# Bone Health Assessment in Pediatrics

## Guidelines for Clinical Practice

Second Edition

Ellen B. Fung
Laura K. Bachrach
Aenor J. Sawyer
*Editors*

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*This second edition of Bone Health Assessment in Pediatrics: Guidelines for Clinical Practice is dedicated to Dr. Elizabeth Szalay, one of our coauthors and most respected colleagues who passed away in December 2014. She was a skilled surgeon, clinician, researcher, and educator in the field of pediatric orthopedic surgery. She not only transformed the lives of many children but her warmth, enthusiasm, and generous mentorship inspired numerous trainees under her leadership. Dr. Szalay was a devoted advocate for underserved youth—Native American children, children with physical disabilities, and those living in extreme poverty. She worked tirelessly to optimize the quality of life for her patients and their families. It is with tremendous respect that her writing is memorialized in this text. We, among many, are very grateful for her unparalleled contributions to healthcare.*

*Ellen B. Fung, Ph.D., R.D., C.C.D.*
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# Foreword

Over the past 20 years, the high interest in pediatric bone disease and the growing body of knowledge on skeletal development have led to the delineation of a new field where clinicians and investigators devote their efforts to the understanding, evaluation and treatment of bone diseases in children. Great momentum was obtained by the development of new non-invasive technologies, and among them densitometry. Such measurements in adult subjects have for a long time brought about unique information with high precision and reproducibility. Their major limitation however is that density results are expressed in two dimensions and extrapolated to represent volumetric density in a 3D bone structure. This is adequate if the size and shape of the studied bone are stable over time. It clearly does not apply to the bones of a growing child wheresize and shape change continuously until growth plates are fused. Thus two-dimensional DXA results had to be adapted to reflect this reality. This challenge has been met as described in details in the first chapters of this book. Interpretation of DXA data using correction parameters to take into account age, sex and body size have generated graphs and tables that are now integral parts of the evaluation of various conditions where bone development and structure are affected. As progress was made, new techniques have emerged that allow for three-dimensional imaging such as QCT, pQCT and HR-pQCT. Now trabecular and cortical bone compartments can be analyzed separately and bone formation evaluated with precision. It may become the equivalent of a non-invasive bone biopsy. Changes in cortical porosity, not captured by DXA will become an important end point in several studies. The only limitation of HR-pQCT is that it can only evaluate appendicular sites due to the amount of irradiation it generates and the design of the equipment. But this also may change in the future. All these considerations and more are covered in details in this Second Edition of *Bone Health Assessment in Pediatrics: Guidelines for Clinical Practice.* As such it represents an indispensable source of information and guidance for any clinician dealing with pediatric bone diseases.

Montreal, QC, Canada — Francis H. Glorieux, OC, MD, PhD

# Preface

Eight years ago, we published the textbook *Bone Densitometry in Growing Patients* to assist clinicians in evaluating bone health in children and adolescents. Since 2007, the field of pediatric bone densitometry has changed dramatically. Despite the emergence of alternative imaging devices, dual energy x-ray absorptiometry (DXA) remains the gold standard method for skeletal assessments in clinical practice. As such, we felt it was important to address some of the changes and new directions in the field with the second edition of the text, slightly modified in title to: *Bone Health Assessment in Pediatrics: Guidelines for Clinical Practice*.

Skeletal health determined in childhood and adolescence influences an individual's lifetime risk of bone fragility. Peak bone mass reached by early adulthood represents the "bone bank" for life. For this reason, optimizing bone acquisition in the first two decades can help prevent osteoporosis. As this awareness of the importance of early bone health has grown over the past decade, so has the concern for young patients facing threats to bone acquisition. These observations have led to greater demands for diagnostic and therapeutic tools to address bone fragility in children and adolescents.

Many of the chapter authors in this text have spent the past decade improving the ability to accurately assess pediatric bone health by DXA through the collection of, large and robust, ethnic-specific reference data sets. Moreover in October, 2013, many of these same individuals came together for the 2nd Pediatric Position Development Conference to draft what are now the 2013 International Society for Clinical Densitometry (ISCD) Guidelines for Pediatric DXA assessment, interpretation, and reporting. As part of these guidelines, a new definition of osteoporosis in pediatrics was adopted, and the relationship between DXA and fracture prediction clarified.

