

## ORIGINAL ARTICLE

# Treatment with a Luteinizing Hormone–Releasing Hormone Agonist in Adolescents with Short Stature

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## ABSTRACT

**BACKGROUND**

Treatment with a luteinizing hormone–releasing hormone (LHRH) agonist increases adult height in children with LHRH-dependent precocious puberty and is prescribed by some practitioners to augment height in short adolescents. We performed a randomized clinical trial to determine whether treatment with an LHRH agonist increases adult height in short adolescents with normally timed puberty.

**METHODS**

Fifty short adolescents (18 boys and 32 girls) with low predicted adult height (mean  $\pm$ SD, 3.3 $\pm$ 1.2 SD below the population mean) received either placebo (24 subjects) or an LHRH agonist (26 subjects). The mean ( $\pm$ SD) duration of treatment was 3.5 $\pm$ 0.9 years in the LHRH-agonist group and 2.1 $\pm$ 1.2 years in the placebo group ( $P$ <0.001). Adult height was measured when bone age exceeded 16 years in girls and 17 years in boys and when the rate of growth was less than 1.5 cm per year.

**RESULTS**

Forty-seven adolescents (94 percent) were followed until they attained adult height. At the time adult height was achieved, the subjects who had been treated with an LHRH agonist were older than those who had received placebo (20.5 $\pm$ 2.1 years vs. 18.0 $\pm$ 2.5 years,  $P$ =0.01) and were taller (standard-deviation score,  $-2.2\pm 1.1$  vs.  $-3.0\pm 1.2$ ;  $P$ =0.01). Analysis of covariance showed that LHRH-agonist treatment resulted in an increase of 0.6 (95 percent confidence interval, 0.2 to 0.9) in the standard-deviation score for height, or an increase of 4.2 cm (95 percent confidence interval, 1.7 to 6.7), over the initially predicted adult height ( $P$ =0.01). Treatment with an LHRH agonist resulted in significantly greater adult height than did placebo in boys and girls, in adolescents with idiopathic short stature, and in those who had a growth-limiting syndrome. The principal adverse event in the LHRH-agonist group was decreased accretion of bone mineral density (mean lumbar vertebral bone mineral density at the time adult height was achieved, 1.6 $\pm$ 1.2 SD below the population mean, vs. 0.3 $\pm$ 1.2 SD below the population mean in the placebo group;  $P$ <0.001).

**CONCLUSIONS**

Treatment with an LHRH agonist for 3.5 years increases adult height by 0.6 SD in adolescents with very short stature but substantially decreases bone mineral density. Such treatment cannot be routinely recommended to augment height in adolescents with normally timed puberty.

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**P**UBERTY FIRST ACCELERATES THE RATE OF growth and then induces epiphyseal fusion, terminating the growth of long bones.<sup>1</sup> In the 1970s, long-acting agonists of luteinizing hormone-releasing hormone (LHRH) were shown to suppress gonadotropin secretion. In children with LHRH-dependent precocious puberty, treatment with LHRH agonists slows bone maturation, delays epiphyseal fusion, and increases adult height.<sup>2-7</sup>

Studies of patients with hypogonadotropic hypogonadism,<sup>8</sup> estrogen insensitivity,<sup>9</sup> or estrogen deficiency<sup>10</sup> have suggested that prolonging the period of growth by delaying senescence of the growth plate<sup>11</sup> can increase adult height. However, changes in the tempo of puberty within the normal range do not influence adult height, since both early- and late-maturing children achieve similar adult height.<sup>12,13</sup> Furthermore, treatment with an LHRH agonist for one to two years in short adolescents with normally timed puberty does not increase adult height.<sup>14-21</sup> However, several studies suggest that combined treatment with growth hormone and an LHRH agonist for three or more years may increase adult height,<sup>22-26</sup> and some clinicians prescribe LHRH agonists to augment height in adolescents with normally timed puberty, despite a paucity of data demonstrating either the safety or the efficacy of such treatment.

We hypothesized that a four-year course of treatment with an LHRH agonist would increase adult height in short adolescents by delaying senescence of the growth plate, thus prolonging the duration of linear growth. We conducted a randomized trial to determine the effect of four years of such treatment on the adult height of adolescents with short stature.

## METHODS

### PATIENTS

Adolescents with a predicted adult height that was at least 2.25 SD below the population mean<sup>27</sup> and with unfused hand and wrist epiphyses were eligible for enrollment, irrespective of the cause of short stature. Subjects were eligible whether or not they were receiving growth hormone therapy.

