needed to compare the relative potencies of the two vitamin D forms on bone health during growth.

Effects on bone of weight-bearing exercise during childhood and adolescence

The role of physical activity

One of the main functions of the skeleton is to ensure mechanical integrity for locomotion. Throughout life, bone mass and architecture are adapted to the strains produced by mechanical load and muscular activity. Muscle mass and strength have been identified as important predictors of bone strength [126]. Conversely, skeletal unloading due to prolonged bed rest or cast immobilization leads to bone loss [127]. Therefore, weight-bearing physical activity may play an important role in the accrual and maintenance of PBM. The type, intensity, frequency and duration of exercise may influence the outcome [128]. As an example, dynamic loading may be more effective for increasing aBMD than static loading [129] and strain may be more important than the number of loadings [130].

Evidence from association studies

Observational studies suggest that the effects of physical activity on the skeleton may be site-specific depending on the level of skeletal maturity. At Tanner Stage I, physically active girls had a higher BMC and aBMD of the whole body and higher cortical vBMD and thickness at the tibial shaft compared with sedentary girls. At Tanner Stage II, active girls had higher values for BMC and aBMD at the lumbar spine only, suggesting that the most beneficial time for physical exercise to exert its positive effects on bone may be during the earlier pubertal period [131]. Furthermore, the results of longitudinal observational studies during 1 [132] and 3 years [133] conducted in peripubertal and pubertal gymnasts showed sustained skeletal benefits in terms of BMC and aBMD. These responses to high impact mechanical loading throughout all stages of pubertal development suggest that the type and intensity of exercise may exert different effects on bone depending on maturity [172–178].

Evidence from randomized controlled intervention trials

The effects of physical activity on bone have also been studied in several randomized controlled trials (Table 3) [134–142]. Prepubertal 6- to 10-year-old boys and girls were randomized into a "jumping" (two-footed jumps off boxes during school days during 7 months) or control (nonimpact stretching exercises) group. After 7 months, BMC at the femoral neck and lumbar spine, aBMD at the lumbar spine, and bone area at the femoral neck increased significantly in jumpers when compared to controls [134]. The effects on

Table 3
Effect of weight-bearing on bone mineral mass accrual (controled trials).

Study	Intervention	Mean age (years)	Duration (months)	Sex	Skeletal sites[a]	Difference (%) between intervention and control groups
Pre-/early pubertal						
Alvis et al. [173]	Running/jumping/climbing	7.9	24	M	L3	3.0 (per year)
Bradney et al. [161]	Aerobics, weight training	10.4	8	M	Whole body/spine/femoral shaft	1.2/2.8/5.6
Courteix et al. [162]	Exercise (7.2 h/week)	10.5	12	F	Whole body/spine/femoral neck	6.3/11.0/8.2
Fuchs et al. [134]	Jumping	7.6	7	M/F	Spine/neck	3.1/4.5
Hasselstrom et al. [174]	Physical education	6.8	36	M/F	Distal forearm	12.5 (girls) (boys: NS)
Heinonen et al. [163]	Jumping	11.0	7	F	Spine/femoral neck	3.3/4.0
Iuliano-Burns et al. [144]	Jumping	8.8	8.5	F	Tibia	3.0
Linden et al. [175]	Running/jumping/climbing	7.8	24	F	Spine/legs	3.8/3.0 (per year)
Macdonald et al. [176]	Jumping	10.2	11	M/F	Whole body/lumbar spine	1.7/2.7 (boys) (girls: NS)
McKay et al. [141]	Jumping	8.5	8	M/F	Trochanter	1.2
McKay et al. [164]	Jumping	10.1	8	M/F	Proximal femur	2.0
McKelvie et al. [165]	Jumping	10.5	7	F	Spine/femoral neck	1.7/1.6
McKelvie et al. [177]	Jumping	10.3	7	M	Whole body/proximal femur	1.6/1.0
McKelvie et al. [139]	Jumping	9.9	20	F	Spine/femoral neck	3.7/4.6
McKelvie et al. [166]	Jumping	10.2	20	M	Femoral neck	4.3
Morris et al. [146]	Aerobics, weight training	9.5	10	F	Whole body/spine/femoral neck	5.5/5.5/4.5
Petit et al. [147]	Jumping	10.5	7	F	Femoral neck	2.6
Specker et al. [167]	Jumping	3.9	12	F	Leg	9.7
Van Langendonck et al. [168]	Jumping	8.7	9	F	Femoral neck	2.4
Pubertal						
Blimkie et al. [169]	Weight training	16.1	6.5	F	Whole body/spine	NS
Heinonen et al. [163]	Jumping	13.7	9	F	Spine/femoral neck	NS
Nichols et al. [170]	Resistance exercise	15.9	15	F	Femoral neck	2.3
Stear et al. [158]	Exercise in music	17.3	15.5	F	Whole body/spine/femoral neck	0.8/1.9/2.2
Weeks et al. [142]	Jumping	13.8	8	M/F	Whole body/femoral neck	3.6/6.0
Witzke et al. [171]	Resistance training	14.6	9	F	Whole body/spine	NS

