Vicente Gilsanz
Osman Ratib

Hand Bone Age

A Digital Atlas of Skeletal Maturity

Second Edition

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Contents

Introduction

1

Bone age assessment is frequently performed in pediatric patients to evaluate growth and to diagnose and manage a multitude of endocrine disorders and pediatric syndromes. For decades, the determination of bone maturity has relied on a visual evaluation of the skeletal development of the hand and wrist, most commonly using the Greulich and Pyle atlas. 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 to provide a more effective and objective approach to skeletal maturity assessments. 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. Clearly, developing an accurate digital reference that integrates the quantitative morphological traits associated with the different degrees of skeletal maturation of 21 tubular bones in the hand and 8 carpal bones in the wrist is not an easy task.

In the development of this digital atlas, we circumvented the difficulties associated with the design of software that integrates all morphological parameters 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. This computer-generated set of images should serve as a practical alternative to the reference books currently available.

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Bone Development

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Skeletal maturity is a measure of development incorporating the size, shape and degree of mineralization of bone to define its proximity to full maturity. The assessment of skeletal maturity involves a rigorous examination of multiple factors and a fundamental knowledge of the various processes by which bone develops.

Longitudinal growth in the long bones of the extremities occurs through the process of endochondral ossification. In contrast, the width of the bones increases by development of skeletal tissue directly from fibrous membrane. The latter is the mechanism by which ossification of the calvarium, the flat bones of the pelvis, the scapulae, and the body of the mandible occurs. Initial calcification begins near the center of the shaft of long bones in a region called the primary ossification center [1].

Although many flat bones, including the carpal bones, ossify entirely from this primary center, all of the long bones develop secondary centers that appear in the cartilage of the extremities of the bone. Maturation in these centers proceeds in a manner identical to that in the primary centers with ossification of cartilage and invasion of osteoclasts and osteoblasts. The bone ossified from the primary center is the diaphysis, while the bone ossified from the secondary center is the epiphysis. As the secondary center is progressively ossified, the cartilage is replaced by bone until only a thin layer of cartilage, the epiphyseal plate, separates the diaphyseal bone from the epiphysis. The part of the diaphysis that abuts on the epiphysis is referred to as the metaphysis and represents the growing end of the bone. As long as the epiphyseal cartilage plate persists, both the diaphysis and epiphysis continue to grow, but, eventually, the osteoblasts cease to multiply and the epiphyseal plate is ossified. At that time, the osseous structures of the diaphysis and epiphysis are fused and growth ceases [1] (Fig. 2.1).

In the fetal phase of life, the principle interest in skeletal growth is associated with the diagnosis of prematurity. The end of the embryonic period and the beginning of the fetus is marked by the event of calcification, which begins at 8 or 9 weeks. By the 13th fetal week, most primary centers of the tubular bones are well-developed into diaphyses, and, at birth, all diaphyses are completely ossified, while most of the epiphyses are still cartilaginous. Ossification of the distal femoral epiphysis

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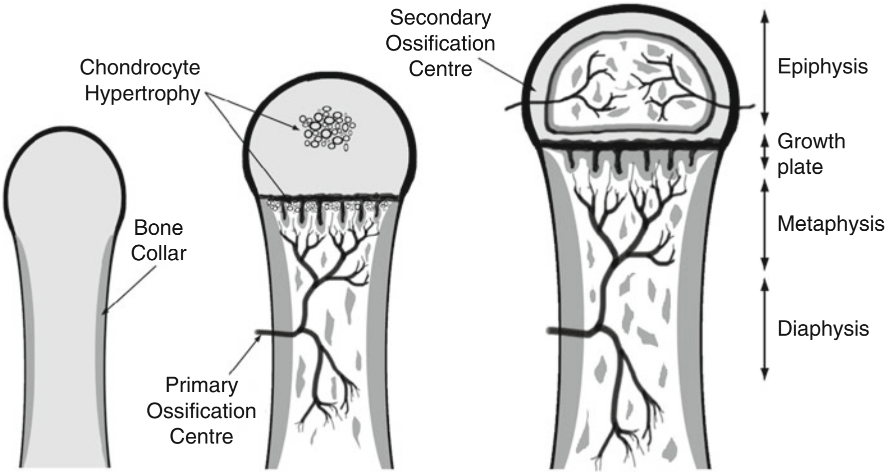

Fig. 2.1 Schematic representation of endochondral bone formation. Skeletal maturity is mainly assessed by the degree of development and ossification of the secondary ossification centers in the epiphysis

begins during the last 2 months of gestation, and this secondary center is present in most full term babies. Similarly, the ossification center for the proximal epiphysis of the humerus usually appears about the 40th week of gestation. On the other hand, the centers for the proximal epiphyses of the femur and tibia may not be present in full term infants, but appear in the first few months of life [2, 3].

