

Short-Term Effect of Testosterone Treatment on Reduced Bone Density in Boys With Constitutional Delay of Puberty

This study demonstrates: (1) that boys with constitutional delay in growth and sexual maturation (CDGP) have decreased bone mineralization beyond that which can be explained by their short stature or delayed bone age, and (2) that in subjects who have received testosterone for 6 months there is increased bone mineralization 6 months later compared with untreated subjects. Bone mineral density (BMD; grams per square centimeter) and bone mineral content (BMC; grams per centimeter) were determined in the nondominant radius by single photon absorptiometry (SPA) in 17 white males with CDGP. BMD and BMC were decreased relative to control data for chronologic age (14.6 ± 1.0 years), height age (11.6 ± 1.6 years), and bone age (11.9 ± 1.6 years). Eight boys received testosterone depot, 100 mg/mo intramuscularly, for 6 months. Six months later (12 months after initiation of testosterone therapy), height, weight, and sexual maturation of the testosterone-treated youths were greater than that of the 9 control subjects, and BMD and BMC had increased substantially as well ($P < 0.001$). BMD increased $+26.2\% \pm 13.6\%$ in testosterone-treated boys versus $+0.54\% \pm 8.7\%$ in nontreated subjects. BMC increased $+41.1\% \pm 28.8\%$ in testosterone-treated boys and $+5.1\%$ in the untreated subjects. The investigators concluded that boys with CDGP have decreased bone mineralization that is disproportionately greater than that related

to their short stature and delayed skeletal maturation, and that short-term administration of testosterone increases bone mineralization.

Bertelloni S, et al. *J Bone Miner Res* 1995;10:1488-1495.

Editor's comment: Approximately 30% of adult lumbar spine BMC is accumulated within a 3-year peripubertal interval, and half of the increase in BMC that occurs during adolescence reflects growth in bone size rather than increase in bone density. Young adult males with CDGP have lower spinal BMD than do control subjects with earlier adolescence, emphasizing the importance of the timing of adolescence as well as the secretion of sex hormones themselves for this process. Whether there are adverse clinical consequences of the lower BMD of CDGP subjects is not known. In the present report, compact bone mineralization has been measured only at the radius by SPA. It will be important to confirm these findings by more extensive evaluation of skeletal mineralization, including sites of trabecular bone such as the lumbar spine and hip, employing dual-energy X-ray absorptiometry. Whether decreased bone mineralization in the male with CDGP should lead to more aggressive therapy is uncertain as yet.

Allen W. Root, MD

Computer-Aided Skeletal Age Scores in Healthy Children, Girls With Turner Syndrome, and in Children With Constitutionally Tall Stature

The aims of the present study were: (1) to evaluate the reliability of a computer-assisted bone age scoring system in healthy children; (2) to compare this method against a manual rating system in healthy children, as well as in subjects with 2 specific entities, manifested by short and tall stature, respectively; and (3) to determine whether a shortened version of the bone age scoring system might substitute for the original long version. Reference curves for bone maturation in Turner syndrome (TS) and constitutionally tall stature (CTS) determined by the computerized system are presented.

Three groups of individuals—healthy children, girls with TS, and children with CTS—underwent bone maturation evaluation. Evaluations were conducted manually using the 13b model of the Tanner-Whitehouse method (TW-RUS), and by the long (13b) and the shortened (6b) models of the computer-aided skeletal age scoring system (CASAS), a transformation of the TW-RUS method into a computerized image analysis system.

As evaluated by the percentage of equal ratings on duplicate (within-observer as well as between-observer) assessments, reliability was high ($\pm 90\%$) in healthy children and similar to those obtained by the manual ratings. The comparability of

CASAS (both 13b and 6b models) with the manual rating system was assessed by calculating the correlation coefficients and evaluating the average and the limits of the range of agreement by a method described by Bland and Altman. Although some of the mean differences of methods were statistically significant, they were not clinically significant, as they were < 0.4 bone age year. Up to 8% of manual insertions occurred in all groups. The percentage was lower in the 6b model than the 13b model, particularly in the CTS children. This suggests that the 6b model of CASAS may have a comparable level of reliability, while introducing a smaller degree of inconsistency.

The authors conclude that CASAS is applicable in TS and CTS. Their data support the use of the 6b model of CASAS, as it is less time-consuming and labor-intensive and provides data almost as reliable as the manual ratings.

Van Teunenbroek A, et al. *Pediatr Res* 1996;39:360-367.

