# Pediatric assessment of skeletal growth

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## INTRODUCTION

Childhood encompasses major changes in sexual development and body composition, which are highly variable and influenced by many genetic, hormonal, nutritional, environmental and socioeconomic factors[1]. In the skeleton, these changes include the maturation, longitudinal growth and acquisition of bone.

## SKELETAL MATURATION

Skeletal maturity is a measure of bone development based primarily on the size, shape and degree of mineralization of the epiphyses and degree of closure of the physeal plates. Assessments of skeletal maturation are frequently used as a diagnostic tool to evaluate clinical conditions associated with generalized growth abnormalities, to monitor response to medical treatment and to determine the growth potential of children. Although measures of skeletal maturation are often confused with measures of skeletal growth, maturation and growth reflect different processes; growth represents a quantitative increase in size or mass, while maturation is a sequence of changes that lead to a highly organized, specialized and mature state. Skeletal maturation is a temporal process that, while expressed in years and months, is only loosely linked to chronological age. Moreover, skeletal maturation is only weakly related to bone size. Indeed, chronological age associated with full skeletal maturity varies greatly among subjects, and children with the same bone age may have very divergent bone dimensions.

There are several methods to assess skeletal maturity, but the most commonly used in clinical practice are the atlas-based technique of Greulich and Pyle[2], followed by the Tanner-Whitehouse bone-specific scoring technique[3] and the Fels method[4].

All use left hand and wrist radiographs to estimate bone age, but the former differs in concept and method from the latter two. The Greulich-Pyle atlas is founded on the assumption that the skeleton matures in a uniform fashion and is based on a reference collection of radiographs from normal Caucasian children of high socioeconomic status of different chronological ages[2]. With the advent of digital imaging, multiple attempts have been made to develop image-processing techniques that automatically extract the key morphological features of ossification in the bones. However, the design of computer algorithms capable of automatically rendering bone age has been impeded by the complexity of evaluating the wide variations in bone mineralization tempo, shape and size encompassed in the large number of ossification centers in the hand and wrist. Recently, these obstacles were circumvented through the selection of an alternative approach: the creation of artificial, idealized, sex- and age-specific images of skeletal development. The models were generated through rigorous analyses of the maturation of each ossification center in the hands and wrists of healthy children and the construction of virtual images that incorporate composites of the average development for each ossification center in each age group[5].

As an alternative to atlas-based techniques, other methods were developed that independently assess the maturation of each bone. The result of such a system would provide maturity standards for each bone considered. A diffuse method based on these principles was conceived by Tanner and Whitehouse and named TW after their initials. The original system (TW1) was refined and published as TW2 and, recently, as TW3[3]. They defined a series of eight maturity indicators for each bone of the hand and wrist and nine for the radius. These maturity indicators were then evaluated not in relation

to chronological age, but in relation to their appearance within the full passage of each specific bone from immaturity to maturity. The Fels method is less frequently used[4].

Females, at any age, have advanced bone age when compared to boys. The difference is present at birth and persists throughout growth, although it is slightly more pronounced after the onset of puberty[2, 6]. Moreover, the skeletal maturation process lasts longer in boys than in girls. The reasons for these gender discrepancies in skeletal maturity remain unknown. For both sexes, however, the rate of skeletal maturation and the pubertal stage of development are clearly related. Conditions that delay skeletal maturation are associated with a postponed onset of puberty[7], while conditions that accelerate skeletal maturation advance the onset of pubertal development[7]. This synchrony between different maturational processes has suggested the concept of 'tempo' to refer to the whole process of maturation[8]. This concept is challenged by the observation of a lack of correlation between skeletal age and chronological age at the onset of puberty. This finding seems, thus, to contradict the notion that skeletal maturation governs the onset of puberty.

## BONE MEASUREMENT TECHNIQUES IN CHILDREN

The development of precise non-invasive methods for measuring bone mineral content has significantly improved our ability to study the influence of genetic and environmental factors on the attainment of bone. These techniques have not only helped to quantify the deficiencies in bone acquisition associated with pediatric disorders, but have also improved our understanding of the childhood antecedents of a condition that manifest in adults - osteoporosis.