After birth, the epiphyses gradually ossify in a largely predictable order, and, at skeletal maturity, fuse with the main body of the bone. Comparing the degree of maturation of the epiphyses to normal age-related standards forms the basis for the assessment of skeletal maturity, the measure of which is commonly called "bone age" or "skeletal age". It is not clear which factors determine a normal maturational pattern, but it is certain that genetics, environmental factors, and hormones, such as thyroxine, growth hormone, and sex steroids, play important roles. Studies in patients with mutations of the gene for the estrogen receptor or for aromatase enzyme have demonstrated that it is estrogen that is primarily responsible for ultimate epiphyseal fusion, although it seems unlikely that estrogen alone is responsible for all skeletal maturation [4].

Clinical Applications for Skeletal Determinations

A single reading of skeletal age informs the clinician of the relative maturity of a patient at a particular time in his or her life, and, integrated with other clinical findings, separates the normal from the relatively advanced or re tarded. Successive skeletal age readings indicate the direction of the child's development and/or show his or her progress under treatment. In normal subjects, bone age should be roughly within 10% of the chronological age. Greater discordance between skeletal age and chronological age occurs in children who are obese or who start puberty early, as their skeletal age is accelerated.

There are two main applications for evaluations of skeletal maturation: the diagnosis of growth disorders and the prediction of final adult height.

Diagnosis of Growth Disorders

Assessments of skeletal age are of great importance for the diagnosis of growth disorders, which may be classified into two broad categories with different etiologies, prognoses and treatments. Primary growth deficiency is due to an intrinsic defect in the skeletal system, such as bone dysplasia, resulting from either a genetic defect or prenatal damage and leading to shortening of the diaphysis without significant delay of epiphyseal maturation. Hence, in this form of growth disorder, the potential normal bone growth (and therefore, body growth) is impaired, while skeletal age is not delayed or is delayed much less than is height.

Secondary growth deficiency is related to factors, generally outside the skeletal system, that impair epiphyseal or osseous maturation. These factors may be nutritional, metabolic, or unknown, as in the syndrome of idiopathic (constitutional) growth delay. In this form of growth retardation, skeletal age and height may be delayed to nearly the same degree, but, with treatment, the potential exists for reaching normal adult height.

The distinction between these categories may be difficult in some instances in which skeletal age is delayed to a lesser degree than height. In general, however, differentiation between primary and secondary categories of growth failure can be determined from clinical findings and skeletal age [5].

Final Height Predictions

The adult height of a child who grows up under favorable environmental circumstances is, to a large extent, dependent on heredity. The final height of the child may, therefore, be postulated from parental heights. Indeed, various methods of final height predictions, which take into account parental height, have been described [6]. A child's adult height can also be predicted from his or her heights at earlier ages, with correlations on the order of 0.8. However, children differ greatly in rate of development; some attain maturity at a relatively early age, while others have a slow tempo and finish growing relatively late. Hence, knowledge of the degree of development increases the accuracy of final height predictions. The only practical guide to acquire this knowledge is by assessment of skeletal maturity, usually estimated from a hand and wrist radiograph.

Tables for prediction of ultimate height based on the individual's height, skeletal age, sex, age, and growth rate have been published. Using skeletal age for prediction of ultimate height, it is also possible to make a rough calculation as follows: measure the individual's height, plot it on a standard growth curve, and extrapolate the value horizontally to the age on the chart that is equal to the bone age. If the point of extrapolation falls between the 5th and 95th centiles, then a guarded prediction of normal adult stature can be given. The closer the extrapolated value is to the 50th centile, the more accurate it is likely to be [5].

