



Fig 2. Frequency distribution of the gain in adult height over pretreatment projected height, using the Lyon projection method.

ment with GH, use of estrogen replacement, parameters used to define adult height, and method used to predict what the adult height would have been without treatment with GH.

Although the cumulative change in TS-specific height SDS shows much variability, the increase in height SDS observed with increasing duration of GH treatment, overall, is highly significant. The importance of the duration of treatment should be kept in mind in evaluating published reports of the effect of GH on adult height in patients with TS. Other variables that affect outcomes favorably are younger CA and BA at the start of treatment and more frequent injections of GH. The lack of a statistically significant effect of the size of the doses of GH on the change in height SDS probably reflects the narrow range of doses used, because other studies have shown a logarithmic relation between the rate of growth and the size of the doses of GH.¹²

The definition of adult height used for analyzing data also may affect the perceived benefit of treatment with GH. The criteria of CA and BA as described previously would likely underestimate (*not* overestimate) adult height and therefore would yield relatively conservative data on the effect of treatment with GH.

The method used to estimate what the adult height would have been without treatment with GH will affect the observed gain in height. Attie and associ-

ates¹¹ compared five methods of predicting adult height in patients with TS, using data from patients with TS in the United States who had not been given growth-promoting drugs. They found that the Lyon projection method,⁴ used in our study, was one of the most reliable means of predicting adult height, with a mean overprediction of only 0.3 cm.

Because the age of the patients in this analysis was greater than the average age of girls with TS who were enrolled in the NCGS, we may expect that outcomes will improve as data from patients who began taking GH at younger ages and who have been taking GH for longer periods of time become available. Nevertheless, even though the patients with TS whom we have described began taking GH at a relatively older age and took it for a relatively short period, 60% still showed clinically meaningful gains in adult height compared with their pretreatment projected height.

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Turner Syndrome and Osteoporosis: Mechanisms and Prognosis

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ABSTRACT. Despite only limited reports of a greater number of fractures during childhood or adulthood, osteoporosis historically has been described as a feature in Turner syndrome, because of the frequent observation of radiographic osteopenia and the coarse trabecular pattern of the carpal bones on radiographs. The pathogenesis of

the skeletal demineralization remains unclear, but the data support the concept of an intrinsic bone defect that is then exacerbated by a number of hormonal factors, including the growth-regulating hormones, the gonadal steroids, and possibly the calcium-regulating hormones. The advent of more refined methods, such as single- and

dual-photon absorptiometry and dual energy x-ray absorptiometry, has led to improved insights into bone mineral density (BMD) status in Turner syndrome (TS). A major limitation of these projection methods is that they report areal and not true volumetric BMD, resulting in an underestimation of the true BMD in smaller subjects. In assessing BMD in TS, various methods have been used to eliminate the confounding effect of bone size. Some consistent patterns do emerge in persons with TS who are not treated with long-term growth hormone (GH) or estrogen therapy. A significant deficit in cortical bone commonly appears in childhood and usually is associated with a low bone-turnover state. Significant osteopenia at predominantly trabecular sites develops during mid- to late adolescence and persists into adulthood, when it is associated with increased bone turnover.

Preliminary BMD data on patients after long-term GH therapy show an absence of osteopenia. With respect to the impact of long-term estrogen therapy, the BMD deficit in adults with TS who have been treated adequately with estrogen, but who have not been treated with GH, is less than it is in those who have been insufficiently treated or not treated at all with estrogen. The available data indicate that long-term GH treatment during the prepubertal and early to midpubertal years optimizes BMD and improves the prognosis for adequate peak bone mass being achieved after a puberty that, most often, has been induced with exogenous estrogen. Long-term treatment with estrogen and progestin that is initiated during mid- to late adolescence and is continued throughout adulthood appears necessary for a normal peak bone mass to be achieved and the BMD to be preserved well beyond the time of peak bone mass.