With all marked changes in the field since the last edition of this text, it was difficult to limit the discussion to 13 short chapters. Those that are included were considered to be the most relevant to the practicing pediatrician. Some of the highlights of this edition include an entire chapter on the assessment of infants and toddlers, a chapter devoted to the assessment of children with disabling conditions,

an in-depth discussion of vertebral fracture and its etiologies, and a thorough review of the advantages and limitations of densitometry techniques including DXA, pQCT, HRpQCT, and MRI. New fracture prediction software including Trabecular Bone Score and Finite Element Analysis are described. In this edition, the limitations of DXA are addressed as are the most recent strategies for handling them including proposed DXA adjustments such as height Z-score. Our overarching goal is to provide the basic analysis and evaluation tools necessary for clinicians to optimize bone health for all children especially those with skeletal fragility.

This second edition is designed to provide distilled but multidimensional perspectives needed by clinicians interested in bone health. It is anticipated that those who work with the most challenging patients need practical guidance on how to measure and report on their bone health. Given that DXA will likely remain the recommended clinical method to clinically monitor bone health for the foreseeable future, this text can provide useful tools, images, and calculations necessary to be successful.

Oakland, CA, USA — Ellen B. Fung
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# Acknowledgments

This book is the culmination of work from dedicated experts in the field of pediatric densitometry. First and foremost we owe our deepest gratitude to the chapter authors who took time out of their busy schedules to share their knowledge and expertise in this second edition of *Bone Health Assessment in Pediatrics: Guidelines for Clinical Practice*.

It has been an honor and pleasure to work with many of these authors for a second time. It has also been truly inspiring to engage with the rising stars in this field who are new contributors to this text. The authors' commitment to this work over the past 18 months, despite many professional and personal demands, reflects their deep dedication to improving the skeletal health of all children and adults.

We are grateful for the enduring support and invaluable input from our mentors: Mary Bouxsein, Roland Fischer, Francis Glorieux, Paul Harmatz, James Kasser, Janet King, Mary Leonard, Bertram Lubin, Robert Marcus, Dolores Shoback, Virginia Stallings, Thomas P. Vail, Elliott Vichinsky, Babette Zemel, and our tireless colleagues Richard Capra, Lisa Calvelli, and Marcela Weyhmiller.

In the publishing arena, we thank Michael Griffin, our copy editor, for his patience and endurance with this text, as well as Richard Lansing from Springer Publishing Group for his foresight to consider a second edition of this unique text.

Despite all of the resources, talent, and commitment, we would not have been able to make this second edition a reality without generous support and sponsorship. We would like to thank the S.D. Bechtel Jr. Foundation, the major sponsor of this project and a decade of research and education in the Pediatric Bone Health Consortium. Last, but certainly not least, we are deeply indebted to our families for their patience, support, and unconditional love. We ask for their forgiveness for the many distracted evenings in front of the computer when we could have spent more focused time with them. They provide each of us the creativity, strength, and encouragement on a daily basis, without which we would not have had the inspiration or energy needed to accomplish this work.

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# Chapter 1
# Rationale for Bone Health Assessment in Childhood and Adolescence

**Maria Luisa Bianchi, Aenor J. Sawyer, and Laura K. Bachrach**

## Introduction

Skeletal health in childhood and adolescence influences the lifetime risk of bone fragility. Peak bone mass (PBM) reached by early adulthood serves at the "bone bank" for life. For this reason, optimizing bone acquisition in the first two decades can help prevent osteoporosis. As awareness of the importance of early bone health has grown, so has concern for young patients facing threats to bone acquisition. This concern has led to increased use of bone densitometry in children and adolescents. Dual energy x-ray absorptiometry (DXA) is the recommended method for clinical use because of its speed, safety, precision, availability, and robust normative pediatric data. Although a valuable tool, DXA can be challenging to interpret in growing patients who represent a moving target for study. Variability in patterns of growth and maturity, particularly in children with chronic disease, must be considered when interpreting DXA findings. The goal of this book is to serve as a resource

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for those acquiring, interpreting, reporting, and utilizing densitometry in pediatric patients. DXA and newer 3-dimensional densitometry techniques (quantitative computed tomography, peripheral QCT, and high-resolution pQCT) are discussed in detail.

This chapter underscores the importance of optimizing PBM to reduce the risk of osteoporosis. The positive and negative factors influencing early bone health are reviewed. Finally, the strengths and limitations of DXA in the clinical management of children at risk for bone fragility are outlined.

## Bone Mineral Accrual

Childhood and adolescence are critical periods for establishing lifetime bone health. During the growing years, bones increase in length, width, and cortical thickness. Increases in bone mass (bone mineral content, BMC) and areal bone mineral density (aBMD) accompany these geometric changes. Gains in bone size and mass are most dramatic during adolescence and slow at the end of the second decade as bones reach their adult size and shape. Final consolidation of bone mineral occurs later and PBM is reached early in the third decade. From birth to adulthood, there is about a 40-fold increase in bone mass [1–4].