Other bone age and height prediction methods commonly in use are those of Bayley-Pinneau, Roche et al. and Tanner-Whitehouse [7–9]. All of these methods use radiographs of the hand and wrist to assess skeletal maturity and were based on population data from normal children followed to adult height. Overall, these methods have 95% confidence intervals of 7–9 cm when used to predict the final height of individuals. It is necessary to realize, however, that estimations of final height are most accurate in children who are healthy, and, in the sick, these predictions are less reliable.

Below is the formula for the prediction of adult height estimated by J.M. Tanner et al. [9]:

$$\begin{aligned}\text{Predicted Final Height} = {} & \text{Height Coefficient} \times \text{Present Height (cm)} + \\ & \text{Age Coefficient} \times \text{Chronological Age (years)} + \\ & \text{Bone Age Coefficient} \times \text{Bone Age (years)} + \\ & \text{Constant}\end{aligned}$$

In girls, these investigators incorporated knowledge of whether or not menarche had occurred, which improved their predictions. The tables for the coefficients for prediction of adult height are on pages 93 and 94.

Conventional Techniques for Skeletal Determinations

In the evaluation of physical development in children, variations in maturation rate are poorly described by chronological age. Thus, for many decades, scientists have sought better techniques to assess the degree of development from birth to full maturity. Measures of height, weight, and body mass, although closely related to biological maturation, are not sufficiently accurate due to the wide variations in body size. Similarly, the large varia tions in dental development have prevented the use of dental age as an overall measure of maturation, and other clinically established techniques are of limited value. As examples, the age at menarche, although an important biological indicator, relates to only half the population, and determinations of sexual development using the Tanner classification, while an extremely useful clinical tool, is subjective and restricted to the adolescent period. Unfortunately, most available maturational "age" scales have specific uses and tempos that do not necessarily coincide.

Skeletal age, or bone age, the most common measure for biological maturation of the growing human, derives from the examination of successive stages of skeletal development, as viewed in hand-wrist radiographs. This technique, used by pediatricians, orthopedic surgeons, physical anthropologists and all those interested in the study of human growth, is currently the only available indicator of

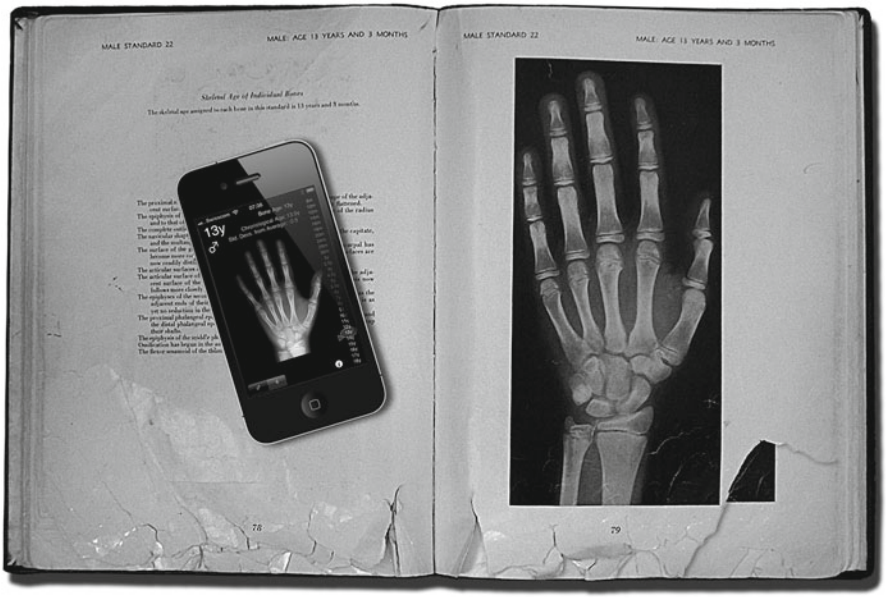

Fig. 2.2 Comparison of the traditional Greulich and Pyle atlas used for determination of bone maturity from hand radiographs and the electronic alternative, a digital atlas of "idealized" hand radiographs that can be reviewed on standard hand-held PDAs

development that spans the entire growth period, from birth to maturity. Essentially, the degree of skeletal maturity depends on two features: growth of the area undergoing ossification, and deposition of calcium in that area. While these two traits may not keep pace with each other, nor are they always present concurrently, they follow a fairly definite pattern and time schedule, from infancy to adulthood. Through radiographs, this process provides a valuable criterion for estimating normal and abnormal growth and maturation (Fig. 2.2).