Dual-energy x-ray absorptiometry (DXA) is, by far, the most widely used technique for measuring bone acquisition in children due to its low cost, minimal radiation exposure, accessibility and ease of use. The availability of DXA has resulted in many large-scale studies of the genetic and environmental determinants of areal bone mineral density (aBMD) in healthy children. Although DXA studies in pediatrics have provided much information regarding changes in aBMD over time, there is still considerable confusion over the interpretation of DXA measures. Most growth-related increases in DXA aBMD values are due to increases in the size, rather than the density, of the bone, and gender differences in aBMD values are also largely due to greater bone size in males[9]. The confounding effect of skeletal geometry on DXA measures is gaining much recognition. Recently, it was suggested that major errors in interpretation occur when using this technique in pediatric populations, leading to the over-diagnosis of osteoporo-

sis in growing subjects. Indeed, several investigators have proposed that osteoporosis should not be diagnosed based on DXA densitometry criteria alone[10, 11]. In a recent study, vertebral bone density was measured using both DXA and computed tomography (CT) in 400 children (100 each of healthy and sick boys and girls)[12].

The results indicated that DXA measures of aBMD underestimate bone accretion in children and adolescents. On average, three times as many subjects were determined to have low bone density (Z-score < - 2.0 for chronological age) by DXA than by CT; this was true for both healthy (2% versus 7%) and sick (10.5% versus 31%) children.

Attempts to overcome this disadvantage with the use of correction factors; i.e. the squared root of the projected area, the height of the subject, the width of the bone, assuming the cross-sectional area of the vertebrae is a cube, a cylinder with a circular base or a cylinder with an elliptic base area[13], etc., are subject to error, as there is no closed formula that defines the size of the vertebrae. Similarly, formulas have been proposed for the femur and the mid-radius, which are also prone to error, especially during growth when there are changes in the size, as well as the shape, of the bone[13].

While DXA and CT Z-scores were related, almost 50% of the variability remained even after age and anthropometric measures were taken into account. Hence, many children are identified as having low bone density by DXA, but not by CT. In contrast, quantitative CT (QCT) using conventional CT scanners or peripheral QCT (pQCT) scanners provide three-dimensional images, allowing for volumetric density measures, an evaluation of bone morphology and an independent assessment of trabecular and cortical bone. Because of its porosity and large surface area, trabecular bone has greater turnover and is a better indicator of bone remodeling than cortical bone. Trabecular bone density determinations by pQCT are commonly obtained by a single scan at a relative location, such as 4 or 8% length of the radius or tibia[14, 15], or a fixed location, such as 10mm from the end of the growth plate[16]. Whereas available data indicate that the short-term reproducibility of these measurements is excellent[13], positioning is critical and, due to the variability of trabecular bone density throughout the metaphysis, any offset in the location to be scanned would significantly influence the values obtained[17]. Additionally, the large range of metaphyseal morphology among subjects, diseases and ages limits comparative cross-sectional studies and interpretation of the same scan location in longitudinal examinations.

Previous studies using pQCT in children have investigated the effects of age- or maturity-related

growth, gender differences, physical activity, disease, geometry and strength[14, 15,18-20]. These studies used a variety of methods, such as measurements at 4 or 10% length of the radius or tibia or at a fixed length 10mm distal to the growth plate. More recent studies, using high-resolution pQCT, have scanned 9-mm-thick sections of long bones to assess trabecular microarchitecture[21]. Overall trabecular mean density and the gradient in trabecular bone density from the physeal plate to the shaft of the bone vary among growing subjects, accounting for the large infra- and inter-subject variability in bone density measures. Subjects in this study showed a substantial range of variability from a 1-mm offset slice positioning with an average of 6.9 mg/cm3 or 16.8%. In addition, longitudinal assessments showed that the slopes of the density curve drastically changed in some children, even over a short period of 6 months.