Additional measures to prevent osteoporosis must be used, such as ensuring adequate calcium intake and ample weight-bearing activities, focusing on preventing injuries and avoiding overtreatment with thyroid hormones. Long-term surveillance with measurement of BMD and of bone turnover in a large TS population into their later adult years is necessary before it can be concluded that the osteopenia observed in TS is a nonprogressive asymptomatic bone defect of no clinical consequences. *Pediatrics* 1998;102:481–485; *Turner syndrome, osteoporosis, osteopenia, growth hormone, estrogen therapy, peak bone mass, bone mineral density.*

ABBREVIATIONS. BMD, bone mineral density; TS, Turner syndrome; GH, growth hormone; IGF-I, insulin-like growth factor I.

The frequent observation of radiographic osteopenia, together with reports of insufficient BMD, in TS has led many investigators to consider osteoporosis an additional feature in this disorder. The pathogenesis of the osteopenia remains unclear. In this review, the relevant findings in TS

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will be presented, followed by a discussion of the potential clinical significance of these findings and the current skeletal prognosis.

PATHOGENESIS OF OSTEOPENIA IN TS

No conclusive data have emerged to explain the mechanisms involved in the skeletal demineralization commonly observed in TS. Low bone turnover is inferred from reports of decreased levels of the markers of bone formation in prepubertal girls with TS. Bergmann and colleagues reported low-normal serum osteocalcin levels and significantly decreased levels of serum procollagen-III N-terminal extension peptide in a group of 6 prepubertal girls (age, 7 to 13 years) with TS.¹ Significantly reduced levels of osteocalcin, alkaline phosphatase, and bone-specific alkaline phosphatase were found in a study in 17 untreated subjects 4 to 20 years of age.² The most striking finding in quantitative histomorphometry of the transcortical iliac crest bone biopsy specimens from 2 adolescents with TS who had not been treated with estrogen was the low percentage of trabecular bone volume and the lack of active bone-forming surfaces.³

These results are consistent with a state of impaired bone formation in TS, at least before later adulthood. The diminished bone deposition may be attributable to a fundamental bone defect that is related to the missing X chromosomal material. The increased mortality in TS from aortic dissection suggests the presence of a connective tissue defect in the blood vessels, a defect that may be expressed in the bone matrix as well. The osteoblasts may produce an abnormal matrix or a matrix that is hyperresponsive to one or more of the systemic or local regulators of bone turnover. Collagen studies on skin or bone in TS have not yet been reported. Mapping of the X chromosome may provide additional insights.

ENDOCRINE STATUS AND ITS POTENTIAL ROLE IN THE PATHOGENESIS OF OSTEOPENIA IN TS

A number of hormonal factors that may exacerbate the presumed underlying bone defect have been identified.

Calcium-regulating Hormones (Parathyroid Hormone, Calcitriol, Calcitonin)

Normal basal levels of calcium and phosphorus, alkaline phosphatase, intact parathyroid hormone, calcidiol, and calcitriol were reported in a group of 14 untreated subjects with TS 4 to 21 years of age.⁴ The administration of oral calcitriol caused a rise in the serum osteocalcin levels in these patients that was similar to that in control subjects, suggesting normal osteoblastic function. However, the parathyroid hormone–calcitriol axis in response to a low-calcium diet in these subjects was impaired relative to that in the control subjects, the cause of which remains unclear. If this finding were to be replicated in additional studies, it could indicate that persons with TS are more vulnerable to bone loss because of long-term low intake of calcium.

Decreased basal levels of calcitonin were reported in one study in 11 untreated subjects with TS 14 to 43 years of age.⁵ Even if a deficiency of calcitonin were

to be confirmed in subsequent studies, it is unlikely that this hormone plays a role in the pathogenesis of osteopenia in TS, because neither calcitonin deficiency in athyrotic subjects nor calcitonin excess in subjects with medullary thyroid carcinoma affects bone density. Overall, the available data provide little evidence to support a substantial role for any of the calcium-regulating hormones in the osteopenia in TS.