Greulich and Pyle and Tanner-Whitehouse (TW2) are the most prevalently employed skeletal age techniques today [10, 11]. Despite their differing theoretical approaches, both are based on the recognition of maturity indicators, i.e., changes in the radiographic appearance of the epiphyses of tubular bones from the earliest stages of ossification until fusion with the diaphysis, or changes in flat bones until attainment of adult shape [12].

The standards established by Greulich and Pyle, undoubtedly the most popular method, consist of two series of standard plates obtained from hand-wrist radiographs of white, upper middle-class boys and girls enrolled in the Brush Foundation Growth Study from 1931 to 1942. Represented in the Greulich and Pyle atlas are 'central tendencies', which are modal levels of maturity within chronological age groups. The skeletal age assigned to each standard corresponds to the age of the children on whom the standard was based. When using the Greulich and Pyle method, the radiograph to be assessed is compared with the series of standard plates, and the age given to the standard plate that fits most closely is assigned as the skeletal age of the child. It is often convenient to interpolate between two standards to assign a suitable age to a radiograph. The apparent simplicity and speed with which a skeletal age can be assigned has made this atlas the most commonly used standard of reference for skeletal maturation worldwide.

Underlying the construction of the Greulich and Pyle atlas are the assumptions that, in healthy children, skeletal maturation is uniform, that all bones have an identical skeletal age, and that the appearance and subsequent development of body centers follow a fixed pattern. However, considerable evidence suggests that a wide range of normal variation exists in the pattern of ossification of the different bones of the hand and the wrist and that this variation is genetically determined. In fact, most standards in the atlas include bones that differ considerably in their levels of maturity [10].

Greulich and Pyle did not formally recommend any specific technique for the use of their atlas. Rather, they suggested that atlas users develop their own method depending on their preferences. Pyle et al. did, however, suggest the rather cumbersome approach that each ossification center be assigned a bone-specific bone age, and the average of the ages calculated. By and large, when there is a discrepancy between the carpal bones and the distal centers, greater weight should be assigned to the distal centers because they tend to correlate better with growth potential [5].

A number of important caveats concerning bone age must be considered. First, experience in skeletal maturity determinations and a similar analytic approach are essential to enhance inter- and intra-observer reproducibility. Clinical studies and trials involving bone age as an outcome measure greatly benefit from the inclusion of experienced readers who use similar approaches in their assessments. Second, the normal rate of skeletal matura tion differs between males and females, and ethnic variability exists. Lastly, these references are not necessarily applicable to children with skeletal dysplasias, endocrine abnormalities or a variety of other causes of growth retardation.

Computer Assisted Techniques for Skeletal Determinations

With the advent of digital imaging, several investigators have attempted to provide an objective computer-assisted measure for bone age determinations and have developed image processing techniques from reference databases of normal children that automatically extract key features of hand radiographs [13–17]. To date, however, attempts to develop automated image analysis techniques capable of extracting quantitative measures of the morphological traits depicting skeletal maturity have been hindered by the inability to account for the great variability in development and ossification of the multiple bones in the hand and wrist. In an attempt to overcome these difficulties, automated techniques are being developed that primarily rely on measures of a few ossification centers, such as those of the epiphyses.

In the design of this digital atlas, the complexities associated with the design of software that integrates all morphological parameters was circumvented through the selection of an alternative approach. We designed artificial, idealized, sex- and age-specific images of skeletal development that incorporated the different degrees of maturation of each ossification center in the hand and wrist. The idealized image was derived from a composite of several hand radiographs from healthy children and adolescents that were identified as the perfect average for each ossification center in each age group.

Our aim was to provide a portable alternative to the reference books currently available, while avoiding the complexity of computer assisted image analysis. The wide adoption of personal digital assistants (PDAs) and pocket computer devices allowed the implementation of a low-cost portable solution that could effectively replace the traditional reference books. Technical challenges included the development of proper compression and image enhancement techniques for interpretation of hand radiographs on a small screen with adequate quality, and the need to store a large number of images on instruments with limited memory capacity.