### PROTOCOL

The study was approved by the institutional review board of the National Institute of Child Health and Human Development. We obtained written assent from the adolescents and written consent from their parents. An assent auditor, who was not involved in

conducting the study, also ensured that the children and parents understood the study design.

Treatment assignments were made in a randomized, double-blind fashion according to a table of random numbers, without any stratification. Patients were assigned to receive either placebo or the LHRH agonist deslorelin (6-D-tryptophan-9-[N-ethyl-L-prolinamide]-10-desglycinamide-LHRH-ethylamide), at a dose of 4 µg per kilogram of body weight, administered each evening by subcutaneous injection, for four years.<sup>2</sup>

The subjects were examined by a pediatric endocrinologist before enrollment, every six months during treatment, and yearly thereafter. At each visit, height was measured 10 times with a calibrated stadiometer (Holtain), and weight was measured with a digital scale (Scaletronix). In addition, a roentgenogram was obtained at each visit to determine bone age, and the pubertal stage was determined.<sup>28,29</sup> Testicular volume was estimated with an orchidometer (Prader).<sup>30</sup> One of us, who was unaware of the treatment assignments, determined bone age according to the method of Greulich and Pyle.<sup>31</sup> Adult height was predicted according to the method of Bayley and Pinneau.<sup>32</sup> Adult height was measured when bone age exceeded 16 years in girls and 17 years in boys and when the rate of growth was less than 1.5 cm per year (i.e., when more than 99 percent of linear growth had occurred).<sup>31</sup>

Plasma gonadotropin, testosterone, and estradiol levels were measured at yearly intervals between 9 and 11 a.m. before or, in the case of gonadotropins, after intravenous administration of 100 µg of LHRH.<sup>33</sup> Metabolic, hepatic, renal, hematologic, and thyroid tests were performed at each visit. When the subjects attained their adult height, we performed dual-energy x-ray absorptiometry in the pencil-beam mode (Hologic QDR-2000) to determine vertebral bone mineral density at L2-L4. Manufacturer's bone mineral density standard-deviation scores for age and sex are reported. A calibration phantom was used according to the manufacturer's specifications. We also used questionnaires to screen the subjects for affective disorders<sup>34</sup> and obtained information on scholastic achievement and social adjustment.

Adolescents who thought that the study medication was ineffective or who found an interruption of normal puberty unacceptable were not encouraged to continue treatment. Instead, they were seen yearly until they achieved adult height so that a valid intention-to-treat analysis could be performed.

**STATISTICAL ANALYSIS**

We calculated that a sample of 50 children was required to detect a difference of 0.55 SD in adult height between the study groups ( $\alpha=0.05$  and  $\beta=0.80$ ). Data were analyzed with the use of Super Anova and StatView 4.02 for the Macintosh (Abacus Concepts). We performed an analysis of variance with repeated measures to determine differences between the groups and over time, using a conservative (Greenhouse–Geisser) F test. Logarithmic transformation of the data was performed where appropriate, and post hoc Fisher paired and unpaired least-significant-difference tests were performed and interpreted with the Bonferroni–Holm adjustment for multiple comparisons. All reported P values are based on two-sided tests.

The primary outcome analysis was an intention-to-treat analysis of covariance, with the standard-deviation score for adult height<sup>35</sup> as the dependent variable, LHRH-agonist treatment as the independent variable, and sex, the presence or absence of growth hormone treatment, the standard-deviation score for initial height, and the predicted and target

standard-deviation scores for adult height as covariates. There were no preplanned interim analyses of efficacy. Categorical data were examined with contingency-table analysis. Pubertal-stage comparisons over time were made with the use of the sign test and the Bonferroni–Holm adjustment. Pubertal-stage comparisons between the study groups were performed with the use of the Mann–Whitney U statistic and the Bonferroni–Holm adjustment. Data are reported as means  $\pm$ SD unless otherwise stated.

**RESULTS****SUBJECTS**

Eighteen boys and 32 girls were enrolled in the study between December 1984 and November 1994. Preliminary data on predicted changes in height for the first 16 adolescents enrolled have been reported previously.<sup>33</sup> At base line, there were no significant differences between the study groups with respect to age, sex, height, bone age, predicted adult height, target adult height, or pubertal stage (Table 1).

