Testosterone Treatment in Adolescent Boys With Constitutional Delay of Growth and Development

Ashraf T. Soliman, Mohammed M. Abdul Khadir, and Maurice Asfour

Administration of androgens to adolescent boys with constitutional delay in growth has been highly controversial. One hundred forty-eight adolescent boys with constitutional delay of growth and puberty with a mean age of 14.3 ± 0.7 years were treated with testosterone enanthate 100 mg intramuscularly each month for 6 months. Growth parameters, sexual maturation, and circulating concentrations of testosterone and insulin-like growth factor-I (IGF-I) were compared with those for 50 age-matched adolescent boys with constitutional delay of growth and puberty with a mean age of 14.1 ± 0.9 years who did not receive any treatment. The mean height growth velocity, height standard deviation score, weight gain, and IGF-I concentration were significantly greater in the treatment group after 1 year of follow-up evaluation. The advancement in bone age equaled that in chronologic age in the treatment group, with no significant change in the bone age to chronologic age ratio (BA/CA) before versus after therapy. All subjects in the treatment group had clearly entered puberty by the end of 1 year. Testicular size increased significantly in the treatment group and they had significantly higher serum testosterone concentrations 6 months after the end of testosterone therapy as compared with the control group, denoting activation of the hypothalamic-pituitary testicular axis. All subjects in the treatment group were psychologically satisfied with the enhanced growth and increased muscle mass, versus only 40% of those in the control group. In conclusion, our regimen appears to be efficacious and safe for treatment of boys with constitutional delay of growth and puberty and has no deleterious effect on skeletal age.

BOYS WITH SHORT STATURE and constitutional delay of growth and puberty comprise a large group of patients seen in pediatric clinics. They are generally reassured that they will attain a normal adult height after going through a delayed but normal puberty. However, significant growth retardation in male adolescents, especially when accompanied by delayed sexual maturation, may be associated with a sense of incompetence and vulnerability, impaired self-esteem, reluctance to participate in athletic activities, social isolation, and impaired academic performance.[1,2]

Androgen therapy has been used in the treatment of such patients in an attempt to induce a rapid growth spurt and improve adult height. However, many of these reports suffer from being retrospective reviews[3,4] or from reporting treatment in a small number of boys.[5,6]

The following prospective randomized study was undertaken in an attempt to investigate the physiologic response to testosterone treatment in a large group of adolescent boys with constitutional delay of growth and puberty.

SUBJECTS AND METHODS

The subjects were teenage boys referred to the University of Alexandria Pediatric Endocrine Clinic for evaluation of short stature and/or delayed puberty. Criteria for entry into the study were as follows: (1) age ≥ 14 and less than 18 years; (2) height less than the fifth percentile; (3) delayed puberty, defined as the P-1 or P-2 stage using the criteria reported by Kelch et al[7] and Winter and Faiman[8] (P-1, prepubertal; P-2, slight increase in testicular size ± minimal pubic hair); and (4) no evidence of endocrine or other systemic disease. These criteria were met by 198 subjects over 5 years, who were prospectively entered onto the study.

Preliminary investigations included measurement of electrolyte, serum free thyroxine (T_4), thyrotropin (TSH), testosterone, and insulin-like growth factor-I (IGF-I) concentrations, urinalysis, and complete blood cell count. Skeletal maturation was determined according to the atlas developed by Greulich and Pyle.[9] All investigations were approved by the University of Alexandria Medical Committee. After informed consent was obtained from both the subject and his parents, subjects were randomly assigned to either the treatment or control group, using a preestablished random-number table. Growth hormone (GH) reserve was estimated using high-dose clonidine (0.15 mg/m^2) in 20 randomly selected subjects from each group.

The treatment group (n = 148) received six intramuscular injections of testosterone enanthate 100 mg, at 4-week intervals. After completion of the treatment, subjects were examined in the clinic at 3-month intervals. One year after entry onto the study (6 months after the last injection), serum testosterone and IGF-I concentrations were measured and bone age was assessed. Subjects in the control group received no hormonal therapy, but were examined at 6-month intervals. As with the treatment group, after 1 year, serum testosterone and IGF-I concentrations were determined and wrist roentgenograms were again obtained.

Testosterone level was measured using the solid-phase radioimmunoassay purchased from Diagnostic Products (Los Angeles, CA), with intraassay and interassay coefficients of variation (CVs) of 6% to 8% and 7% to 10%, respectively. GH level was measured using Nichols Institute immunoradiometric GH assay kits (San Juan Capistrano, CA), with intraassay and interassay CVs of 8% and ≤10%, respectively. IGF-I level was measured using the Nichols Institute double-antibody radioimmunoassay, with intraassay and interassay CVs of less than 9% and less than 11%, respectively.

Statistical analyses were performed using the paired *t* test to compare data in the same group before and after 1 year of follow-up evaluation and the unpaired *t* test to compare data among the two groups. The Wilcoxon test was used when data were not normally distributed. Statistical significance was achieved when *P* was less than .05.

From the Departments of Pediatrics and Medicine, University of Alexandria, College of Medicine, Alexandria, Egypt; and the Department of Pediatric Endocrinology, Royal Hospital, Muscat, Oman.