Editor's comment: This challenging article compares CASAS scores, particularly those obtained with the 6b model, with manually obtained TW-RUS scores, in the evaluation of the bone maturation in 3 populations of children. Although some

inconsistencies were noted, the methods were comparable. The main advantage of the computerized method over the manual rating method is that it uses a continuous scale instead of an interval scale. This diminishes the error of the interpretation of maturity stages, as the difference of 1 interval stage in the rating of a particular bone may result in an increase of 0.3 bone age years. The 6b model was less time-consuming than the 13b model, and yielded acceptable readings of bone maturation. The main disadvantage of CASAS is the need for special equipment (hardware and software),

which increases the cost. The curves for bone maturation in TS girls and CTS children presented in this article will enhance our understanding of the dynamics of growth, whether spontaneous or in response to specific therapeutic modalities. The procedure has been technically described by Tanner and Gibbons (J Pediatr Endocrinol 1994;7:141-145), in an article that is highly recommended to those of you who wish to review the details of the system and its principles.

Fima Lifshitz, MD

Intranasal Administration of GHRP Hexarelin Accelerates Growth in Short Children

The investigators administered the growth hormone-releasing peptide (GHRP) hexarelin (His-D-2-methyl-Trp-ALA-Trp-D-Phe-Lys-NH₂) to 8 short prepubertal children (7 males, 1 female; 5.3 to 11.6 years of age). All subjects had normal growth hormone (GH) secretion (>10 ng/mL) in response to provocative stimulation as well as a substantial increase in GH concentrations (>20 ng/mL) following 1 intranasal inhalation of hexarelin (20 µg/kg). Hexarelin (60 µg/kg/dose) was administered intranasally 3 times daily while the children were recumbent. Mean growth rate increased from 5.3 ± 0.8 cm/y to 8.3 ± 1.7 cm/y during the first 6 to 8 months of therapy (P<0.001). Skin-fold thickness declined and head circumference increased during therapy. Serum levels of insulin-like growth factor 1 (IGF-1), inorganic phosphate, and alkaline phosphatase increased during administration of hexarelin. No adverse local or systemic clinical or biochemical events were recorded during this treatment period. The authors concluded that, over the short term, intranasal hexarelin accelerates growth in short children with intact GH secretion.

Editor's comment: The natural compound whose biologic activity is mimicked by the various synthetic GHRPs is unknown. GHRP acts through a somatotrope receptor that is separate from that for GH-releasing hormone (GHRH) and through a different intracellular signaling pathway (GHRH-adenylyl cyclase/cyclic adenosine monophosphate; GHRP-phosphoinositol). The primary site of action of the GHRPs may be within the hypothalamus rather than directly at the pituitary, as they are inactive in the absence of GHRH. GHRPs are active when administered intravenously, subcutaneously, intranasally, and orally. The present report demonstrates the short-term effects of GHRP administered intranasally. We may anticipate that these agents will also be active during short- and long-term oral administration. If experience demonstrates the safety and effectiveness of oral GHRP, yet another therapeutic agent may be available for the management of the carefully selected short, GH-sufficient child.

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Laron Z, et al. *Clin Endocrinol* 1995;43:631-635.

Nondisjunction in Human Sperm: Evidence for an Effect of Increasing Paternal Age

It is well established that increased maternal age is associated with an increased risk of chromosomal trisomy in offspring, ie, the maternal age effect. In contrast, the existence of a paternal age effect has been controversial, with most epidemiologic evidence favoring the absence of such an effect. One of the difficulties has been separating paternal from maternal age effect.

Griffin et al have taken a different approach to the question of paternal age effect. They directly analyzed sperm. Sperm are normally monosomic; they contain only 1 copy of each autosome plus an X or a Y chromosome, ie, 23 X or Y. The authors used fluorescent in situ hybridization (FISH) to count the number of X, Y, and number 18 chromosomes in about 400,000

individual sperm from 24 men, ranging in age from 18 to 60 years. By using probes for both the X and Y chromosomes and chromosome 18, they could distinguish between disomy involving 1 chromosome and diploidy involving a whole complement of chromosomes. Moreover, in cases of disomy for the sex chromosomes, they could distinguish between nondisjunction that occurred during the first meiotic division, which would produce disomic sperm carrying both an X and a Y chromosome, and nondisjunction that occurred during the second meiotic division, which would produce disomic sperm carrying 2 X or 2 Y chromosomes. When such sperm fertilize normal ova, trisomic embryos would be produced containing 47,XXX, 47,XXY or 47,XYY chromosome complements.