

# Letrozole Significantly Improves Growth Potential in a Pubertal Boy With Growth Hormone Deficiency

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**ABSTRACT.** Clinical experience with using an aromatase inhibitor to suppress estrogen production during puberty for improvement of growth potential in adolescents with short stature is limited. This report documents treatment of such a patient with a combination of growth hormone and letrozole, a third-generation aromatase inhibitor. Our case demonstrates a favorable outcome on a short-term basis. *Pediatrics* 2005;115:e245–e248. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-1536](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-1536); bone mineral density, growth hormone, hormonal control, short stature, aromatase inhibitor.

ABBREVIATIONS. AI, aromatase inhibitor; BMD, bone mineral density; GH, growth hormone; PTH, parathyroid hormone; IGF, insulin-like growth factor.

Estrogen plays a critical role for the pubertal growth spurt, skeletal maturation, and accrual and maintenance of bone mass in females as well as males.<sup>1–4</sup> It is now evident that gene mutations of aromatase or estrogen receptor that result in impairment of estrogen production or action have similar phenotypes, including abnormally tall stature with eunuchoid proportions, a lack of pubertal growth spurt, unfused epiphyses, and osteopenia. Aromatase, encoded by the *CYP19* gene located on chromosome 15q21.2 and expressed in bones, is the key enzyme for estrogen biosynthesis.<sup>2,4</sup> It has been proposed that an aromatase inhibitor (AI) can be used to improve the final adult height in short pubertal boys. The hypothesis is that suppressing estrogen formation after the onset of puberty would delay the closure of the epiphyses, thus allowing for an extended period of growth without affecting the progression of androgenic development. Potential adverse effects of AIs, such as reduced bone mineral density (BMD), metabolic effects including a propensity for insulin resistance and dyslipidemia, and impairment of the hypothalamic-pituitary-gonadal axis, need to be considered.<sup>5</sup> To date, a couple of studies, at least in the short term, indicate that the use of an AI is safe and promising.<sup>6–8</sup>

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## CASE REPORT

A white male was first seen for evaluation of short stature at 14 years 8 months old. He was healthy with no other medical problems, and his birth weight and length were reported as normal. Family history was unremarkable. His father's height was 177.8 cm, and his mother's height was 162.5 cm. His midparental target height was 176.7 cm (calculated as the average of parents' heights + 6.55). His initial examination revealed the following: height, 143 cm (<3rd percentile; z score -2.94); upper/lower segment ratio, 1.0; weight, 44.5 kg (11th percentile); pubic hair, Tanner II; testicular volume, 4 to 6 mL; bilateral gynecomastia. Growth hormone (GH) deficiency was diagnosed after a standard comprehensive work-up (GH peak: 6.1 ng/mL, poststimulation), and GH treatment (0.3 mg/kg per week) was initiated at 15 years. The patient responded well (Fig 1). After 14 months of GH treatment, his height increased from 144.5 to 158 cm (z score: from -2.94 to -2.04), a gain of 13.5 cm (Table 1). However, although his puberty advanced to Tanner stage IV for pubic hair and testicular volume increased to 10 mL (Tanner III), his final adult-height prediction still remained 2 SDs below his target height. Letrozole (2.5 mg/day) was added at 16 years 2 months, when his bone age was 14 years. He was treated with the combination GH/letrozole for 17 months, after which letrozole was discontinued. He tolerated the treatment well. Gynecomastia resolved within a few months after combination therapy. Pubertal maturation proceeded to Tanner V (testicular volume: 15–20 mL). After 17 months of treatment, he gained an additional 10 to 168 cm, and his bone age advanced only 9 months (Greulich-Pyle method).<sup>9</sup> His height z score improved further, from -2.04 to -1.08 (Table 1), and his adult-height prediction as estimated by the Bailey-Pineau method<sup>9</sup> improved from 166.4 to 175.3 cm, corresponding to his target height. His upper/lower segment ratio was maintained at 1.0. Weight gain was noticed during the course of treatment (Fig. 1). His BMI increased from 22 (76th percentile) to 24 (83rd percentile) after GH and to 27 (92nd percentile) after the addition of letrozole.