Indicators of Skeletal Maturity in Children and Adolescents

3

The purpose of this section is to describe which bones in the hand and wrist are the most suitable indicators of skeletal maturity during the different phases of postnatal development. In the majority of healthy children, there is an established sequence of ossification for the carpal (Fig. 3.1), metacarpal and phalangeal bones, which is remarkably constant and the same for both sexes. Overall, the first ossification center to appear in hand and wrist radiographs is the capitate, and the last is, most often, the sesamoid of the adductor pollicis of the thumb [18].

The first epiphyseal center to appear is that of the distal radius, followed by those of the proximal phalanges, the metacarpals, the middle phalanges, the distal phalanges, and, finally, the ulna. There are, however, two main exceptions to this sequence: the epiphysis of the distal phalanx of the thumb commonly appears at the same time as the epiphyses of the metacarpals, and the epiphysis of the middle phalanx of the fifth finger is frequently the last to ossify.

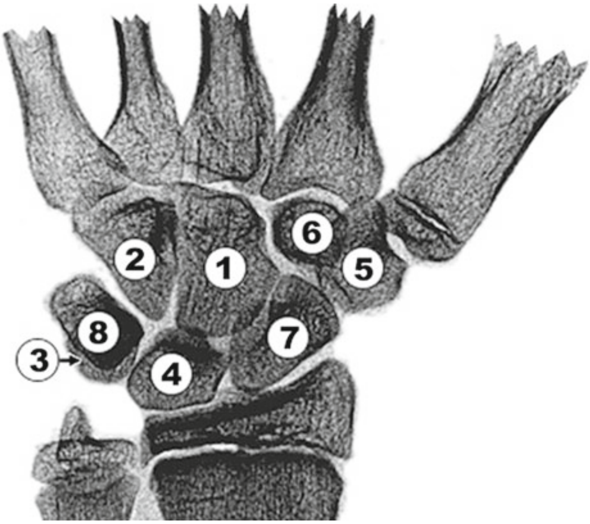

Fig. 3.1 Depiction of the order of appearance of the individual carpal bones. The usual sequence is: capitate *1*, hamate *2*, triquetral *3*, lunate *4*, trapezium *5*, trapezoid *6*, navicular or scaphoid *7* and pisiform *8*. The distal epiphysis of the radius ossifies before the triquetum and that of the ulna before the pisiform

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Since the predictive value of the ossification centers differs and changes during growth, the reviewer should primarily focus on the centers that best characterize skeletal development for the subject's chronological age. To facilitate bone age assessments, we have divided skeletal development into six major categories and highlighted in parentheses the specific ossification centers that are the best predictors of skeletal maturity for each group:

1. Infancy (the carpal bones and radial epiphyses);
2. Toddlers (the number of epiphyses visible in the long bones of the hand);
3. Pre-puberty (the size of the phalangeal epiphyses);
4. Early and Mid-puberty (the size of the phalangeal epiphyses);
5. Late Puberty (the degree of epiphyseal fusion); and,
6. Post-puberty (the degree of epiphyseal fusion of the radius and ulna).

While these divisions are arbitrary, we chose stages that reflect pubertal status, since osseous development conforms better with the degree of sexual development than with the chronologic age. The features that characterize these successive stages of skeletal development are outlined in schematic drawings depicting their appearance as seen in posterior anterior roentgenograms of the hand and wrist.

Infancy

Females: Birth to 10 months of age
Males: Birth to 14 months of age

All carpal bones and all epiphyses in the phalanges, metacarpals, radius and ulna lack ossification in the full-term newborn. The ossification centers of the capitate and hamate become apparent at about 3 months of age and remain the only useful observable features for the next 6 months. At about 10 months of age for girls, and about 1 year and 3 months of age for boys, a small center of ossification in the distal epiphysis of the radius appears. Due to the lack of ossification centers, assessment of skeletal maturity using hand and wrist radiographs during infancy is difficult. Estimates of bone maturation in the first year of life frequently require evaluation of the number, size and configuration of secondary ossification centers in the upper and lower extremities (Fig. 3.2).