The results of a recent study highlight the limitations of current pQCT methodology using single scans as outcome measures in cross-sectional and longitudinal studies assessing trabecular bone density, and highlight the need for developing pQCT acquisition techniques that provide more reproducible determinations by examining the entire length metaphysis[22].

## SKELETAL CHANGES DURING GROWTH

Skeletal size and shape change dramatically during the pubertal period due to genetic, hormonal and mechanical influences. Bone growth involves changes in length and width by means of longitudinal bone formation and periosteal bone formation versus endosteal bone resorption, respectively.

Longitudinal bone growth occurs through the addition of cartilage tissue to the growth plates at the proximal and distal ends of the long bones and vertebrae[23].

The major systemic hormones that regulate longitudinal bone growth during childhood are GH and IGF-I, thyroid hormones and glucocorticoids and, during puberty, sex steroids. For decades, it was accepted that estrogen, in girls, and androgen, in boys, were the primary sex steroids regulating pubertal growth. This vision has been radically changed recently and now it is clear that both androgen and estrogen play important roles in regulating boys' longitudinal growth.

Bone mass increases throughout childhood and adolescence and reaches its peak shortly after sexual and skeletal maturity. The greater bone mass in men than women has been documented by means of neutron activation analysis, measurement of the calcium content of selected regions of the skeleton, and the techniques of radiogrammetry and absorptiometry[24-26]. Of the two components of

bone mass, bone density and bone size, the latter is responsible for the gender differences in bone mass. Neither CT measures of the tissue density of cancellous bone (a reflection of the size and number of trabeculae), nor CT values for the material density of bone (a reflection of its degree of mineralization) differ substantially between men and women[27, 28]. Differences in morphology of cancellous and cortical bone must be considered for the appropriate interpretation of bone density data. Cancellous bone exists as a three-dimensional lattice of plates and columns (trabeculae). The trabeculae divide the interior volume of the bone into intercommunicating pores, which are filled with a variable mixture of red and yellow marrow. Because of the relatively small size of trabeculae when compared to the pixel, the CT unit of measurement, values for cancellous bone density reflect not only the amount of mineralized bone and osteoid, but also the amount of marrow per pixel[29]. Similar limitations apply to in vitro determinations of the volumetric density of trabecular bone which are obtained by washing the marrow from the pores of a specimen of cancellous bone, weighing the bone and dividing the weight by the volume of the specimen, including the pores. Bone density determinations of cancellous bone are, therefore, directly proportional to the bone volume fraction and inversely proportional to the porosity of the bone. The relatively large coefficient of variation for values of cancellous bone density reflects the considerable variation in the dimensions of the pores throughout the vertebral body.

In contrast, the cortex in the long bones is frequently sufficiently thick to circumvent volume averaging errors[30]. At these sites, measurements of cortical bone density reflect the material density of bone and are primarily based on the degree of mineralization on the cortex. These measurements are analogous to in vitro determinations of the intrinsic material density of bone, which are commonly expressed as the ash weight per unit volume of bone. On average, values for cortical bone density are eight times higher than those for cancellous bone density, a finding consistent with histomorphometric studies, indicating an equivalent difference in the porosity of these two structural organization forms of bone tissue. Otherwise, cancellous bone can be viewed as a porous structure comprised of bone tissue with the same mechanical properties and composition as cortical bone[31].

Regardless of gender, the tissue density of cancellous bone increases during puberty (Figure 1). Although the factors that account for the increase in cancellous bone density remain to be determined, it is reasonable to suspect that they are, in part, mediated by the actions of sex steroids. It should be stressed that neither before nor after completion of puberty does cancellous bone density (CBD) differ

in men and women and that the small gender differences in the temporal sequence of CBD likely reflect gender differences in the appearance of sexual characteristics and accelerated growth spurt. While, for both sexes, growth acceleration begins in early adolescence, peak growth velocity in boys is typically reached 2 to 3 years late, and boys continue growing for approximately 2 to 3 years longer than girls[32] (Figure 1). Interestingly, the differences between males and females in the commencement of increases in CBD parallel the differences in the tempo of peak height velocities.