Growth-regulating Hormones (GH, Glucocorticoids, Insulin, Thyroid Hormones)

The GH–insulin-like growth factor I (IGF-I) axis is a powerful determinant of bone mass, and subtle abnormalities of this axis in TS have been reported by a number of investigators.^{6,7} It has been concluded from these studies that the gradually increasing levels of gonadal sex steroids supplement endogenous GH secretion, causing the elevation in IGF-I levels that occurs during normal puberty. The deficiency in both GH and IGF-I that occurs in pubertal girls with TS may contribute to their osteopenia.

Saggese and associates reported findings that suggest an important role of GH therapy in increasing the peak bone mass in children with classic GH deficiency.⁸ The low levels of serum osteocalcin and of C-terminal propeptide of type I procollagen that have been reported in children with GH deficiency suggest reduced bone formation. The data that are emerging in TS appear somewhat analogous to those in GH deficiency.

Thyroid hormones increase bone turnover, but with a greater increase in resorption than formation, so that excess levels of thyroid hormones can lead to a decrease in bone mass. Because there is a higher prevalence of overt hypothyroidism in TS, avoiding overtreatment with thyroid hormones is important.

Glucocorticoid secretion has not been reported to be abnormal in TS and therefore is presumed not to contribute to the osteopenia. A greater prevalence of insulin resistance, a risk factor for the development of noninsulin-dependent diabetes mellitus, in TS has been well established, but there is no evidence for its having a role in the osteopenia.

Sex Steroids

Estrogen

The vast majority of girls with TS are estrogen-deficient during both their pre- and postpubertal years. It is possible that normal prepubertal estrogen levels augment bone accretion, but this has not yet been shown. The absence of rising estrogen levels in pubertal persons with TS causes both a failure to shift to endosteal cortical bone growth and a lack of the usual estrogen-mediated accelerated phase of trabecular bone deposition.⁹ Estrogen deficiency therefore is likely to play a major role in the osteopenia in TS.

The situation in TS should not be considered analogous to postmenopausal osteoporosis or surgical menopause, both of which are characterized by a phase of accelerated bone resorption and are manifestations of a state of estrogen withdrawal. The bone

density, biopsy, and marker data in nonestrogen-treated adolescents with TS are more consistent with a prolonged phase of suboptimal bone accretion. The markers of bone turnover are higher in untreated than in estrogen-treated adults with TS, but the ratio of the markers of bone resorption to bone formation is not greater, as it is in early menopause during the phase of accelerated bone loss.¹⁰

Progesterone

The effect of progesterone on bone mass remains uncertain; thus, it is not clear whether the progesterone deficiency in TS contributes to the osteopenia.

Androgens

Androgens may increase the bone mass in females through an indirect effect on increasing the muscle mass and by aromatization to estrogen. Adrenarche in TS appears to be normal, but ovarian androgen production is presumably low. However, it remains unlikely that the androgen status plays a significant role in the osteopenia.

SKELETAL DEMINERALIZATION IN TS

Radiographic osteopenia, or skeletal demineralization, is commonly observed in persons with TS during both the pre- and postpubertal years, and it does not appear to be related to cytogenetic findings. A coarse trabecular pattern of the carpal bones, seen on conventional hand–wrist films, also has been reported in TS.¹¹ Radiogammetry, the first quantitative method used to assess the amount of cortical bone, showed deficient periosteal growth before age 11 years and a failure to shift to endosteal bone formation after that age.^{12,13}

The advent of more refined methods, such as single- and dual-photon absorptiometry and dual energy x-ray absorptiometry, has led to improved insights into the BMD status in TS. A major limitation of these projection methods is that they report areal and not true volumetric BMD, which results in an underestimation of the true BMD in smaller persons, such as persons with TS. Various methods have been used to minimize the confounding effects of bone size, such as controlling or normalizing for bone age, height, weight, body mass index, and pubertal stage and using a mathematical model to estimate the bone volume, which yields a measurement called bone mineral apparent density.¹⁴