Toddlers

Females: 10 months to 2 years of age
Males: 14 months to 3 years of age

The ossification centers for the epiphyses of all phalanges and metacarpals become recognizable during this stage, usually in the middle finger first, and the

Fig. 3.2 During infancy, bone age is primarily based on the presence or absence of ossification of the capitate, the hamate and the distal epiphysis of the radius. The capitate usually appears slightly earlier than the hamate, and has a larger ossification center and rounder shape. The distal radial epiphysis appears later

fifth finger last. Bone age determinations are primarily based on the assessment of the number of identifiable epiphyseal ossification centers, which generally appear in an orderly characteristic pattern, as follows:

1. Epiphyses of the proximal phalanges;
2. Epiphyses of the metacarpals;
3. Epiphyses of the middle phalanges; and,
4. Epiphyses of the distal phalanges.

Two common exceptions to this rule are:

1. The early appearance of the ossification center of the distal phalanx of the thumb, which is usually recognizable at 1 year and 3 months in males, and 1 year and 6 months in females (Fig. 3.3); and,
2. The late appearance of the ossification center of the middle phalanx of the fifth finger, which is the last phalangeal epiphysis to appear.

The number and degree of maturation of the carpal bones in the wrist are less useful indicators at this stage, as only three or four (capitate, hamate and lunate and, at times, trapezoid) are recognizable.

Fig. 3.3 During this stage, bone age is primarily based on the number of recognizable epiphyseal ossification centers in the phalanges and metacarpals

Pre-puberty

Females: 2 years to 7 years of age
Males: 3 years to 9 years of age

Assessments of skeletal maturity in pre-pubertal children are primarily based on the epiphyseal size of the phalanges as they relate to the adjacent metaphyses. During this stage of development, the ossification centers for the epiphyses increase in width and thickness, and eventually assume a transverse diameter as wide as the metaphyses. More weight is given to the size of the epiphyses in the distal phalanges than to that in the middle phalanges, and even less to that in the proximal phalanges. However, since the development of the distal phalanges appears similar at several different ages, at times the assessment is also based on the degree of maturity for the epiphyses of the middle phalanges. On very rare occasions when there continues to be doubt, the development of the proximal phalanx may be included in the assessment (Figs. 3.4 and 3.5).

The epiphysis of the ulna and all carpal bones, with the exception of the pisiform, usually become recognizable before puberty. However, these ossification centers, like those of the metacarpals, are less reliable indicators of bone age at this stage of life.

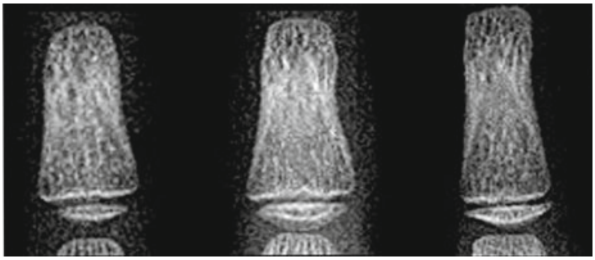

Fig. 3.4 Depiction of the progressive growth of the width of the epiphyses, which, during this stage of development, become as wide as the metaphyses

Fig. 3.5 Assessments of bone age are primarily based on the degree of difference in width between the smaller epiphyses and the larger metaphyses at the distal and middle phalanges

Early and Mid-puberty

Females: 7 years to 13 years of age
Males: 9 years to 14 years of age

As in pre-pubertal children, assessments of skeletal maturity in early and mid-puberty are also based on the size of the epiphyses in the distal phalanges (first) and the middle phalanges (second). The epiphyses at this stage continue to grow and their widths become greater than the metaphyses. Thereafter, the contours of the epiphyses begin to overlap, or cap, the metaphyses. This capping effect is depicted in a two-dimensional radiograph as small bony outgrowths, like tiny horns, on both sides of the shaft (Figs. 3.6 and 3.7).

Fig. 3.6 Depiction of the progressive growth of the epiphyses, which, during this stage of development, become larger than the metaphyses. Special attention is also placed on epiphyseal shape, which, prior to epiphyseal fusion, overlaps the metaphyses, depicting tiny horn-like structures at both ends of the epiphysis (picture at *far-right*)

Fig. 3.7 During this stage of development, like for prepubertal and late-pubertal children, assessments are based primarily on the distal and middle phalanges