Gender differences in bone mass are a result of differences in bone size that evolve during growth[28, 33]. Several reports indicate that, throughout childhood and adolescence, girls have smaller vertebral body dimensions compared to boys of similar age, degree of sexual development and anthropometric measures[9, 33, 34]. On average, the cross-sectional area of the vertebral bodies is 11% smaller in prepubertal girls than in prepubertal boys matched for age, height and weight[9, 33]. While it is commonly believed that sex differences in skeletal morphology and physiology occur at or around puberty[35], this notion is challenged by the finding of sex differen-

ces in bone size prior to the pubertal period[36, 37]. The gender disparity increases with growth and is greatest at skeletal maturity, when the cross-sectional dimensions of the vertebrae are about 25% smaller in women than in men, even after taking differences in body size into consideration[28].

The smaller vertebral size is probably key to explain the four- to sevenfold higher incidence of vertebral fractures in elderly women, as compared to men[38]. Vertebral size has been demonstrated to be an important determinant of vertebral fractures in elderly women with osteoporosis. A small vertebral body imparts a mechanical disadvantage that increases the stress within the spine and becomes increasingly important as bone density declines with age[39].

In the appendicular skeleton, cross-sectional growth is primarily related to body weight. Some reports indicate that the cross-sectional and cortical bone areas of the femoral shaft do not differ between males and females matched for age, height and weight[9], a notion consistent with analytical models proposing that long bone cross-sectional growth is strongly driven by mechanical loads[40]. In contrast, other studies suggest that boys have
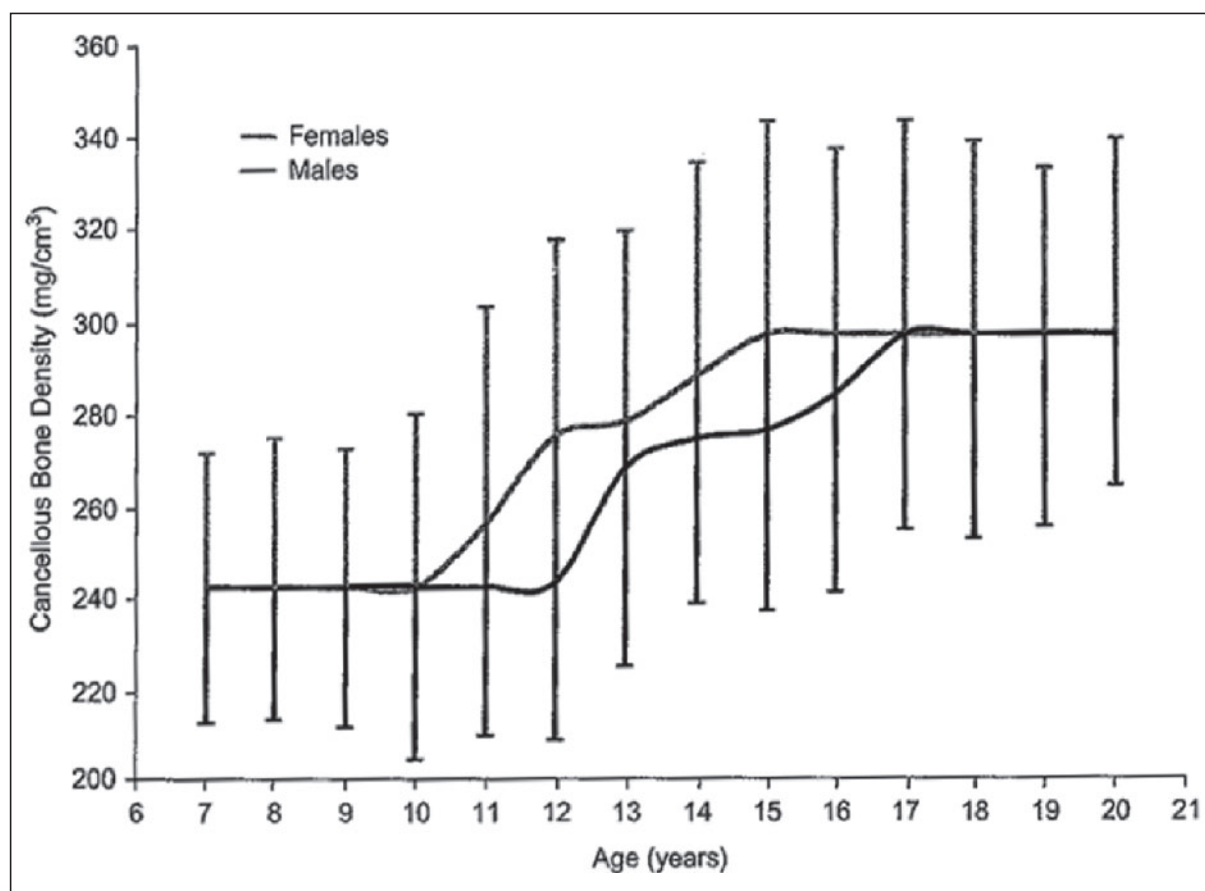