[a] BMC/BMD assessed by DXA or pQCT, adapted from Hind and Burrows [143].

Table 4
Key messages for daily practice.

- Bone mass is a key determinant of fracture risk at any age.
- Bone mineral mass gain during childhood and acquisition of Peak Bone Mass during adolescence represent critical windows of opportunity for interventions aimed at maximizing bone mass.
- Calcium, milk proteins, vitamin D and physical exercise are critical for healthy bone development during childhood.
- Regular intake of dairy products and vitamin D as well as regular weight-bearing physical activity, such as jumping, were shown to contribute to maximizing bone mineral mass gain during childhood in association studies and randomized controlled intervention trials.

BMC at the proximal femur were shown to be sustained for up to 7 months [135] and up to 8 years after the intervention was stopped [136,137]. Long-term school-based jumping intervention programs over 2 years in pre-pubertal girls and boys showed similar results, with greater BMC gains at the lumbar spine and femoral neck in the intervention compared with the control group [139–141]. The benefits of the intervention were mostly observed in early pubertal girls. In adolescents (mean age 14 years), a randomized controlled trial of the effects of regular in-school jumping (10 min of jumping activity instead of regular physical education warm up) during 8 months suggested that bone mineral mass accrual may be sex-specific. Whole body BMC was increased in boys and BMC preferentially at the proximal femur and lumbar spine in girls [142]. Finally, in a recent meta-analysis of 22 clinical trials on the effects of physical activity in children and adolescents, all trials (9/9) in pre-pubertal children, 6/8 trials in early pubertal and 2/5 trials in pubertal children reported significant positive effects of exercise on bone, suggesting that weight-bearing exercise may enhance bone mineral gain in children, particularly during early puberty [143]. Interaction with nutritional intakes is also to be taken into account. Indeed, in a single blind, prospective, controlled study in pre- and early-pubertal girls randomized participants to moderate-impact exercise with or without calcium or low-impact exercise with or without calcium, it was reported a multiplicative and site-specific interaction between exercise and calcium at the femur (7.1%, $p<0.05$), a main effect (only) for exercise at the tibia-fibula and a main effect (only) for calcium at the humerus [144]. A more recent study of pre- and early-pubertal boys by the same group demonstrated that exercise and calcium together increased femur BMC by 2% more than either exercise or calcium alone [145].

These results indicate that early and sustained effects of physical activity on bone may depend upon the type and intensity of the physical activity program as well as on a "window of opportunity" (maturity level of the child). Indeed, some studies have found that a physical activity intervention resulted in significant bone mass gains in early pubertal, but not prepubertal girls [147–165]. The American College of Sports Medicine recommends that, based on the consistent evidence from intervention studies implemented as part of school-programs for 7 to 20 months [134,139–141,146,147], physical activity that aims to maximize bone mineral mass in children should include activities that generate relatively high ground-reaction forces, such as jumping, skipping, and running [148]. Because of differences in skeletal maturity, specific exercise intervention may be to be started at a younger age in girls than in boys.

Conclusion

Peak bone mass acquired through bone mineral accrual during childhood and adolescence may be a key determinant of bone health and future fracture risk during adulthood (Fig. 1). While the larger part of the variance of PBM is attributable to genetic factors, some determinants of PBM are amenable to intervention during childhood and adolescence. Increasing daily calcium and protein intake with dairy products, preventing or correcting highly prevalent vitamin D insufficiency, and increasing weight-bearing physical activity all have the potential to improve and sustain bone health and protect against fractures during childhood, adolescence and later in life. Thus, adequate calcium nutrition, good vitamin D status, and weight bearing physical activity are prerequisites for a healthy skeleton during childhood and adolescence (Table 4).

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