Clinical Practice Committee Publication

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2010;73:2–5
DOI: 10.1159/000271910

Received: March 11, 2009
Accepted: March 20, 2009
Published online: January 15, 2010

# Bone Age Assessment in the Workup of Children with Endocrine Disorders

Gian Luigi Spadoni Stefano Cianfarani

'Rina Balducci' Center of Paediatric Endocrinology, Department of Public Health and Cell Biology, Tor Vergata University, Rome, Italy

**Key Words**
Bone age · Growth · Short stature · Puberty · Adult height prediction

**Abstract**
Bone age is a measure of developmental age, or physiological maturity, which represents more truthfully than chronological age, how far an individual has progressed towards full maturity. It is particularly helpful in the clinical workup of children with growth and/or puberty disorders as well as in treating decisions, such as whether to start replacement therapy in a patient with hypogonadism. Skeletal maturity assessment plays a pivotal role in confirming the diagnosis of normal variants of growth such as familial short stature and constitutional delay of growth, in interpreting hormone tests during puberty, and in the diagnosis of precocious puberty and hyperandrogenism. On the other hand, it is important to recognize that overemphasizing bone age evaluation can be misleading if not used in the proper settings. Adult height prediction is based on skeletal maturity assessment and can be used to predict with acceptable accuracy which adult height will be achieved by a 'normal' child. However, the predictions do not apply to children with endocrine or bone pathologies affecting growth.



## Introduction

In most children growth, puberty and related endocrine changes follow a well-orchestrated pattern but the pace of maturation varies widely so that these events should be related to physical maturity rather than chronological age. Skeletal maturation is a surrogate of developmental age, or physiological maturity, which represents more truthfully than chronological age, how far an individual has progressed towards full maturity and may hence be considered a sort of 'biological age'.

Skeletal maturation is marked by an orderly and reproducible sequence of recognizable changes in the appearance of the skeleton during childhood. Such changes include the timing and sequence of the appearance of the centers of ossification, specific alterations in the contours of the bones, and the timing and sequence of the ultimate closure of the growth plates. Radiographically, skeletal maturity can be assessed by comparing the radiographic appearance of portions of an individual child's skeleton with the standardized appearance in a comparable population of children at various stages in their progress toward maturity. Radiographic assessment of skeletal maturity in the child is most frequently based on the appearance of the hand and wrist.

Bone age assessment is particularly useful in the clinical evaluation of early and late maturers. Although bone

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


1663–2818/10/0731–0002$26.00/0

Accessible online at:
www.karger.com/hrp

Stefano Cianfarani, MD
'Rina Balducci' Center of Pediatric Endocrinology, Department of Public Health and Cell Biology, Room E-178, Tor Vergata University, Via Montpellier 1
IT–00133 Rome (Italy)
Tel. +39 06 7259 6178, Fax +39 06 591 7415, E-Mail stefano.cianfarani@uniroma2.it

**Table 1.** Indications and limitations of bone age assessment

| |
|---|
| Bone age is necessary |
| In the diagnosis of FSS and CDGP |
| For interpreting hormone levels at pubertal age |
| For diagnosis of precocious puberty or hyperandrogenism |
| For deciding whether or not to treat the above-mentioned conditions |
| For predicting adult height in normal children |
| Bone age is useful |
| In evaluating any child with growth and/or puberty disorders |
| In deciding when to start replacement therapy in hypogonadism |
| In monitoring children on GH therapy |
| Bone age may be misleading |
| In evaluating children with bone disorders |
| In predicting adult height in pathological conditions |
| If considered an absolute diagnostic marker |
| If, during the follow-up of a patient or in comparing groups of patients, different readers are involved or different methods are employed |

age assessment may provide precious information, it should always be considered ancillary to a more comprehensive clinical, auxological and laboratory approach (table 1).

## Methods of Bone Age Assessment

In principle, any part of the skeleton could be used to determine skeletal maturity, but in practice the hand and wrist represent the most convenient area. They are easily X-rayed without fear of any radiation being delivered to the reproductive organs.

The two most widely used methods are the 'atlas' method of Greulich-Pyle [1–3] and the bone scoring method of Tanner-Whitehouse (TW2 method) [4, 5]. They are not always comparable and cannot be considered interchangeable. Therefore, in the follow-up of an individual or in comparing different groups of patients it is crucial to use the same method.

With the Greulich-Pyle atlas method, developed from films taken in the 1930s and 1940s, each bone is matched with a similar-appearing bone in a series of standard radiographs of bones of increasing age. This is still the most frequently used method; certainly its easy use and the fact that moving quickly from the preceding to the following standard makes it difficult, at least for the experienced reader, to have an error greater than the time interval which separates two X-ray standards.