Two biologically similar but separate cellular processes direct skeletal development mediated by the bone-building osteoblasts and the bone-resorbing osteoclasts [5]. Bone modeling occurs only during the growing years prior to closure of the epiphyseal plates. Bone resorption and formation occur simultaneously or sequentially at different locations, in response to the various stimuli inducing and controlling bone growth and maturation. Bone modeling results in changes in bone size, shape, and mass. Bone remodeling, by contrast, is the process of bone turnover and maintenance which continues throughout life. With bone remodeling, bone resorption and formation occur at the same location without altering bone shape. Bone remodeling serves to replace old or damaged bone with new, healthy bone, thus repairing microfractures and preserving the tissue's mechanical properties. Remodeling also has a major role in the maintenance of the body's calcium homeostasis [5, 6].

Both cross-sectional and longitudinal studies have examined the tempo and patterns of skeletal growth and development [7–11]. Gender-related differences become manifest during puberty. The onset of puberty and peak height velocity occurs at an earlier age in girls, while the duration and magnitude of the pubertal growth spurt are greater in boys. Males eventually achieve a higher bone mass and density than females at both lumbar spine and femoral neck, but their peak values are reached at an older age [9, 11, 12]. In a longitudinal study of over 220 Canadian children aged 8–14 years, peak BMC velocity was reached at $12.5 \pm 0.9$ years in females and $14 \pm 1$ years in males; peak height velocity preceded peak BMC velocity by approximately 6 months [13]. The dissociation between linear growth and bone mass accrual may partially explain the increased rate of forearm fractures that is observed in girls aged 8–12 years and in boys aged 10–14 years [14, 15].

Kirmani et al. studied the changes in micro-architecture and strength at the ultra-distal radius through adolescence with pQCT [16]. Cortical thickness and density decreased from pre- to mid-puberty in girls (but not in boys), then rose to higher levels at the end of puberty in both sexes. Total bone strength increased linearly in both sexes, and after mid-puberty was higher in boys than in girls. The ratio of cortical to trabecular bone volume decreased transiently during mid- to late puberty in both sexes, with cortical porosity at its greatest. These changes would result in a transient reduction in cortical bone strength during mid-puberty which might explain the peak incidence of forearm fractures occurring at this age [16].

An estimated 40–60 % of adult bone mass is accrued during adolescence, with over 25 % of these gains accrued during the 2 years of peak skeletal growth. In both genders, about 90 % of PBM is accrued by 18 years of age with the remaining 10 % in the skeletal consolidation phase during the third decade [11, 17, 18]. About 85 % of the adult bone mass is cortical bone and 15 % is trabecular bone. Changes in these two bone compartments differ during periods of bone accrual and subsequent bone loss with aging [19]. PBM appears to be complete by the end of the second decade in the axial skeleton, which consists of mostly trabecular bone; PBM is achieved some time later in the appendicular skeleton, comprised primarily of cortical bone [20]. The peak density of trabecular bone is strongly influenced by the hormonal and metabolic factors associated with sexual maturation while mineral acquisition of cortical bone is slower [21]. Although the pattern of skeletal development follows these general timelines, the evolution of bone mass/density is subject to great individual variability.

## Determinants of Bone Acquisition and Peak Bone Mass

Bone mineral accrual and PBM are influenced by both heritable and modifiable factors as detailed below. Reaching one's genetic potential requires adequate nutrition, activity, and hormone production. Illness, prescribed medications (corticosteroids, anticonvulsants, etc.), and life habits (alcohol, tobacco, etc.) constitute additional influences [22, 23].

### *Heritability*

Genetic factors account for an estimated 60–80 % of the PBM variance as shown in studies of twins and parent/child pairs [24–26]. For example, one observational study of over 400 family participants reported a 3.8-fold increase in a son's likelihood of low bone density if his father had low bone density. The daughter's risk was increased 5.1-fold if her mother had low bone density [27].

The specific genes responsible for determining bone size and mass and the risk of osteoporosis have not yet been identified with certainty [28–31]. Polymorphisms in the vitamin D receptor (*VDR*) gene, estrogen receptor alpha (*ESR1*) gene, type I

collagen A1 chain (*COL1A1*) genes have been associated with BMD, BMC, and fracture risk but each explains only 1–3 % of the variability in PBM. Genes encoding transforming growth factor-1 (TGF-1), apolipoprotein E, and low-density lipoprotein receptor-related protein-5 (*LRP5*) have also been investigated [32–35]. A large-scale meta-analysis of the genome-wide association studies (GWAS) found that 20 gene loci were associated with BMD but these genes contributed for only 2–3 % of the inter-individual variability of BMD [36].