Submitted June 30, 1994; accepted October 21, 1994.

Address reprint requests to Ashraf T. Soliman, MD, Chief, Pediatric Endocrinology, Royal Hospital, PO Box 1331 Seeb, Code 111, Muscat, Oman.

0026-0495/95/44

Table 1. Clinical and Biochemical Data of All the Subjects (mean ± SEM)

	Treatment Group (n = 148)		Control Group (n = 50)	
	Baseline	After 1 Year	Baseline	After 1 Year
Weight (kg)	34.7 ± 0.64	39 ± 0.66	36.2 ± 0.9	37.4 ± 0.8
Weight gain (kg/yr)	1.8 ± 0.02	4.8 ± 0.04*	1.65 ± 0.04	2.8 ± 0.04
Height (cm)	143 ± 0.7	153 ± 0.6	144.5 ± 0.85	149.8 ± 0.92
HtSDS	2.54 ± 0.03	2 ± 0.04*	2.4 ± 0.08	2.65 ± 0.08
GV (cm/yr)	4.6 ± 0.14	11.5 ± 0.36*	4.8 ± 0.1	6.1 ± 0.12
BMI (kg/m^2)	16.3 ± 0.25	17.6 ± 0.32	16 ± 0.3	16.9 ± 0.32
Tanner score	1.6 ± 0.05	2.6 ± 0.06*	1.4 ± 0.04	1.8 ± 0.05
Testicular diameter (cm)	2.6 ± 0.05	3.5 ± 0.05*	2.4 ± 0.05	2.7 ± 0.04
Bone age (yr)	11.5 ± 0.09	12.6 ± 0.08	11.1 ± 0.07	11.9 ± 0.07
BA/CA	0.85 ± 0.005	0.87 ± 0.005	0.86 ± 0.004	0.81 ± 0.004
Testosterone (ng/dL)	56.2 ± 0.6	292 ± 3.2*	66.5 ± 1.8	104.5 ± 2.1
IGF-I (ng/mL)	149 ± 1.5	258 ± 2.9*	160 ± 3.1	198 ± 4.3
GH (μg/L)				
Basal	1.75 ± 0.03	ND	1.2 ± 0.04	ND
Peak*	15.4 ± 0.27	ND	14.2 ± 0.15	ND

Abbreviations: GV, growth velocity; BMI, body mass index; HtSDS, height standard deviation score; ND, not determined.
*$P < .05$ among the two groups.
†After clonidine.

RESULTS

Table 1 lists anthropometric and biochemical data for all subjects before and after 1 year of follow-up evaluation. In the treatment group, height standard deviation score, growth velocity, and weight change increased significantly after therapy as compared with the control group. Sexual maturation as evidenced by Tanner scoring and testicular size increased significantly in the treatment group versus the control group.

Hormonal data are listed in Table 2. Endogenous secretion of testosterone was significantly greater in the treatment group 6 months after the last testosterone injection versus the control group. No significant change in skeletal maturation or the bone age to chronologic age ratio (BA/CA) was found after 1 year of follow-up evaluation among the two groups. The GH response to clonidine was normal in the two groups before the study. Serum IGF-I concentrations increased significantly after treatment with testosterone and were slightly higher in the treatment group versus the control group after 1 year of follow-up evaluation. Free T_4 and TSH concentrations were normal in all subjects before inclusion in the study. Blood urea, serum creatinine, and the hepatic enzymes alkaline phosphatase and alanine transferase were normal in all boys in the treatment group before and after therapy.

For the treatment group, changes in height, weight, and testicular size after therapy in relation to the degree of bone age delay before starting therapy are listed in Table 3. The effect of testosterone therapy on height, weight, and testicular size increments was significantly pronounced in boys with a higher grade of bone age delay before therapy.

Table 2. Hormonal Data of the Two Groups of Boys (mean ± SEM)

	Treatment Group (n = 148)		Control Group (n = 50)	
	Baseline	After 1 Year	Baseline	After 1 Year
Testosterone (ng/dL)	56.2 ± 6	292 ± 32*	66.5 ± 18	104.5 ± 21
IGF-I (ng/mL)	149 ± 15	258 ± 29	160 ± 31	198 ± 43
GH (μg/L)				
Basal	1.75 ± 0.3	ND	1.2 ± 0.4	ND
Peak*	15.4 ± 2.7	ND	14.2 ± 1.5	ND
Free T_4 (pmol/L)	14.6 ± 1.5	15.3 ± 1.5	16.1 ± 2.2	15.9 ± 1.9
TSH (μIU/mL)	1.6 ± 0.3	ND	1.2 ± 0.4	ND

Abbreviation: ND, not determined.
*After clonidine.