**Table 1. Base-Line Characteristics of 50 Adolescents with Short Stature, According to Treatment Group.\***

Characteristic	LHRH Agonist (N=26)		Placebo (N=24)	
	Girls (N=15)	Boys (N=11)	Girls (N=17)	Boys (N=7)
Chronologic age (yr)	12.0 $\pm$ 1.3	13.4 $\pm$ 1.3	12.1 $\pm$ 1.4	13.2 $\pm$ 0.8
Weight (kg)	28.7 $\pm$ 16.9	37.2 $\pm$ 13.1	35.4 $\pm$ 9.7	38.5 $\pm$ 14.7
Height (cm)	131.2 $\pm$ 7.3	138.7 $\pm$ 10.3	133.0 $\pm$ 9.2	137.3 $\pm$ 9.3
SDS for height	-2.6 $\pm$ 0.6	-2.5 $\pm$ 1.0	-2.5 $\pm$ 1.0	-2.5 $\pm$ 1.3
Bone age (yr)	11.5 $\pm$ 1.5	13.2 $\pm$ 1.3	12.4 $\pm$ 1.6	12.9 $\pm$ 2.0
Predicted adult height (cm)	144.7 $\pm$ 6.2	155.6 $\pm$ 7.7	142.1 $\pm$ 7.9	157.1 $\pm$ 7.5
SDS for predicted adult height	-2.8 $\pm$ 1.0	-2.8 $\pm$ 1.0	-3.2 $\pm$ 1.1	-2.6 $\pm$ 1.0
SDS for target adult height†	-0.9 $\pm$ 0.6	-0.6 $\pm$ 1.0	-0.6 $\pm$ 1.5	-1.0 $\pm$ 1.0
Tanner stage for pubic hair	2.8 $\pm$ 0.8	3.2 $\pm$ 0.6	3.0 $\pm$ 0.9	3.0 $\pm$ 0.8
Median	3	3	3	3
Range	1–4	2–4	1–4	2–4
Tanner stage for breast development	2.8 $\pm$ 0.6		3.2 $\pm$ 0.9	
Median	3		3	
Range	2–4		2–5	
Testicular volume (cm <sup>3</sup> )		10.8 $\pm$ 4.2		9.0 $\pm$ 2.4

\* There were no significant differences between the treatment groups. Plus–minus values are means  $\pm$ SD. SDS denotes the standard-deviation score for age and sex,<sup>35</sup> and LHRH luteinizing hormone–releasing hormone.

† Target adult height was based on the mean height of the two parents, adjusted for sex.

Twenty-six subjects had received specific diagnoses associated with short stature (Table 2); the other 24 had received the diagnosis of idiopathic short stature after other identifiable causes of short stature<sup>36</sup> had been ruled out. Three subjects with central hypothyroidism had normal levels of serum thyroid-stimulating hormone, slight decreases in free thyroxine levels, a subnormal surge in the nocturnal thyroid-stimulating hormone level,<sup>37</sup> and no other endocrine abnormalities; in all three, free thyroxine had been restored to normal levels with levothyroxine therapy at least six months before enrollment.<sup>33</sup>

All the adolescents were tested for growth hormone deficiency. Three were treated with growth hormone, at a dose of 0.3 mg per kilogram per week, because the peak growth hormone level was less than 7  $\mu$ g per liter after three stimulation tests (with arginine, insulin, and levodopa).<sup>36</sup> An additional 11 adolescents, with approximately equal distribution between the LHRH-agonist and placebo groups, received growth hormone therapy through their referring physicians, independently of the study protocol and in the absence of a definitive diagnosis of growth hormone deficiency. In this group of subjects, growth hormone was generally prescribed at a dose of 0.3 mg per kilogram per week, given in divided doses either three times or six times a week.

Forty-seven adolescents (94 percent) were followed until they reached adult height. Three adolescents (one in the LHRH-agonist group and two in the placebo group) left the study during the first year and were lost to follow-up. Eight adolescents randomly assigned to receive the LHRH agonist and 20 randomly assigned to receive placebo discontinued the injections before completing the four-year treatment period. All 47 subjects for whom data on adult height were available were included in the analyses, according to the intention-to-treat principle. The average duration of treatment was  $3.5 \pm 0.9$  years in the LHRH-agonist group and  $2.1 \pm 1.2$  years in the placebo group ( $P < 0.001$ ).

#### HORMONAL RESPONSES AND PUBERTAL DEVELOPMENT

At enrollment, all the adolescents had midpubertal peak luteinizing hormone responses to LHRH.<sup>38</sup> Treatment with an LHRH agonist resulted in levels of LHRH-stimulated plasma luteinizing hormone and follicle-stimulating hormone that were lower than pretreatment levels ( $P < 0.001$ ) and the levels in the adolescents who received placebo ( $P = 0.006$ ).