## *Modifiable Factors*

An estimated 20–40 % of variability in PBM can be explained by modifiable factors such as nutrition and activity. Consequently, the achievement of an individual's full genetic potential of PBM can be influenced by these factors [37, 38]. The fact that the PBM is established in the first two decades of life underscores the importance of early lifestyle on bone health. Osteoporosis can be viewed as a disease of older adults with its roots early in life [39–41]. Bone health appears to begin in utero with calcium transport across the placenta to the fetus. Maternal serum concentration of 25(OH)-D is positively associated with the infant's bone mass at birth [42]. Birth weight, an indicator of healthy fetal development, is associated with bone mass in both early and late adulthood [43]. Conversely, poor early growth has been related to a higher risk of hip fracture in later life [44]. The Southampton Women's Survey [45], a prospective study of over 12,500 initially nonpregnant women aged 20–34 years and their children, has confirmed the importance of early bone health. To date, about 1000 children have been studied by DXA at birth, 4, and 6 years. The results confirm the hypothesis that "there may be critical periods where growth velocity relates very strongly to longer-term measures of bone development, thus offering potential opportunities for early intervention to optimize skeletal strength" [41]. Another mother-offspring cohort study found that fetal weight gain and post-natal catch-up in weight were associated with total-body BMD measured at 6 months of age. Children who remained in the lowest weight tertile after birth were much more likely to have low total-body BMD at 6 months of age [46].

### Nutrition

#### Calcium

Calcium is a key nutrient for skeletal health throughout life, allowing for optimal gains in bone mass during the growing years and reducing bone loss in later life [10, 47]. Calcium appears to be a threshold nutrient with skeletal mass increasing as calcium intake increases until a plateau is reached at which gains are constant. Defining the calcium "threshold" for children of varying ages remains controversial [48]. Estimates of the requirement for calcium come from studies of calcium balance, mineral accrual, and

**Table 1.1** Calcium and Vitamin D—dietary reference intakes

| | Calcium | | Vitamin D[a] | |
|---|---|---|---|---|
| Age | RDA[b] (mg/d) | UL[c] (mg/d) | RDA[b] (IU/d) | UL[c] (IU/d) |
| 0–6 months | (200)[d] | 1000 | (400)[d] | 1000 |
| 6–12 months | (260)[d] | 1500 | (400)[d] | 1500 |
| 1–3 years | 700 | 2500 | 600 | 2500 |
| 4–8 years | 1000 | 2500 | 600 | 3000 |
| 9–13 years | 1300 | 3000 | 600 | 4000 |
| 14–18 years | 1300 | 3000 | 600 | 4000 |
| 19–30 years | 1000 | 2500 | 600 | 4000 |
| Females—Pregnancy and Lactation | | | | |
| 14–18 years | 1300 | 3000 | 600 | 4000 |
| 19–30 years | 1000 | 2500 | 600 | 4000 |

*Table adapted from*: A. C. Ross, C. L. Taylor, A. L. Yaktine, and H. B. Del Valle, *Editors;* Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board; Institute of Medicine. ***Dietary Reference Intakes for Calcium and Vitamin D.*** Washington, DC: The National Academies Press 2011 (ISBN 978-0-309-16394-1 available in PDF from The National Academies Press at *http://www.nap.edu/catalog.php?record_id=13050*) (page 7 and 9)

[a]Vitamin D: 40 International Units (IU) = 1 μg

[b]RDA = Recommended Dietary Allowance: daily intake meeting or exceeding the requirements for 97.5 % of population

[c]UL = Tolerable Upper Intake Level: the highest average daily intake that is likely to pose no risk of adverse effects to almost all individuals in the general population

[d]RDAs have not been established for infants: this value is an adequate average intake (AI) based on observed or experimental intakes

fractures. In 2011, the Institute of Medicine published updated dietary reference intakes for calcium and vitamin D (see Table 1.1) [49], which were subsequently endorsed by the American Academy of Pediatrics [47]. During the critical period for bone acquisition from age 9 to 18, the recommended daily calcium intake is 1300 mg.

Despite persistent controversies about the optimal calcium intake, it is evident that calcium intake before and during puberty can contribute to the maximization of PBM within an individual's genetically determined potential. Several observational studies of children and adolescents in different countries have demonstrated an association between habitual calcium intake and BMC and/or BMD [48, 50–53]. A large, retrospective study of older, white American women also found that a higher milk intake during childhood and adolescence was associated with higher BMC and reduced fracture risk in adulthood [54]. Contrary to previous concerns, a calcium-rich diet in childhood has been linked to a reduced rather than increased mortality in adulthood from stroke [55].