Figure 1. Mean and standard deviations of vertebral cancellous bone density (CBD) in males and females. CBD increases and reached peak values earlier in females than in males.

larger femur cross-sectional area and cortical bone area than girls, measured both with QCT and magnetic resonance imaging[41] and that the total bone cross-sectional area and the cortical area measured at the tibial midshaft by pQCT are greater in boys than in girls during puberty[19]. Like in the actual skeleton, larger bone dimensions in the appendicular skeleton confer a greater mechanical resistance to stress, thus reducing fracture risk in males.

The greater male bone size primarily results from enhanced periosteal bone formation, affected by both androgen and estrogen[42]. Periosteal bone formation is significantly reduced following androgen deficiency in growing male rats, while it is increased in estrogen-deficient female rats, leading to the traditional view of stimulatory androgens in males versus inhibitory estrogens in females on periosteal growth[43]. The available data indicate that periosteal bone formation in males may not be solely dependent on androgen action, but also, at least in part, on estrogen action[44].

## PEAK BONE MASS

The amount of bone in the skeleton, at any age, is the result of the amount of bone gained during growth, from uterine life to skeletal maturity, and the loss of bone that occurs with aging. Bone acquisition during adolescence is the main contributor to peak bone mass (PBM) which, in turn, is a major determinant of osteoporosis and fractures, most commonly in the vertebrae[45], in the elderly. Since current treatment for osteoporosis in elderly subjects does not significantly restore loss of bone even after prolonged treatments, efforts are being directed toward developing preventive measures that increase bone mass before it reaches its peak.

Because of difficulties in longitudinally studying subjects from childhood to an elderly age, the contention that senile osteoporosis is the result of inadequate bone acquisition during growth remains unproven. This notion is supported, however, by data showing that there is a strong resemblance between mother-daughter bone traits and that this resemblance is present even before the daughters have begun puberty[46, 47]. Additional support for this concept comes from the knowledge that genes associated with the normal variations in bone mass in elderly women are also related to variations in bone density in children[48-50]. If bone loss were the exclusive determinant of late-life bone mass, one would not expect such a strong resemblance in bone traits between girls and their mothers or an association between candidate genes and bone mass to be depicted in childhood. Data from previous investigations, showing strong correlations between yearly bone mass measurements in prepubertal girls, suggest that bone traits can be tracked during growth[46]. Thus, the genetic

control of bone phenotypes associated with fragility fractures in the elderly appears to be expressed very early in life and is tightly maintained throughout childhood and adolescence.