Similarly, during LHRH-agonist treatment, estradiol levels in the girls and testosterone levels in the boys were significantly lower than base-line levels ( $P = 0.003$ ) and the levels in the placebo group ( $P = 0.007$ ). After the study medication had been discontinued, hypothalamic-pituitary-gonadal function did not significantly differ between the two groups.

Among the girls, breast stage did not change significantly in the LHRH-agonist group but increased significantly in the placebo group ( $P = 0.003$ ). Among the boys, testicular volume decreased significantly in the LHRH-agonist group ( $P = 0.01$ ) and increased significantly in the placebo group ( $P = 0.002$ ). After the study medication had been discontinued, further pubertal development occurred in both groups. At the last follow-up visit, the stage

**Table 2. Diagnoses in Study Subjects.\***

Diagnosis	LHRH Agonist (N=26)		Placebo (N=24)	
	total no.	no. receiving growth hormone	total no.	no. receiving growth hormone
Idiopathic short stature	11	3	13†	3
Cushing's syndrome, successfully treated	2	1	1	1
Central hypothyroidism	1	0	2	0
Isolated growth hormone deficiency	1	1	1	1
Medulloblastoma, cured with craniospinal irradiation, and growth hormone deficiency	0		1	1
Hypophosphatemic rickets	1	1	1	1
Fetal alcohol syndrome	1	0	0	
Russell-Silver syndrome	5‡	1	2	0
Meningocele	1	0	0	
Holt-Oram syndrome	1	0	0	
Hypochondroplasia	1	0	0	
Spondyloepiphyseal dysplasia	0		1	0
Leri-Weill dyschondrosteosis	0		1	0
Brachydactyly type E	0		1	0
Trichorhinophalangeal syndrome	1	0	0	

\* LHRH denotes luteinizing hormone-releasing hormone.

† Two patients withdrew from the study during the first year and were lost to follow-up.

‡ One patient withdrew from the study during the first year and was lost to follow-up.

of breast development in girls, testicular volume in boys, and the pubic-hair stage in both did not differ significantly between the study groups.