There is a significant deficit in radial BMD during childhood and adolescence in persons with TS who are not treated with GH or estrogen, and this deficit is observed not only for their chronologic age but also for their body mass index and bone age. Only by correcting for height does the radial BMD in persons with TS appear normal. Collectively, the data suggest a deficit at the radius, a largely cortical site, throughout childhood, which supports the earlier findings by radiogammetry.^{3,15–17}

The data on spinal BMD, a predominantly trabecular site, are less impressive. One study reported a small but significant deficit in lumbar BMD for chronologic age and body mass index, but not for bone age or height age.¹⁵ The magnitude of the deficit in

spinal BMD is less than that at the radius, and in one study, the deficit was observed only at age 14 years and older.³

Cross-sectional BMD studies in adults with TS through the 6th decade of life have focused primarily on the effect of long-term estrogen therapy on BMD.^{10,18-21} Most of the studies did not correct for body size and, because the subjects had not been treated with GH and were significantly shorter than age-matched control subjects, the deficits in BMD that were shown with the projection methods that were used are likely exaggerated. Nonetheless, the reports consistently show that longer durations of estrogen therapy reduced the deficits in BMD, with severe osteopenia occurring in those adults in whom the use of estrogen had been delayed until after adolescence. Unlike the pattern observed in children and adolescents, the magnitude of the BMD deficit at trabecular sites is equal to or greater than that of the deficits observed at primarily cortical sites. This finding may be explained by the pattern of loss that occurs with aging combined with the greater impact of estrogen on trabecular bone.

EFFECTS OF HORMONE TREATMENT ON BMD IN TS

Effect of Long-term GH Therapy on BMD

There are no conclusive prospective data on the effect of short-term GH therapy (≤ 2 years) on BMD in patients with TS, and no long-term prospective studies have been published to date.^{1,22} However, two cross-sectional studies in prepubertal and pubertal patients with TS who were treated with GH for an average of 3.2 years show a lack of osteopenia at several skeletal sites. The first study, in prepubertal patients, assessed BMD at the total body, femoral neck, and lumbar spine in the patients with TS relative to that in a normal control group matched for height, bone age, weight, and body mass index. The lumbar BMD in the patients with TS was significantly greater than that in the control group, and there were no differences in total body or femoral neck BMD.²³ The second study, which involved both prepubertal and pubertal subjects, measured BMD at the lumbar spine and total body.²⁴ The results were

analyzed according to chronologic age, bone age, height, pubertal stage, and calculation of bone mineral apparent density, and by all these measures, the BMD status in the subjects with TS was equal to or greater than that in the control subjects. Both lumbar and total body BMD and bone mineral apparent density were greater in the group with TS than in the control subjects matched for height. The results of studies that evaluated lumbar BMD in patients with TS who were or were not treated with GH are summarized in Table 1; these results suggest that long-term therapy with GH before puberty improves BMD status. This apparent BMD boost from long-term GH therapy may make it possible to delay using estrogen therapy in patients with TS until later adolescence, if GH therapy is needed to maximize final adult height, without compromising peak bone mass.

Effect of Estrogen Therapy on BMD

As discussed above, the cross-sectional studies in adults with TS unequivocally show the bone-enhancing effect of long-term estrogen therapy. There is a paucity of short-term prospective data on the effect of estrogen on BMD in TS, but the data that are available consistently show a positive effect. Most of these data are from small subsets of patients from the larger cross-sectional studies in adolescents with TS in whom estrogen was started during the study period and in whom a second measurement of BMD was obtained after the estrogen had been started.^{1,24,25} There have been no long-term prospective studies of the effect of estrogen on BMD in TS. Such longitudinal studies are needed not only for comparing the efficacy of different estrogen and progestin regimens but also for determining the optimal time to initiate estrogen therapy to ensure that an adequate peak bone mass is achieved.