With the TW2 method each bone is matched with a set of 8 standard ages and its stage is rated. Each stage of each bone has a score attached to it, which is derived mathematically so that the sum of the scores for all the bones represents the best overall estimate of skeletal maturity. The Tanner-Whitehouse standards are based on a large-scale random sample of urban and rural children taken in the 1950s. Scoring bone by bone makes the TW2 method potentially more accurate than the Greulich-Pyle atlas method. However, the TW2 method is consistently time consuming and based on a combined score; assigning to each of the 20 bones a single score chosen among 8 or 9 maturity stages may eventually lead to a higher risk of error than the comprehensive analysis method of Greulich-Pyle. An automatic measurement of bone age using computerized image analysis based on TW2 was proposed to facilitate and speed up the reading [6].

## Adult Height Prediction

In normal children, bone age closely correlates with the remaining growth potential and it has been included in the equations used for predicting adult height. Each bone age assessment method refers to its specific adult height prediction method: namely the Bayley-Pinneau method for the Greulich-Pyle method of bone age assessment and the TW2 height prediction method for the TW2 bone age method. The predictions, however, do not apply to children with endocrine or bone pathologies affecting growth and should be restricted to normal children because a delay in bone age does not necessarily mean a bigger growth potential.

## Conditions in Which Bone Age Assessment Is Necessary

*Normal Variants of Growth: Familial Short Stature and Constitutional Delay of Growth and Puberty*

The vast majority of short children referred to the pediatric endocrinologist do not have any pathological conditions but their patterns of growth represent normal variants of the growth process. Classically, normal variants of growth comprise familial short stature (FSS) and constitutional delay of growth and puberty (CDGP). To be identified both conditions require the ascertainment of a normal growth rate. FSS children present a stature within the target height range and no bone age delay, whilst CDGP subjects show short stature, bone age delay

(usually more than 2 years), delayed onset of puberty, and often familial history of delayed puberty.

*Interpretation of Endocrine Tests during Puberty*

Bone age is extremely helpful in the interpretation of the GnRH test carried out to distinguish delayed puberty from hypogonadism. Subnormal peak gondotropin responses to GnRH test indicate a gonadotropin defect only if the child has a biological age consistent with the physiological rise in gonadotropins. In practice a bone age of 13 years may be considered the threshold to expect the pubertal gonadotropin response. Therefore, we should not expect pubertal values of LH and FSH in a child with a bone age less than 13 years.

*Precocious Puberty and Hyperandrogenism*

In case of anticipated or premature appearance of the secondary sex characteristics, bone age should be used in the differential diagnosis. It often occurs that a girl exhibits the symmetrical or asymmetrical growth of mammary glands before the age of 8 years. This sign might be due to a simple transitory increase of peripheral sensibility to estrogens known as premature thelarche or to the presence of elevated levels of estrogens, secondary to the precocious activation of the hypothalamic-pituitary axis in true precocious puberty or an ovarian or adrenal overproduction in gonadotropin-independent precocious puberty. Bone age will be consistent with chronological age in the former case and advanced in the latter, provided that precocious puberty has developed over a sufficient period of time to allow an acceleration of bone maturation. Therefore, in recent onset precocious puberty normal bone age could be misleading, and the GnRH test should be performed.

The onset of premature pubarche raises the same kind of problem in terms of a differential diagnosis: is the pubarche just an expression of peripheral hypersensitivity to androgens or a sign of hyperandrogenism (e.g. in congenital adrenal hyperplasia, CAH)? The latter case is almost invariably associated with advanced bone age which hence represents an important diagnostic tool.

*Treating Decisions in Children with the Above Mentioned Conditions (Precocious Puberty and CAH) and Monitoring the Response of Skeletal Maturation to the Treatment with GnRH Analogs and Hydrocortisone*

One of the main objectives of the therapy in children with precocious puberty and CAH is the achievement of an acceptable adult height. Whilst some patients are at risk of subnormal adult height and deserve specific treatment, a subset of children will have a good spontaneous height outcome. The degree of bone age advancement and the actual height of the child play a key role in selecting children to be treated with either GnRH analogs (precocious puberty) or hydrocortisone (CAH). Once therapy is started, skeletal maturation assessment will be helpful to monitor the effect of therapy on the advancement of bone age and, ultimately, on the adult height prognosis.