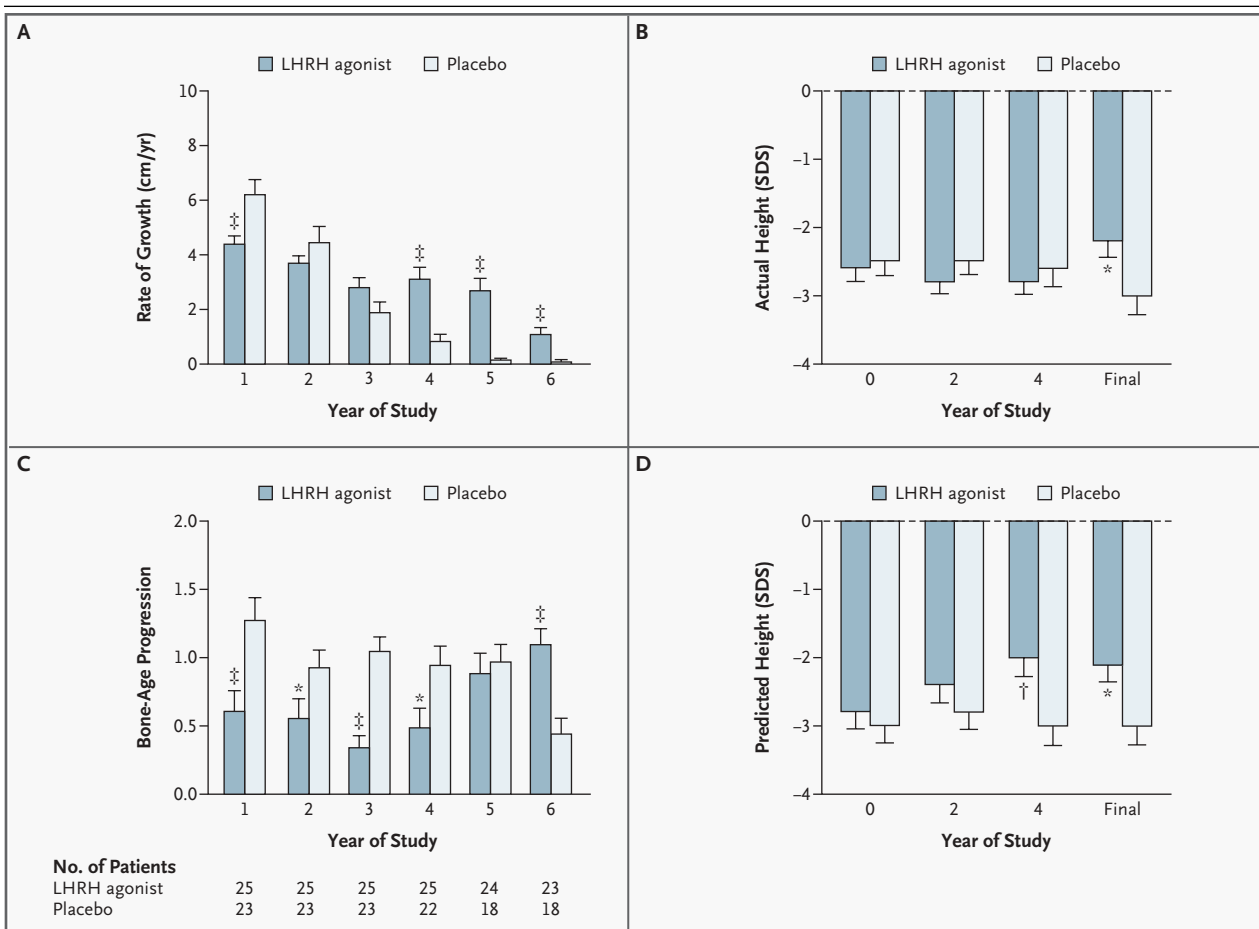
**RATE OF GROWTH**

During the first year of treatment, the rate of growth was lower in the group treated with an LHRH agonist than in the placebo group ( $P=0.004$ ), but it did not differ significantly between the two groups during the next two years (Fig. 1). During the fourth year, however, and for the next two years, the subjects who received an LHRH agonist had a higher rate of growth than those who received placebo ( $P=0.003$ ). During the sixth year, the mean increase in

height was  $1.1\pm 1.2$  cm in the LHRH-agonist group, as compared with  $0.1\pm 0.3$  cm in the placebo group ( $P=0.003$ ). As a result, adult height was achieved at an older age in the patients who received an LHRH agonist ( $20.5\pm 2.1$  years, vs.  $18.0\pm 2.5$  years in the placebo group;  $P=0.01$ ). The rate of growth during the year before adult height was achieved did not differ significantly between the two groups ( $P=0.14$ ).

**BONE AGE**

The mean increase in bone age during the first four years was lower in the LHRH-agonist group than in the placebo group ( $2.0\pm 1.3$  years vs.  $4.2\pm 1.2$  years,  $P<0.001$ ). After the discontinuation of treatment,



**Figure 1. Rate of Growth (Panel A), Rate of Bone-Age Progression (Panel B), and Standard-Deviation Score (SDS) for Actual Height (Panel C) and Predicted Adult Height (Panel D) among Adolescents with Short Stature Who Were Assigned to Receive a Luteinizing Hormone–Releasing Hormone (LHRH) Agonist or Placebo.**

Bone-age progression was calculated as the change in bone age divided by the change in chronologic age. The T bars indicate standard errors. For rate of growth and bone-age progression, the sample decreased as the patients reached their adult height and completed their follow-up visits (the numbers of patients in Panels A and C are shown in Panel C). For measured and predicted adult height, data are shown for all 47 patients who were followed until they reached adult height. Asterisks denote  $P<0.05$ , the dagger  $P<0.01$ , and double daggers  $P<0.005$  for the comparison with placebo.

bone age increased by approximately one year per year. At the time adult height was achieved, bone age did not differ significantly between the LHRH-agonist group and the placebo group ( $17.9\pm 0.9$  and  $17.7\pm 1.0$  years, respectively;  $P=0.51$ ).