The positive effects of calcium on height and BMC/BMD have also been supported by findings from several prospective randomized placebo-controlled trials [9, 56–58]. The skeletal effects have varied with the amount and source of calcium supplement, the skeletal region, and the age and maturity of the child [48, 57, 58]. Gains are greater at sites rich in cortical (appendicular skeleton) rather than trabecular bone (spine) [48].

Two meta-analyses have similarly confirmed the benefits of calcium supplementation and dairy products on bone mass during growth [59, 60]. The first one summarized 21 randomized controlled trials including 3821 subjects (aged 4–17.3 years) and found that greater calcium intake, with or without vitamin D, significantly increased total body and lumbar spine BMC in children with low intake at baseline [59]. The second one analyzed 19 randomized controlled trials including 2859 subjects (aged 3–18 years) and reported a small, positive effect of calcium supplementation (300–1200 mg/day) for total body BMC and upper limb BMD [60].

Whether the benefits from calcium supplementation are sustained after discontinuation is also controversial. Some studies have detected benefits for one or more years [9, 61] while other data suggest that the effects are lost soon after discontinuation [48]. A meta-analysis of several studies found that benefits of calcium supplementation persisted only at the upper limb [60].

### Phosphorus

Despite the fact that phosphate makes up at least half of bone mineral mass, there is less concern about this nutrient in pediatrics. Phosphorus deficiency is rare because the element is abundant in common foods. In fact, concerns have been raised about overconsumption of phosphorus especially from soft drink consumption. Wyshak et al. found that the incidence of fractures in adolescent girls was correlated with the amount of carbonated beverages consumed [62]. The association between soft drinks and poor bone health is perhaps more likely explained by displacement of milk from diet than by high phosphorus intake [63]. A meta-analysis of 88 studies found an inverse relationship between soda consumption and intake of milk [64].

### Vitamin D

Vitamin D is essential for efficient absorption of calcium. Only 10–15% of dietary calcium is absorbed without vitamin D [65]. With few exceptions (oily fish), natural foods are not a significant source of vitamin $D_2$ (ergocalciferol) or $D_3$ (cholecalciferol). In some countries milk and other foods are fortified with vitamin D while in others, only infants and small children are routinely provided with supplemented products.

The essential role of vitamin D for bone health has been demonstrated by several studies. A longitudinal study of 198 children observed that when mothers had low levels of 25-hydroxyvitamin D (25OHD) during the late months of pregnancy, the children had low total-body and spine BMC at 9 years of age [42]. A 3-year longitudinal study of 171 healthy Finnish girls aged 9–15 years found that girls with severe vitamin D deficiency during puberty may fail to achieve their genetic potential for PBM, particularly at lumbar spine [66].

Vitamin D deficiency is relatively common, particularly in northern countries, in dark-skinned individuals, and in those with inadequate exposure to sunlight. Levels of 25OHD below 30 nmol/L [12 ng/ml] have been observed during winter and

spring in up to 50 % of children living in Denmark, Finland, Poland, Greece, Germany, and Switzerland [66–71]. Vitamin D deficiency is more common in black and Hispanic teenagers, and in winter [65–74]. Obese children and adolescents are also at increased risk, possibly due to vitamin D sequestration in body fat [74–76]. Milder forms of vitamin D deficiency are typically asymptomatic but may still compromise optimal bone growth and mineralization. Vitamin D deficiency, not sufficiently severe to cause rickets, may also lead to secondary hyperparathyroidism.

Severe vitamin D deficiency (serum 25OHD below 15 nmol/L [6 ng/ml]) causes nutritional rickets in children and osteomalacia in adults. Low intestinal calcium absorption and secondary hyperparathyroidism lead to defective mineralization of growth plates and bones, with bone deformities and high risk of fractures. Fortification of infant foods with vitamin D has greatly reduced the incidence of rickets during the first 2 years of life in developed countries [17] but this condition remains a major health problem where vitamin-D–fortified foods are not available. Severe vitamin D deficiency is also associated with reduced bone mass in adolescents [73, 77]. A prospective study of 6712 physically active girls (age 9–15 years) found that greater intake of vitamin D (not calcium or dairy foods) during childhood was associated with reduced risk of stress fractures [78].

### Protein

Adequate protein intake is necessary to build the bone matrix. Proteins also influence the secretion and action of insulin-like growth factor 1 (IGF-1), an osteogenic hormone needed to achieve optimal PBM. Inadequate protein intake adversely affects bone mass acquisition [79, 80]. A study by Chevalley et al. showed a positive correlation between protein intake and both BMC and BMD in pre-pubertal boys. With high protein intake, greater physical activity was associated with greater BMC at both axial and appendicular sites [81]. On the contrary, children with inadequate protein and caloric intake exhibited growth retardation and decreased formation of cortical bone [82].