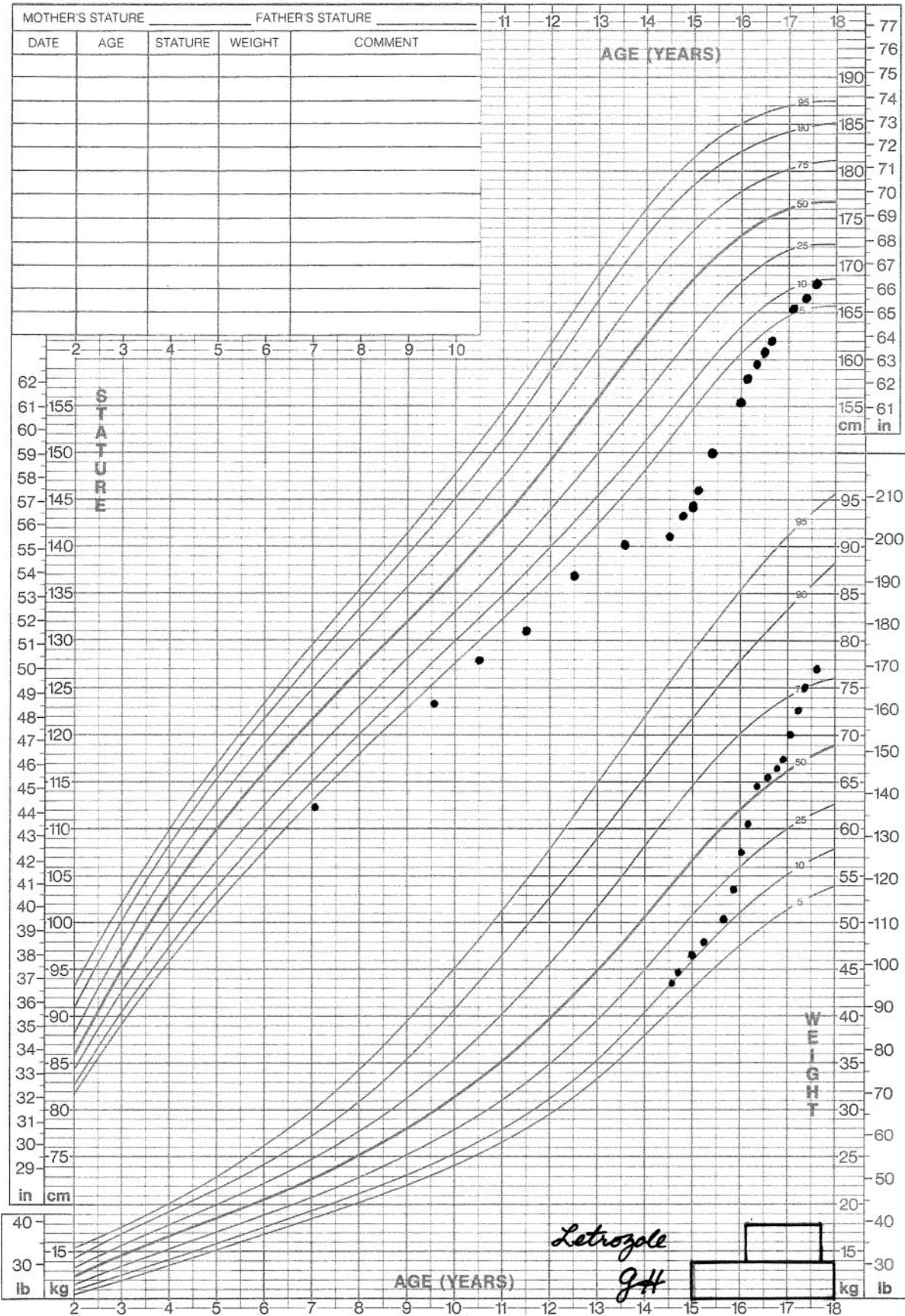
Bone turnover markers were monitored. Four months after starting letrozole, the patient started to receive calcium supplementation (1200 mg/day) and vitamin D<sub>2</sub> (400 IU/day) because of a mildly elevated intact parathyroid hormone (PTH) level of 69.9 pg/mL (reference: 10–65 pg/mL), low-normal 25-h vitamin D<sub>3</sub> level of 23 ng/mL (reference: 10–69 ng/mL), and mildly elevated 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> level of 78 pg/mL (reference: 27–71 pg/mL). Alkaline phosphatase was stable in the reference range, and PTH normalized after calcium and vitamin D supplementation. Bone markers including osteocalcin and N-telopeptide were decreased during therapy with letrozole and GH (see Table 1). Aerial bone density was determined by using a Hologic DEXA scanner (Bedford, MA), and the results were expressed as age-, gender-, and ethnicity-adjusted z scores. Although there was no pretreatment BMD study, a series of studies obtained at 4, 14, and 17 months during therapy actually showed some improvement of z score from -2.50 to -1.90.