DISCUSSION

This was a prospective study designed to determine the growth response to testosterone enanthate therapy (100 mg intramuscularly per month for 6 months) in boys with constitutional delay of growth and sexual development. In our patients, testosterone treatment stimulated a rapid increase in height velocity and weight gain, versus the gradual acceleration seen in the control group. In the treatment group, these growth changes were more pronounced in boys with a greater delay in bone age. The advancement in bone age (the respective mean of bone age and BA/CA) did not differ significantly between the treatment group and the control group after 1 year of follow-up evaluation; the increase in skeletal age equaled that in chronologic age. Six months after testosterone treatment ended, the mean height velocity remained at a normal pubertal rate (8.6 ± 0.4 cm/y). All subjects in the treatment

Table 3. Changes in Height, Weight, and Testicular Diameter in Relation to Bone Age Delay (mean ± SEM)

Bone Age Delay (yr)	No. of Subjects	Weight (kg/mol)	Height (cm/mol)	Testicular Diameter (cm/yr)
1-1.9	41	0.318 ± 0.035	0.812 ± 0.1	0.864 ± 0.024
2-2.9	51	0.423 ± 0.03*	0.906 ± 0.026*	1.04 ± 0.026*
3-3.9	46	0.53 ± 0.11*	1.016 ± 0.1*	1.128 ± 0.025*

*$P < .05$ among groups.

group had clearly entered puberty by the end of the 1-year period. Although the development of secondary sexual characteristics in our patients could have been caused by either exogenous or endogenous androgens, the increase in testicular size and testosterone levels above baseline values ($P < .01$, paired analysis) 6 months after stopping therapy indicated that adequate amounts of gonadotropins were being secreted.

Short courses of testosterone therapy have been shown to increase GH secretion by increasing GH pulse amplitude,[10] and in general, changes in serum IGF-I concentration in early puberty parallel changes in statural growth and GH secretion.[11,12] In our treatment group, IGF-I levels increased significantly after versus before therapy and were slightly higher than levels in the untreated group 6 months after the last dose of testosterone. This denoted that the stimulatory effect of testosterone therapy on the somatotropic (GH) axis and consequently on statural growth was maintained by endogenous testosterone secretion after the short course of testosterone therapy. The normal hepatic enzyme and serum creatinine concentrations 6 months after testosterone therapy denoted the safety of such treatment; however, long-term effects still need to be investigated.

The psychologic effect of the enhanced growth and increased muscle mass induced by testosterone therapy was clearly encouraging. Subjectively, boys in the treatment group were all pleased with the results after 1 year of follow-up evaluation as compared with boys in the control group (only 40% of whom were satisfied with their growth). The only side effect encountered was painful spontaneous erections in two patients of the 148 subjects, which did not necessitate interruption of therapy.

On the basis of our results, we conclude that pharmacologic treatment of constitutional delay of growth and puberty may be considered in adolescent boys with a chronologic age of 14 years and delayed bone age who desire medical intervention. Our regimen appears to be safe and efficacious and has no deleterious effect on skeletal age.

REFERENCES

1. Gordon M, Crouthamel C, Post EM, et al: Psychosocial aspects of constitutional short stature: Social competence, behavior problems, self-esteem, and family functioning. J Pediatr 101:477-480, 1982

2. Galatzer A, Rosenblith E, Laron Z: Psychological and rehabilitational aspects of short stature and delayed puberty, in Gedda L, Parisi P (eds): Auxology: Human Growth in Health and Disease. London, UK, Academic, 1978

3. Marti-Henneberg C, Niirianen AK, Rappaport R: Oxandrolone treatment of constitutional short stature in boys during adolescence: Effect on linear growth, bone age, pubic hair and testicular development. J Pediatr 86:783-787, 1975

4. Kaplan JG, Moshang T, Bernstein R: Constitutional delay of growth and development: Effect of treatment with androgens. J Pediatr 82:38-42, 1973

5. Richman RA, Kirsch LR: Testosterone treatment in adolescent boys with constitutional delay in growth and development. N Engl J Med 319:1563-1567, 1988

6. Rosenfeld RG, Northcraft GB, Hintz RL: A prospective, randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. Pediatrics 69:681-687, 1982

7. Kelch RP, Grumbach MM, Kaplan SL: Studies on the mechanism of puberty in man, in Saxena BB, Beling C, Gandy HM (eds): Gonadotropins. New York, NY, Wiley-Interscience, 1972, pp 524-534

8. Winter JSD, Faiman C: Pituitary-gonadal relations in male children and adolescents. Pediatr Res 6:126-131, 1972

9. Greulich WW, Pyle SI: Radiographic Atlas of Skeletal Development of the Hand and Wrist (ed 2). Stanford, CA, Stanford University Press, 1959

10. Ulloa-Aguirre A, Blizzard RM, Garcia-Rubi E, et al: Testosterone and oxandrolone, a nonaromatizable androgen, specifically amplify the mass and rate of growth hormone (GH) secreted per burst without altering GH secretory burst duration or frequency of the GH half-life. J Clin Endocrinol Metab 71:846-850, 1990

11. Binoux M, Gourmelen M: Statural development parallels IGF-I levels in subjects of constitutionally variant short stature. Acta Endocrinol (Copenh) 114:524-528, 1987

12. Brook CGD, Hindmarsh PC: The somatotropic axis in puberty. Endocrinol Metab Clin North Am 21:767-782, 1992