The optimal type and quantity of protein for bone health remain to be determined [83, 84]. Milk and dairy products are probably the best sources of the calcium and proteins for bone health. Alternative sources of calcium include some vegetables, tofu, and almonds [85]. Long-term milk avoidance is associated with shorter height and lower BMC and aBMD [86–88]. Pre-pubertal children with low milk intake may be at greater risk of fractures, mainly of the distal radius [89, 90]. A 7-year study found regular intake of dairy products to be positively associated with hip and spine aBMD and greater total and cortical area at the proximal radius [91].

## Exercise

The skeleton and muscles are interrelated in a more complex way than simple locomotion. According to the “mechanostat” model of bone growth and bone loss, muscle activity and weight load (gravity) continuously apply forces to the

skeleton [92, 93]. The resulting strains stimulate bone modeling and remodeling. Throughout life, the bone's cellular and biochemical reaction to mechanical strains translates into a continuous adaptation in terms of both bone mass and bone architecture that maintains and optimizes bone strength. Osteocytes imbedded in bone act as mechanosensors, transmitting signals to osteoblasts to build bone [94, 95]. Not surprisingly, muscle mass and strength are important predictors of bone strength [96–99] and conversely, prolonged immobilization and skeletal unloading lead to bone loss [100].

Regular physical activity is a major determinant of the accrual and maintenance of PBM. The type, intensity, frequency, and duration of exercise are all important. Dynamic loading seems more effective than static loading and the magnitude of the strain on bone may be more important than the number of repetitions [101]. Two observational studies of adolescent gymnasts found they had sustained increases in both BMC and aBMD [102, 103]. Several randomized controlled studies in children and adolescents reported positive effects from jumping and other high-impact activities [102–111]. Gains in hip BMC were 3.6 % greater in prepubertal children who completed a 7-month high-impact jumping program than in controls who completed non-impact stretching activities. Significant differences between the groups persisted even after 8 years (1.4 %, $p < 0.05$) [106]. A review of 22 intervention trials in children and adolescents concluded that physical activity had significant positive effects on bone, and weight-bearing exercise may enhance bone mineral gain in children, particularly during early puberty [112].

The sustained benefits of activity are mediated at least in part through changes in bone geometry. A systematic review of 14 intervention and 23 observational studies evaluated the effect of physical activity on bone structure (cross-sectional area, cortical thickness) as well as mass. Results indicated that changes in bone structure rather than bone mass were most often related to significant increase in bone strength. Prepuberty and peripuberty may be the best periods for improving bone strength through physical activity in both sexes [113].

There appear to be additive or even synergistic effects from various lifestyle factors. For example, one study found that physical activity enhanced the response to calcium supplementation at weight-bearing sites [107]. Conversely, gains from physical activity may be blunted in individuals who have inadequate intake of calcium or calories [114].

## Importance of Peak Bone Mass

PBM is recognized as a key determinant of bone health and fracture risk in adulthood and old age. After early adulthood, BMC and BMD remain stable and then inevitably decline with menopause and aging. With enough bone loss, a "bone fragility" threshold is reached where fractures are more likely. Factors that enhance early bone accrual or slow the subsequent bone loss may help reduce the risk of osteoporosis (Fig. 1.1).

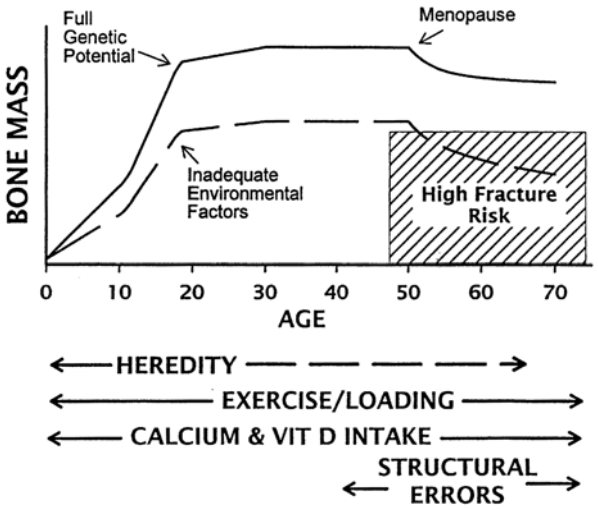


**Fig. 1.1** Diagrammatic representation of the bone mass life-line in individuals who achieve their full genetic potential for skeletal mass and in those who do not. (The magnitude of the difference between the curves is not intended to be to scale.) Along the bottom of the graph are arrayed several of the factors known to be of particular importance. (© Robert P. Heaney 1999, used with permission.) From: Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. Osteoporosis Int 2000;11:985–1009