*Adult Height Prediction (Projection) in Normal Children*

Bone age is essential for predicting adult height according to both Bayley-Pinneau and TW2 methods. Projected height represents a method to roughly predict adult height. It consists of plotting actual height on centile curves according to the bone age rather than the chronological age.

## Conditions in Which Bone Age Assessment Is Helpful

*Evaluation of Children with Growth and/or Puberty Disorders*

Skeletal maturity should be evaluated in any child with growth and/or puberty retardation. In this context, the assessment of bone age provides helpful information to distinguish between FSS and CDGP. However, when delayed skeletal maturation is associated with a reduced growth rate, endocrine disorders such as growth hormone (GH) deficiency, hypothyroidism as well as chronic systemic diseases, such as celiac disease, must be considered. On the other hand, it should be pointed out that these conditions may need time to determine bone age retardation. Therefore, a bone age consistent with chronological age does not rule out the possibility of a recent onset of a serious disease such as organic GH deficiency.

*Start of Replacement Therapy in Children with Hypogonadism*

We have already pointed out the helpfulness of bone age assessment in a child with delayed puberty in order to determine the right time to perform the GnRH stimulation test and to interpret the results. In addition, skeletal maturity plays a key role in the decision of when replacement therapy should be initiated. In case of slightly delayed bone age, in the absence of psychological problems recommending immediate treatment, therapy could be postponed in a child with associated short stature to ameliorate the height prognosis.

*Monitoring of Children on GH Replacement Therapy*

Periodic bone age assessment is required in a child on GH therapy to evaluate the changes in the ratios of height for chronological age and height for bone age.

## Conditions in Which Bone Age Assessment May Be Misleading

*Evaluation of Children with Bone Disorders*

In bone disorders skeletal maturation can be altered and, consequently, the evaluation of bone age may be misleading. In such cases the wrist X-ray can provide important information on chondrogenesis and osteogenesis but should not be used to determine bone age.

*Adult Height Prediction in Children with Precocious Puberty or Born Small for Gestational Age*

Although in these conditions the assignment of bone age is accurate, the pace of skeletal maturation is unpredictable so that adult height prediction provides misleading results. Adult height prediction is, in fact, accurate only when performed in normal children.

*FSS, Constitutional Growth Delay, and GH Deficiency if Considered an Absolute Diagnostic Marker*

Skeletal maturity is essential for differentiating FSS from CDGP. However, there are FSS children with associated CDGP who may have delayed bone age. Bone age is useful in the workup of children with GH deficiency. It is in general true, however, that some GH deficiency children do not have a significantly retarded bone age [7].

*Last but Not Least*

As stated above, in the follow-up of children the same method of bone age assessment should be employed. Less obvious, but not less important, is that ideally the same reader should evaluate the films because bone age evaluation has a strong subjective component.

## Further Information Obtainable from an Accurate Assessment of Left Hand and Wrist X-Ray

In evaluating hand and wrist X-ray we should not miss the opportunity to look for bone shape abnormalities:

(1) Radiopaque transverse line expression of temporary arrest of long bone growth and the subsequent resumption of growth can be visible on radiographs. These are commonly referred to as Harris lines. Harris lines are related to episodes of temporary arrest of longitudinal growth caused by nonspecific stress impacts such as malnutrition, illness, and psychogenic stress [8].

(2) Several disorders of chondrogenesis and/or osteogenesis can result in typical images such as wider and stunted bones (hypochondroplasia), irregular methaphyses (Turner syndrome), and shortness of the 4th and 5th metacarpal (pseudohypoparathyroidism) [9].

## References


1 Greulich WW, Pyle SI: Radiographic Atlas of Skeletal Development of Hand and Wrist. Stanford, Stanford University Press, 1959.

2 Pyle SI, Reed RB, Stuart HC: Patterns of skeletal development in the hand. Pediatrics 1959;4:886–903.

3 Gilli G: The assessment of skeletal maturation. Horm Res 1996;5(suppl 2):49–52.

4 Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H: Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 Method), ed 2. London, Academic Press, 1983.

5 Cox LA: Tanner-Whitehouse method of assessing skeletal maturity: problems and common errors. Horm Res 1996;5(suppl 2):53–55.

6 Tanner JM, Gibbons RD: Automatic bone age measurements using computerized image analysis. J Pediatr Endocrinol 1994;7:141–145.

7 Growth Hormone Research Society: Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000;85:3990–3993.

8 Harris HA: Bone Growth in Health and Disease. London, Oxford University Press, 1933.

9 Hochberg Z: Endocrine Control of Skeletal Maturation. Basel, Karger, 2002.