#### HEIGHT

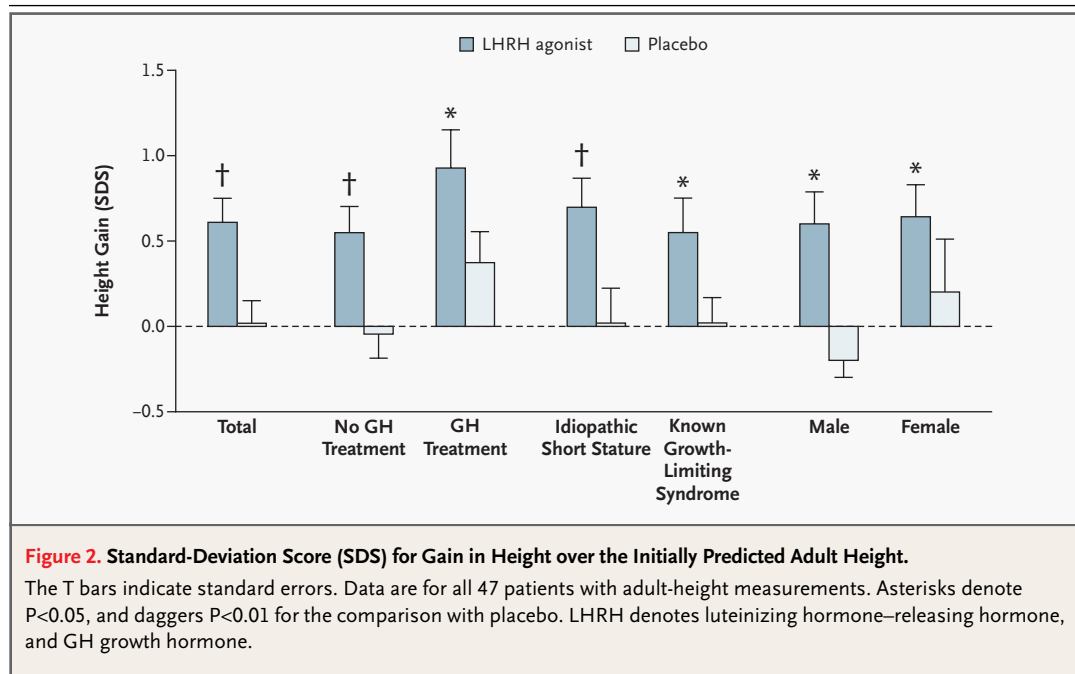
At base line and at two years, neither height nor the standard-deviation score for predicted adult height differed significantly between the study groups (Fig. 1), although at two years, the predicted adult height in the LHRH-agonist group exceeded the predicted height before treatment ( $P<0.001$ ). By the fourth year, however, the standard-deviation score for predicted height was significantly higher in the LHRH-agonist group ( $P=0.007$ ). The gain at four years was largely maintained at the time adult height was achieved (mean standard-deviation score for predicted height,  $-2.0\pm 1.2$  at four years and  $-2.2\pm 1.1$  when adult height was attained;  $P=0.14$ ).

Measured height remained similar in the two study groups until after the completion of treatment (Fig. 1). Although the adolescents who received placebo had largely completed their growth at four years, with a mean gain of only  $0.6\pm 0.7$  cm thereafter, the adolescents who received an LHRH agonist had an additional gain of  $5.9\pm 3.5$  cm ( $P<0.001$ ). At the time adult height was achieved, the patients who had received an LHRH agonist were signifi-

cantly taller than those who had received placebo (standard-deviation score,  $-2.2\pm 1.1$  vs.  $-3.0\pm 1.2$  [ $P=0.01$ ]; measured height,  $153.9\pm 9.5$  cm vs.  $146.9\pm 10.0$  cm [ $P=0.02$ ]). Adult height was less than 2 SD below the population mean in 52 percent of the LHRH-agonist group but in only 28 percent of the placebo group ( $P=0.04$ ). In both groups, however, adult height was below midparental height (i.e., the adjusted mean of the two parents' height), which was  $-0.8\pm 0.8$  SD in the LHRH-agonist group and  $-0.7\pm 1.4$  SD in the placebo group.

When actual adult height was compared with predicted adult height at enrollment, the gains were significantly greater for the patients treated with an LHRH agonist (gain in the standard-deviation score for height,  $0.6\pm 0.6$  vs.  $0.0\pm 0.6$  [ $P=0.003$ ]; gain in absolute height,  $4.2\pm 4.5$  cm vs.  $0.5\pm 4.1$  cm [ $P=0.004$ ]). The primary efficacy analysis of covariance indicated that the effect of LHRH-agonist treatment on height was an increase of 0.6 (95 percent confidence interval, 0.2 to 0.9) in the standard-deviation score, or 4.2 cm (95 percent confidence interval, 1.7 to 6.7;  $P=0.01$ ).