As shown in Table 1, there was an initial increase in serum insulin-like growth factor 1 (IGF<sub>1</sub>) from 124 to 824 ng/mL, undoubtedly reflecting the effects of GH therapy, which was then maintained in the high to upper-normal range (reference: 182–839 ng/mL). Basal follicle-stimulating hormone ranged from 9 to 12 mIU/mL (reference: 1.2–11.0 mIU/mL), and luteinizing hormone ranged from 5 to 7 mIU/mL (reference: 0.2–7.0 mIU/mL), both of which are in the high-normal range. Serum testosterone increased from 43 to 460 ng/dL after letrozole and then stabilized between 251 and 450 ng/dL (Tanner V; reference: 300–900 ng/dL). Serum

**PHYSICAL GROWTH  
NCHS PERCENTILES\***

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



\*Adapted from: Hamill PVV, Drizz TA, Johnson CL, Reed RB, Roche AF, Moore WM: Physical growth: National Center for Health Statistics percentiles. AM J CLIN NUTR 32:607-629, 1979. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

Fig 1. Growth chart.

TABLE 1. Patient Data

	15 y	15 y 2 mo	16 y 2 mo	16 y 4 mo	16 y 6 mo	16 y 10 mo	17 y 2 mo	17 y 4 mo	17 y 7 mo
Time	-14 mo	-12 mo	0 mo	2 mo	4 mo	8 mo	12 mo	14 mo	17 mo
GH (0.3 mg/kg per wk)	+	+	+	+	+	+	+	+	+
Letrozole (2.5 mg/d)	-	-	+	+	+	+	+	+	-
Height, cm	144.5	146.0	158.0	159.5	161.0	162.2	165.5	166.5	168.0
z score of height	-2.94	-2.92	-2.04	-1.92	-1.72	-1.72	-1.35	-1.25	-1.08
BMI	22.0	22.0	24.0	25.5	25.0	25.0	25.5	26.0	27
Tanner stage	2	2	3	3	3	4	4	5	5
Bone age	13 y 6 mo		14 y			14 y 3 mo			14 y 9 mo
Predicted adult height, cm	158.0		166.4			173.0			175.3
IGF1, ng/mL	124.0		824.0			700.0			804.0
Follicle-stimulating hormone, mIU/mL				740.0			527.0		792.0
Luteinizing hormone, mIU/ml				10.0			9.0		9.0
Testosterone, ng/dL				7.0			5.0		5.0
Estradiol, pg/mL				460.0		270.0	251.0		450.0
Intact PTH, pg/mL				6.0		8.0	9.0		9.0
Alkaline phosphatase, U/L	238.0		287.0	360.0	69.9	50.3	12.0		22.0
Osteocalcin, ng/mL				332.0		275.0	312.0		256.0
N-Telopeptide, nM BCE/mM creatinine				134.3		115.0	23.0		29.2
BMD, z score				682.0		398.0	421.0		370.0
				-2.50					-1.70

+ indicates off prescription; —, on prescription; BCE, bone collagen equivalents.

estradiol was stable at 6 to 9 pg/mL (Tanner V; reference: 3–45 pg/mL) despite the pronounced rise in testosterone. Estradiol was assayed at the Mayo Medical Laboratories (Rochester, MN) by radioimmunoassay after extraction and chromatography; the testosterone assay was performed in our pediatric endocrine laboratory by a similar method. The estradiol-to-testosterone ratio decreased from 0.123 to 0.013 (a 9.4-fold decrease) after starting letrozole treatment, suggesting a relative suppression of estradiol. The estradiol-to-testosterone ratio was subsequently maintained in a range of 0.021 to 0.036 (a 3.8- to 5.9-fold decrease). Serial liver-function tests during and after letrozole treatment were normal.