The time of life in which PBM is attained has been the subject of considerable controversy, with estimates for the axial skeleton ranging from soon after the completion of sexual and skeletal maturity at the end of the second decade to the fifth decade of life. Moreover, it is likely that the timing of peak values differs between the axial and appendicular skeletons.

The results of a recent study in the axial skeleton indicate that CT values for vertebral bone mineral content and bone density reach their peak around the time of sexual maturity and cessation of longitudinal growth. In contrast, DXA values for vertebral bone mineral content and bone mineral density continue to increase beyond sexual and skeletal maturity (Figure 2). These studies corroborate anatomical data indicating trabecular bone loss as early as the third decade[27, 51, 52].

In the appendicular skeleton, the range of ages published in cross-sectional studies for the timing of PBM has varied significantly from 17-18 years of age to as late as 35 years of age[53, 54]. Longitudinal
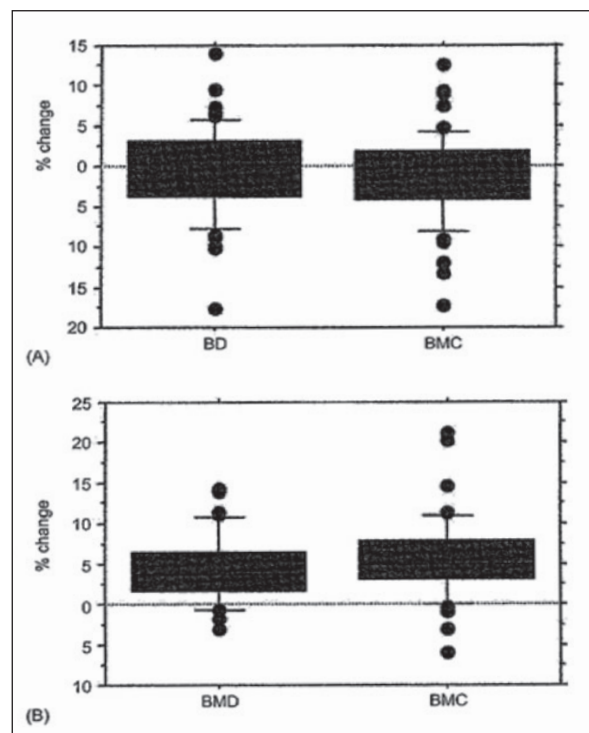


Figure 2. Box and whisker plots of CT cancellous bone density (BD) and bone mineral content (BMC) of the third lumbar vertebra (A) and DXA values for bone mineral density (BMD) and BMC (B) showing no changes between baseline and follow-up values by CT, but highly significant changes when using DXA.

DXA studies indicate that the rate of increase in skeletal mass slows markedly in late adolescence and that peak values in the femoral neck, like those in the spine, are achieved near the end of puberty in normal females[55-57]. It should, however, be stressed that, in both men and women, the cross-sectional dimensions of the long bones in the appendicular skeleton continue to grow throughout adulthood and into old age by subperiosteal bone apposition. This increase in bone width occurs in all sample populations studied[58].

## CONCLUSION

The main areas of progress in osteoporosis research during the last decade have been the general recognition that this condition, which is the cause of so much pain in the elderly, has its roots in childhood and the identification of the structural basis accounting for much of the variations in bone strength among humans. Considerable progress has been made in elucidating the basis for the gender differences in bone strength and the greater incidence of fragility fractures in elderly women when compared to men. Available data indicate that there is very little difference in measures of cancellous bone density in the vertebral body between sexes. In contrast, females have a smaller vertebral cross-sectional area when compared with males, even after accounting for differences in body size: a gender difference that becomes most apparent after puberty. Hence, vertebral fractures are likely more common in women than in men because women have smaller vertebrae. Although, at present, the reasons for the reported gender difference in the incidence of hip fractures have yet to be clearly defined, it is tempting to think that complete phenotypic characteristics responsible for variations in femoral strength will be soon delineated. Such knowledge will provide a more rational way to identify those subjects prone to develop fractures and towards whom osteoporosis prevention trials should be geared.

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