In older adults, the risk of fracture doubles for each standard deviation (SD) that BMD falls below the healthy young adult mean value. An intervention that results in a 10 % increase in PBM in youth (+1 SD in BMD) could thus reduce an individual's future fracture risk by 50 % [18, 23]. The magnitude of benefit from increasing PBM bone or reducing subsequent bone loss has been modeled [115]: a 10 % increase in PBM would delay by 13 years the time a woman meets criteria for osteoporosis (a BMD value of 2.5 SD or more below the young adult mean). By contrast, postponing the age at menopause or reducing the rate of age-related bone loss would delay osteoporosis by less than 2 years. In summary, optimization of nutrition and activity during childhood and adolescence can be viewed as an important and effective strategy to prevent or delay osteoporosis.

## Threats to Pediatric Bone Health

The expected gains in bone mass and geometry described above can be compromised by a number of heritable or acquired disorders as discussed in more detail in Chap. 4 [17, 116, 117]. Osteogenesis imperfecta (OI), the most common of the genetic disorders of bone, is characterized by increased bone fragility due to reduction in the quantity or quality of type 1 collagen caused by mutations in the *COL1A1* and *COL1A2* genes [118]. Loss of function mutations in the low-density lipoprotein

receptor-related protein 5 (*LRP5*) gene result in reduced bone formation and low bone mass (as seen in osteoporosis-pseudoglioma syndrome) [119]. High bone mineral density syndromes including osteopetrosis and pychnodysostosis are also associated with greater bone fragility [120].

The diverse causes of secondary osteoporosis share one or more skeletal risk factors [116, 117]. For example, Crohn disease [121, 122] and the rheumatologic disorders [123] are marked by chronic inflammation, undernutrition, reduced mobility, and exposure to osteotoxic drugs. In cerebral palsy and Duchenne muscular dystrophy (DMD), reduced mobility results in narrower long bones with thinner cortices that are more vulnerable to fracture [124, 125]. In DMD, glucocorticoid therapy and delayed puberty increase the risk of vertebral fracture. Children with malignancy [126, 127] or undergoing transplantation [127, 128] are vulnerable to fracture during treatment with chemotherapy, radiation, or immunosuppression; hormone deficiencies may follow. Finally, the improved survival in patients with cystic fibrosis [129] and thalassemia [130] has been complicated by diabetes, hypogonadism, undernutrition, and reduced exercise capacity. Depending upon age at onset and disease severity, these chronic conditions can impair bone growth and mineral acquisition with or without secondary bone loss. The potential for recovery from these skeletal complications depends upon the course of the acquired disease and the age of the patient.

Even apparently healthy children and teens with a history of low-trauma forearm fractures appear to be at increased risk for future bone fragility. When compared with children without a history of forearm fracture, children who fracture have lower bone mass, increased body fat, and less physical activity [131]. They have been shown to have a greater incidence of future fracture not only during childhood [131] but as adults as well [132].

Bone densitometry is an important tool to monitor the skeletal effects of these genetic and acquired disorders. Specific indications for ordering a bone density study for patients with these conditions are discussed in detail in Chap. 4. The International Society of Clinical Densitometry (ISCD) Position Development Conference (PDC), a working group of pediatric bone experts, generated comprehensive guidelines for DXA use in 2007 [133]. These guidelines were revised in 2013 to recommend that densitometry be considered when the patient might benefit from intervention and when the densitometry results would influence management [134].

## Densitometry as a Diagnostic Tool

Bone densitometry was developed as a noninvasive means to assess skeletal status and aid in identifying patients at greatest risk for fracture, ideally before fractures occur. In older adults, densitometry has proven useful in predicting fracture risk, thus guiding clinical management. In fact, low BMD is sufficiently linked to the likelihood of fracture in post-menopausal women that it can be used as part of the

diagnostic criteria for osteoporosis. Older patients with a BMD that is equal to or more than 2.5 SD below the young adult mean (T score of −2.5) are diagnosed with "osteoporosis." Densitometry results have been combined with clinical variables (including age, height, weight, prior fractures, glucocorticoid use, smoking, alcohol intake, and others) to create a Fracture Risk Assessment Tool (FRAX). FRAX may provide a more precise estimate of the risk that an adult patient will have a hip or other fracture in the next 10 years than DXA alone [135].