Lipid profile and fasting plasma glucose were normal after 17 months of combination therapy, although the fasting insulin level was elevated at 41 mIU/mL. An oral glucose-tolerance test showed no impairment of glucose tolerance. The growth chart and hormonal and other data are presented in Fig 1 and Table 1.

## DISCUSSION

The effect of estrogen on the dynamic processes of bone turnover is multifactorial. Its actions involve other hormones and factors such as GH, IGFs and their binding proteins, other growth and morphogenic factors, thyroid hormone, vitamin D, retinoids, PTH and PTH-related peptide, cytokines, and their receptors.<sup>10</sup> Although it is clear now that estrogen plays a major role in the pubertal growth spurt, skeletal maturation, and the accrual and maintenance of bone mass in both females and males, there is also evidence supporting a direct role for androgen on bone mass accrual.<sup>11–13</sup> Manipulating hormone levels by AIs to decrease estrogen and increase androgen levels is an attractive option for extending the period of growth of short boys in puberty.

Our case documents a favorable outcome with GH and AI therapy in the enhancement of growth potential at least on a short-term basis. The adult-height prediction improved significantly while pubertal maturation proceeded unimpeded. Letrozole has been well tolerated by the patient. Potential adverse effects of AIs including decreased bone accretion and maturation and abnormalities in pubertal maturation have to be monitored carefully. Although BMD in our patient was at -2.5 (z score) after initiation of letrozole, it subsequently improved, which is likely because of the beneficial effect of GH and probably also the increase in endogenous testosterone. Biochemical markers of puberty including serum testosterone, gonadotropins, and changes in the estradiol-to-testosterone ratio showed the expected effects of relative estrogen suppression, and the hormone levels eventually remained in the normal range for the pubertal stage.

After 17 months' treatment of GH and letrozole, the lipid profile was normal. The only adverse finding was an indication of insulin resistance, with an elevated fasting insulin level. The cause of this insulin resistance (whether due to the patient's excess weight or the treatment) is impossible to determine in this single case. Overall, the degree of the aromatase inhibition significantly improved height prediction without a negative impact on either the gonadotropin-testicular axis or bone health.

Recent studies by Dunkel and co-workers<sup>6–8</sup> in Finland showed results generally consistent with our observations. The authors compared the effect of letrozole plus testosterone to testosterone alone in

treating boys with delayed puberty. After 18 months of treatment, their letrozole group increased the average predicted final adult height by 5.1 cm. In our own patient treated with comparable doses of letrozole in addition to GH, the predicted final height increased by 8.9 cm. It is encouraging to note that in the patients of Dunkel and co-workers, no detrimental effects on BMD were found.<sup>7</sup>

Gonadotropin-releasing hormone analog (GnRHa) therapy has been used for the treatment of short stature in pubertal boys and girls.<sup>14</sup> Detrimental effects of GnRHa on body composition, muscle strength, and protein, lipid, and calcium metabolism, in addition to inhibiting virilization in males, have been the subject of several publications.<sup>15–17</sup> These effects make the use of these analogs unsuitable in the long term if the sole purpose of treatment is to increase final height. The conclusion from a recent study by Yanovski et al stated that “treatment with an LHRH [luteinizing hormone-releasing hormone] 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.”<sup>18(p908)</sup> Thus, the use of a potent selective aromatase blocker offers the advantage of continued virilization and maintenance of pubertal body composition<sup>5,7</sup> in boys while potentially delaying skeletal maturation. We therefore believe that the use of an AI with or without GH is a better option for enhancing the growth potential of short pubertal boys. Although our case and the Finnish studies showed a short-term benefit using an AI, long-term controlled studies are necessary to establish its safety and efficacy.

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