enter puberty with little exposure to GH therapy may be experiencing catch-up growth after the onset of puberty. Continued use of GH in those with greater exposure before puberty serves only to maintain the gain in height SDS that was achieved before puberty. The different models all predicted the response to GH therapy during puberty with $R^2$ values near .5. Without bone age delay as a variable, the $R^2$ was .477; adding bone age data, whether from locally determined bone ages, centrally determined bone ages, or from hand–wrist or knee radiographs, increased the $R^2$ value to $\sim$.51. Except for age at enrollment in NCGS substudy VII, the effects of other significant variables are intuitive and consistent with our expectations. The positive effect of age at enrollment on the change in height SDS appeared to be counterintuitive. On further analysis, it was found that the age at the last visit during GH treatment was positively correlated with our defined growth response endpoint ($r = .389$), which suggests that the older a patient was at the last visit, the greater was the response to treatment. Because the age at NCGS substudy VII baseline and the age at the last visit on treatment were positively correlated, the effect of the first age variable was confounded with the effect of the second age variable.

Data from NCGS substudy VII indicate that bone age determinations are an important predictor of the response to GH therapy, even during puberty. It appears that in most patients, knee radiographs do not provide sufficient additional information to justify their being used when the hand–wrist bone age is consistent with the clinical picture. However, there may be some patients in whom the hand–wrist bone age does not reflect the clinical situation, and a knee bone age determination is warranted. Locally determined bone ages appear to provide adequate clinical information, and centrally determined bone ages are unnecessary except in studies in which precise bone age determinations are important.

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REFERENCES

2. Roche AF, Wainer H, Thissen D. Skeletal Maturity: The Knee Joint as a Biological Indicator. New York, NY: Plenum Medical Book Co; 1975

Regular Monitoring of Bone Age Is Not Useful in Children Treated With Growth Hormone

Darrell M. Wilson, MD

ABSTRACT. Although bone age estimates are traditionally used to monitor children receiving growth hormone therapy, few data support this practice. Bone age determination is fraught with technical difficulties, resulting in high interobserver differences. Longitudinal studies show that an individual’s bone age can change erratically over time. The resulting errors in predicted adult heights based on these bone age determinations are large. Moreover, growth hormone therapy appears to accelerate bone maturation. The radiographic evidence of this acceleration can be delayed. In this setting, improvements in predicted adult heights can be artfactually large. Routine monitoring of bone age during GH therapy is unnecessary. Pediatrics 1999;104:1036–1039; Bayley and Pinneau, bone age determination, Greulich and Pyle, predicted height, radiography, Tanner and Whitehouse.

ABBREVIATION. GH, growth hormone.

Monitoring is useful only if it guides the hand of therapy. In this article, I review the role of repeated bone age determinations in individual patients during growth hormone (GH) therapy. For monitoring, as for diagnosis, the tests used should be accurate and reproducible. Moreover, they should help predict some clinically important out-
come (preferably one that can be modified by altering how the patient is treated). Bone age monitoring during GH therapy should be judged on how well it assists in optimizing growth and avoiding side effects.

**BONE AGE DETERMINATION METHODS**

Bone age can be determined at many skeletal sites, and the left hand and wrist are by far the most commonly used. Measurements from radiographs can be translated into bone ages by using a number of different algorithms. The most common method in the United States is to compare the radiograph measurements with the standard plates in the atlas of Greulich and Pyle. This method is somewhat subjective. More objective methods are available but, being more complex and time-consuming, they are not used much in general clinical practice, particularly in the United States. Bone age determinations are commonly used to predict final height. Some clinicians obtain subsequent bone ages at intervals to monitor changes in the predicted final height in children who are treated with growth-altering therapies. As with bone age determinations, different algorithms can convert radiographic data into estimates of final height. The most commonly used algorithm for predicting height uses the data from Bayley and Pinneau, as adapted by Post and Richman.

**Fig 1.**

A, The effect of GH therapy started at age 6 years on the growth (heavy solid line) of a boy with a combination of familial short stature and delayed puberty contrasted with his expected growth (dotted line). The 10th, 50th, and 90th percentiles for normally growing boys are shown for comparison (thin solid lines). B, The effect of GH therapy on the bone age (heavy solid line) contrasted with the boy’s expected bone age (dotted line). C, The effect of GH therapy on the predicted final height (heavy solid line) contrasted with the boy’s expected final height (dotted line).
ERRORS IN BONE AGE DETERMINATIONS

Bone age determination is fraught with technical difficulties. Proper radiographic methods are necessary to ensure accurate measurement.6 Interobserver differences are high, particularly in clinical settings. King et al7 compared the bone ages reported by three second-year radiology registrars using 50 consecutive radiographs for skeletal age assessment. By using the method of Greulich and Pyle,3 the average spread (the difference between the highest and the lowest of the three determinations) in girls and boys with mean chronologic ages of 10.8 and 10.2 years, respectively, was 0.96 year. This spread was not statistically different from that by using the Tanner and Whitehouse II method (0.74 year).

Differences in bone age determinations of this magnitude can have a substantial clinical impact. As an example, a 124 cm-tall (5th percentile for height) 9-year-old boy with a bone age of 9 years has a predicted final height of 164.9 cm by using the method of Bayley and Pinneau.4 A recalculation using a bone age interpretation of 8 years—well within the expected range of repeated readings—predicts a final height of 171.5 cm. Conversely, a bone age of 10 years predicts a final height of 158.2 cm. These differences in predicted final height are comparable with the incremental height gain reported in patients without GH deficiency who are treated with long courses of GH therapy.