Accurately identifying pediatric patients at greatest risk for fracture is especially important because treatment options are limited for younger individuals [116]. However, the interpretation of DXA data is more difficult and its role in fracture prediction less certain than in adults. In part this reflects the challenges of measuring bones that are changing in size, shape, and mass throughout the first two decades of life. The tempo of skeletal development varies among individuals, depending on pubertal development and skeletal maturation, and can be altered by illness. BMD measurements by DXA are 2-dimensional (BMC/bone projection area) and the results are influenced by bone size: this means that, in the presence of equivalent "volumetric" BMD (BMC/bone volume), children with smaller bones will apparently have lower BMD by DXA than children with larger bones [134]. Therefore it is important to account not only for sex, age, and ethnicity, but also for pubertal development, skeletal maturation, and bone size when interpreting BMD, particularly if growth and puberty have been altered by chronic disease. This may include adjustment for height Z-score or for skeletal maturation (bone age) as discussed in more detail in the Chaps. 6 and 7.

The association between bone densitometry and fracture risk in pediatrics is less well established than in adults. Furthermore, there is no established FRAX tool for younger patients to consider the contribution of clinical risk factors. The 2013 ISCD PDC guidelines included a comprehensive review of the current literature linking bone densitometry to pediatric fractures [136]. Most studies to date have explored which DXA parameter(s) best correlated with fractures after low- or moderate-trauma in healthy youth, because fractures are common; 50 % of boys and 30 % of girls will sustain at least one broken bone during childhood and adolescence, most commonly in the upper limb [137]. These studies found that low whole-body BMC or BMD corrected for bone size as well as low bone area for body size, were most strongly correlated with fracture risk [138]. However, even when the best estimates of skeletal mass and size from DXA and pQCT were combined, the predictive value for fractures was limited. The area under the receiver operator curve linking fracture to various densitometry measures ranged from 0.56 to 0.59, distinguishing those with forearm fractures from controls without fractures little better than chance alone [139]. A study using high-resolution pQCT detected alterations in bone microarchitecture associated with an increased risk of low-trauma forearm fractures, suggesting that this newer 3-dimensional methodology may offer more insights into fracture risk [140].

Extrapolating from observations made in healthy youth may not be appropriate for those with chronic illness. Unlike healthy youth who are most likely to sustain upper extremity fractures, children with immobilization disorders such as cerebral

palsy or DMD more commonly fracture the lower extremity [141]. For these patients, BMD measured at distal lateral femur is more predictive of fracture than spine BMD. By contrast, younger patients with acute lymphoblastic leukemia (ALL) face a greater risk of vertebral compression fractures. One study found that 16 % of patients with ALL had at least one vertebral fracture at diagnosis [142] and an additional 16 % sustained an incident spine fracture during the first year of chemotherapy [143]. Spine BMD was highly correlated with fracture risk with an 80 % increased odds of vertebral fracture for every SD that spine BMD fell below expected mean for age [143].

After considering the limitations of densitometry to predict pediatric fractures, the 2007 PDC guidelines concluded that "the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometry criteria alone" [133]. In 2013, criteria for the diagnosis of osteoporosis were expanded to include a child or teen who sustains one or more vertebral compression fractures without local bone disease or high-energy trauma [134]. Measuring BMD in these patients can add to the assessment but is not required. Alternatively, osteoporosis can be diagnosed in patients with a combination of low bone mass (BMC or BMD more than 2 SD below the mean for age) and a significant fracture history (two or more long bone fractures by age 10 years, or three or more long bone fractures before age 19).

Although a single BMD measurement cannot be used to diagnose osteoporosis in children, densitometry is considered a valuable part of a comprehensive skeletal health assessment. Such an evaluation includes a review of prior chronic illness, medications, nutrition, activity, fracture history, and family history which can help to identify potential risk factors for bone fragility [116]. Recommended laboratory tests include a complete blood count, sedimentation rate, serum calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone, 25OHD, blood urea nitrogen (BUN), creatinine, celiac screen, and urinary calcium to creatinine ratio. In addition, measurement of sex, thyroid, and growth hormones and genetic testing for OI may be indicated depending upon the clinical situation.

## Future Directions for Densitometry

The future role of DXA in the management of pediatric patients appears promising, bolstered by advances in two areas of clinical investigation. Valuable insights have come from studies comparing DXA findings with those using the newer 3-dimensional densitometric techniques (discussed in detail in Chap. 11). Quantitative computed tomography (QCT), peripheral QCT (pQCT), and high-resolution pQCT (HRpQCT) capture elements of bone microstructure, geometry, and volumetric BMD not possible with DXA. These devices can also evaluate the trabecular and cortical compartments of bone separately. QCT, pQCT, and HRpQCT remain largely research tools because of a lack of standardized protocols for acquiring and analyzing scans, cross-calibration problems between devices, and the