Preplanned analyses showed that the gain in height over that predicted at base line among the patients treated with an LHRH agonist was independent of sex ( $P=0.04$ ), the presence or absence of concomitant growth hormone treatment ( $P=0.03$ ), and the presence or absence of a growth-limiting



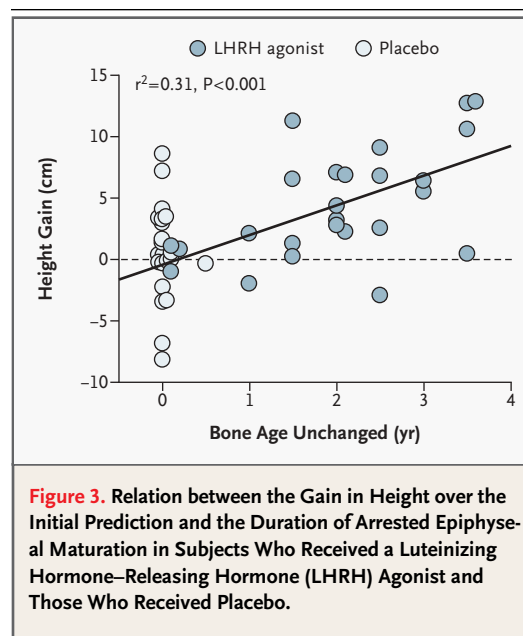
syndrome ( $P=0.04$ ) (Fig. 2). There were no significant interactions between treatment and sex or between treatment and initial stature. There was also an apparent effect of growth hormone (difference in height gain between patients who received growth hormone treatment and those who did not,  $0.4\pm 0.6$  SD;  $P=0.04$ ).

Height in a sitting position, measured at the time adult height was achieved in 43 patients, did not differ significantly between the LHRH-agonist group and the placebo group ( $83.3\pm 5.0$  cm and  $82.0\pm 5.3$  cm, respectively). However, the difference between adult height and height in a sitting position (a measure of subschial leg length) was significantly greater in the LHRH-agonist group ( $70.4\pm 6.6$  cm, as compared with  $66.2\pm 6.0$  cm in the placebo group;  $P=0.02$ ).

The increase in adult height over the initially predicted adult height in the LHRH-agonist group was not significantly correlated with bone age ( $r^2=0.04$ ,  $P=0.16$ ) or chronologic age ( $r^2=0.002$ ,  $P=0.76$ ) at base line. However, the gain in height was positively correlated with the duration of arrested bone maturation during LHRH-agonist treatment ( $r^2=0.31$ ,  $P<0.001$ ) (Fig. 3). The maximal bone age during LHRH-agonist treatment was generally between 13.0 and 14.0 years in girls and between 13.5 and 14.5 years in boys.

#### ADVERSE EVENTS

Vertebral bone mineral density at L2–L4 at the time adult height was reached was significantly lower in the LHRH-agonist group than in the placebo group ( $1.6\pm 1.2$  SD below the population mean vs.  $0.3\pm 1.2$  SD below the population mean,  $P<0.001$ ). Eighteen patients in the LHRH-agonist group and five in the placebo group had bone mineral density that was more than 1 SD below the population mean ( $P=0.003$ ); seven patients in the LHRH-agonist group and one in the placebo group had bone mineral density that was more than 2 SD below the population mean ( $P=0.05$ ). Because many of the syndromes associated with short stature may affect bone mineral, we also compared bone mineral density among the adolescents with idiopathic short stature who received an LHRH agonist and those who received placebo ( $1.3\pm 1.0$  SD and  $0.8\pm 1.0$  SD below the population mean, respectively;  $P=0.20$ ); 82 percent of those with idiopathic short stature in the LHRH-agonist group, as compared with 32 percent of those in the placebo group, had bone mineral density that was more than 1 SD below the population



**Figure 3.** Relation between the Gain in Height over the Initial Prediction and the Duration of Arrested Epiphyseal Maturation in Subjects Who Received a Luteinizing Hormone-Releasing Hormone (LHRH) Agonist and Those Who Received Placebo.

mean ( $P=0.02$ ). We also examined the correlation between bone mineral density and the duration of LHRH-agonist treatment ( $r^2=0.007$ ,  $P=0.30$ ), the duration of arrested bone maturation ( $r^2=0.30$ ,  $P=0.001$ ), and height gain ( $r^2=0.24$ ,  $P=0.001$ ). Two subjects in the LHRH-agonist group and one in the placebo group had a traumatic fracture of a digit during the study. Among the 18 subjects in the LHRH-agonist group and the 12 subjects in the placebo group in whom bone mineral density was measured a mean of  $2.7\pm 1.7$  years after adult height had been reached, the change in bone mineral density did not differ significantly between the two groups ( $0.025\pm 0.053$  and  $0.039\pm 0.037$  g per square centimeter of body-surface area per year, respectively;  $P=0.54$ ). Among subjects in whom bone mineral density was more than 2 SD or more than 1 SD below the population mean at the time adult height was achieved, bone mineral density did not exceed these levels during follow-up.

Reactions at the injection site included erythema, ecchymosis, and in rare cases, induration. None of the reactions required treatment or cessation of the study medication. A major depressive episode was diagnosed in three subjects in the LHRH-agonist group and in two in the placebo group.