Longitudinal studies show that changes in an individual subject’s bone age over time are frequently erratic, making it difficult to monitor any independent impact of therapy. Benso et al8 obtained two bone age determinations (Tanner and Whitehouse II method, radius and ulna scores), separated by 1 year, in 410 boys 6 and 14 years of age. The changes in their bone ages were widely scattered. An increase of 1 chronologic year was associated with an increase in bone age ranging from 0 to >3 years. Such natural variations in the rate of change in bone age make it difficult to detect an impact of GH therapy in any individual patient.

POTENTIAL GOALS OF MONITORING BONE AGE DURING GH THERAPY

There is little evidence that routine monitoring of bone ages during GH treatment provides data that should be used to modify the therapeutic approach. The conspicuous lack of guidelines on how to use longitudinal data on bone age to modify the therapy indicates that clinicians recognize implicitly the limitations of this form of clinical monitoring. The inherent low rate of change and the broad natural variation over time make bone age determination an unlikely candidate test for detecting any potential side effects of GH therapy.

DANGERS OF BONE AGE DETERMINATION DURING GH THERAPY

Bone ages (and the predicted final heights that are determined from these studies) may be, in fact, misleading during treatment. Bone age determinations are based on radiographic changes, which require the deposition of macroscopic amounts of bone mineral. This deposition takes time.

Long-term GH therapy appears to accelerate bone maturation. When such therapy is started, there is a delay before this acceleration is apparent radiographically as an increased bone age. Consequently, bone age determinations made during therapy tend to underestimate the true maturational state of the skeleton. During some phases of the therapy, height predictions based on artifactually young bone ages will be skewed by overestimations of the salutary effect of the therapy on the predicted final height.

This potential problem can be illustrated by using the example of a boy with familial short stature and delayed puberty who is growing near the 1st percentile (Fig 1). GH treatment is started at 6 years of age, leading to accelerated growth. The effect of the therapy on bone age advancement is delayed until a few years later, when his bone age increases to more than would be expected in an untreated person. This delay in bone age acceleration leads to a transient over-prediction of his final height. The specifics, of course, vary from case to case but, as many investigators have noted, the height predictions made during GH
therapy frequently differ significantly from the actual final height.

Growth data from a study of GH treatment (with and without oxandrolone) in girls with Turner syndrome is instructive (Fig 2). During the first 6 years of this study, the investigators compared the cumulative growth of the subjects in the treatment groups with their expected growth. At 6 years, the group treated with both GH and oxandrolone had grown ~20 cm more than the historical control group. When the therapy was complete, however, the final incremental gain in this group was only 10.5 cm. As the authors report, bone age advancement was faster and growth stopped sooner in the treated girls than in the control subjects. Clearly, predictions of final height made during therapy can be misleading.

CONCLUSIONS

Many inherent characteristics of bone age determinations limit their usefulness in monitoring the effects of GH therapy. There is little clinical evidence that routine monitoring of bone age assists in the management of patients who are treated with GH. Routine monitoring of bone age during GH therapy is unnecessary.

Regular Monitoring of Bone Age Is Useful in Children Treated With Growth Hormone

Francine Ratner Kaufman, MD*, and Judy P. Sy, PhD‡

ABSTRACT. Objective. This study was undertaken to determine whether serial bone age (BA) radiographs were obtained in patients with growth hormone deficiency and to assess whether there were differences in outcome between subjects with and without monitoring of BA radiographs.

Research Design and Methods. Data were collected from the National Cooperative Growth Study database on growth hormone-deficient subjects who were treated for at least 3 years. Comparisons were made among three groups of subjects: 1) those with BAs at entry versus those without; 2) those with BA values in the first year of follow-up if an entry radiograph had not been done versus those with no first-year examination; and 3) those with a BA at entry and yearly for 3 years versus those with no radiographs during the same period. Differences in the change in height standard deviation score (SDS); change in height age, age, pubertal progression, number of visits, growth hormone dosage; and number of growth hormone injections per week were compared.

Results. Of the 6,191 subjects assessed, 93% had at least one BA radiograph obtained; there was a mean of 3.6 ± 2.6 total number of BA radiographs per patient during the 5.2 ± 1.9 years of follow-up. Subjects with BA values at entry were older and had slightly higher cumulative height SDS and height age change compared with those without BA values at entry. Subjects with BA assessment during the first year were older and had shorter growth hormone treatment time and slightly better cumulative change in height SDS and height age than did those without BA in the first year. Comparing those with serial BA determination for the first 3 years of treatment versus those with no BA values, those with BA were older, more pubertal, seen more often, had more growth hormone injections per week of a comparable growth hormone dosage, and had slightly larger cumulative change in height SDS and height age than those without x-rays.

Conclusions. These data suggest that National Cooperative Growth Study investigators find it of benefit to obtain baseline and follow-up measurements of BA in most subjects treated with growth hormone. Subjects with BA monitoring do slightly better than do those whose skeletal maturation is not measured. BA assessment should be considered part of the follow-up of patients treated with growth hormone therapy.

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REFERENCES

2. Gilli G. The assessment of skeletal maturation. Horm Res. 1996;45:49–52

From the *Division of Endocrinology and Metabolism, Children’s Hospital, Los Angeles; and the ‡Department of Pediatrics, the University of Southern California School of Medicine, Los Angeles; and the Department of Medical Affairs, Genentech, Inc, South San Francisco, California.

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