CLINICAL MANIFESTATIONS OF OSTEOPOROSIS IN TS

Symptomatic osteoporosis has not been widely reported in TS. Ross et al reported that the incidence of wrist fractures in a group of untreated

TABLE 1. Lumbar BMD in Subjects With Turner Syndrome

Investigators (method)	No. of Subjects (age, y)	BMD for				
		CA	BA	BMI	HA	Tanner stage
Without GH treatment						
Ross et al ¹⁵ (dual-photon absorptiometry)	78 (9-13)	↓	WNL	↓	WNL	—
Rubin et al ³ (dual-photon absorptiometry)	21 (6-13)	WNL	—	—	—	—
	13 (14-18)	↓	—	—	—	—
With GH treatment						
Neely et al ²⁴ (dual energy x-ray absorptiometry)	19 (14.3 [mean])	WNL	↑ (<12.5 y) WNL (>12.5 y)	—	↑	↑ (stages 1, 2) WNL (stages 3-5)
Lanes et al ²³ (dual energy x-ray absorptiometry)	12 (6-11)	—	↑	↑	↑	—

In all the studies, the comparisons were made with the values in control groups of girls without TS. CA indicates chronologic age; BA, bone age; BMI, body mass index; HA, height age; WNL, within normal limits.

girls with TS 9 to 13 years of age was significantly higher than that in normal children (9.1 per 1000 per year vs 3.5 per 1000 per year; $P < .003$).¹⁵ A significantly higher frequency of fractures than in a control group ($P = .014$) was reported in a group of adults with TS, and half of the fractures occurred at typical osteoporotic sites (wrist, spine, femoral neck).¹⁸ The classic vertebral crush fracture syndrome, which is associated with the greatest degree of physical deformity and pain, has not been reported to occur more frequently in TS. It is possible that some degree of underreporting has occurred, because few persons with TS who have reached the 5th decade of life and beyond, the time that this fracture syndrome might evolve, are being cared for by academic physicians. The recent establishment of a TS database by the National Turner Syndrome Society may help clarify this possibility. Therefore, before it can be concluded with certainty that there is no higher incidence of vertebral crush fractures in TS, an older population of women with TS should be followed and screened with spinal radiography. Furthermore, long-term follow-up care of older patients with TS into their 7th and 8th decades of life would be necessary before it could be determined whether there is a greater incidence of hip fractures in TS.

SUMMARY

The findings reviewed here suggest a state of impaired bone formation during childhood, with a larger deficit at predominantly cortical sites. A significant deficit may develop during adolescence and adulthood at largely trabecular sites. A postulated intrinsic bone defect may be responsible for the bone mass deficits observed during childhood, and hormonal factors appear to contribute to the osteopenia that occurs later.

Long-term GH therapy during childhood and adolescence may ameliorate the deficits in bone mass and improve the prognosis for an adequate peak bone mass. Long-term estrogen and progestin therapy initiated during mid- to late adolescence and continued through adulthood appears necessary for a normal peak bone mass to be achieved and for bone mass to be preserved throughout adulthood. Interrupted courses of estrogen therapy should be avoided, because these may mimic a state of estrogen withdrawal.

Additional measures to prevent osteoporosis should be used in persons with TS, such as ensuring adequate calcium and nutritional intake, encouraging ample weight-bearing activities, stressing the importance of avoiding injuries, and avoiding over-treatment with thyroid hormones. Long-term prospective studies of BMD and bone turnover in the current population with TS are necessary to establish appropriate guidelines for preventing osteoporosis. Elucidating the mechanism(s) of the postulated intrinsic bone defect would make it possible to develop more specific pharmacologic approaches to reverse the osteopenia.

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