Educational achievement was similar in the two groups. Eighty-seven percent of the subjects in the LHRH-agonist group and 57 percent of those in

the placebo group attended college ( $P=0.17$ ); there were no significant differences in self-reported grade-point averages in high school ( $3.3\pm 0.8$  and  $2.9\pm 0.6$ , respectively) or college ( $3.4\pm 0.4$  and  $3.2\pm 0.5$ , respectively). As of the last follow-up visit, three subjects in the placebo group and two in the LHRH-agonist group were married, and a total of 10 children (4 children of subjects in the LHRH-agonist group and 6 children of subjects in the placebo group) had been born, all of whom were healthy.

## DISCUSSION

To test the hypothesis that suppression of sex hormones can postpone epiphyseal fusion and increase adult height in adolescents with short stature and normally timed puberty, we compared the effect of LHRH-agonist therapy with that of placebo on adult height. We found that treatment with an LHRH agonist markedly retarded the progression of bone age and significantly increased adult height. The mean treatment effect was a gain of 0.6 SD in height, as compared with the predicted adult height at base line. LHRH-agonist treatment had no apparent lasting effects on secondary sexual development or on hypothalamic–pituitary–gonadal function but significantly decreased bone mineral density; 69 percent of the subjects who received an LHRH agonist (vs. 21 percent of those who received placebo) had a bone mineral density that was more than 1 SD below the population mean.

Our finding that treatment with an LHRH agonist increased adult height in adolescents with normally timed puberty is consonant with observations in patients who have a pathologically delayed onset of puberty<sup>8,39,40</sup> or who have genetic mutations that prevent estrogen from inducing bone fusion during adolescence.<sup>9,10</sup> The results of our study are also consistent with several earlier studies showing that there is little change in adult height after one to two years of LHRH-agonist–induced pubertal delay, either with or without concurrent growth hormone treatment,<sup>14–21</sup> and with studies of combined growth hormone and LHRH-agonist therapy that suggest that longer periods of treatment with an LHRH agonist may increase adult height.<sup>22–26</sup> Our data show that treatment with an LHRH agonist alone increases the adult height of short adolescents who do not have growth hormone deficiency. With a treatment period of nearly four years, the growth period was prolonged sufficiently to result in a moderate gain in adult height among adolescents with

idiopathic short stature and those with recognized growth-limiting syndromes.

Growth hormone, a relatively safe and moderately effective<sup>41–43</sup> medication that is often used in an attempt to increase height in children with short stature who do not have growth hormone deficiency, was prescribed for 11 of our patients, none of whom had growth hormone deficiency. The patients treated with both growth hormone and an LHRH agonist had the greatest gain in height. Because growth hormone treatment was not randomly assigned, we can make no definitive statement about its effects. Use of growth hormone did not affect the magnitude of the gain in height attributable to LHRH-agonist therapy.

Reduced lumbosacral bone mineral density during treatment and inadequate catch-up accretion of bone mineral after treatment were the main adverse effects in the LHRH-agonist group. Low bone mineral density at the end of adolescence is of particular concern because up to 45 percent of total adult skeletal mass is normally accrued between the ages of 11 and 18 years.<sup>44</sup> The risk of fracture in adulthood doubles with each 1 SD decrease in bone mineral density.<sup>45</sup> A limitation of our study is the lack of base-line data on bone mineral density, particularly in the adolescents with growth-limiting syndromes, although the bone mineral density in the adolescents with idiopathic short stature who were treated with an LHRH agonist was also more likely than that in placebo-treated adolescents to be more than 1 SD below the population mean. Since there was no evidence of accelerated accretion of bone mineral after the completion of linear growth, and since adolescents with low bone mineral density due to reversible conditions (e.g., boys with constitutionally delayed puberty<sup>46–48</sup> and girls with anorexia nervosa<sup>49</sup>) do not have complete catch-up growth in bone mineral density, it is likely that our subjects will never have complete recovery of bone mineral density.

Finally, the psychosocial effects of delaying the completion of pubertal development may be of considerable concern. In-depth studies of the psychological effects of LHRH-agonist treatment in adolescents are required to address this issue.

We conclude that prolonging the growth period by delaying sex hormone–induced growth-plate senescence moderately increases adult height but decreases bone mineral density in adolescents with short stature. For most adolescents, the potential benefits of such treatment will not outweigh the

risks. LHRH-agonist treatment cannot be routinely recommended to augment height in short adolescents with normally timed puberty.

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