

Musculoskeletal Analyses of the Forearm in Young Women with Turner Syndrome: A Study Using Peripheral Quantitative Computed Tomography

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Turner syndrome (TS) is associated with multiple skeletal abnormalities. Fracture incidence appears to be increased, but the reasons for this are not entirely clear. In the present study, we used peripheral quantitative computed tomography to evaluate bone mass, density, geometry, and strength of the radial metaphysis and diaphysis as well as maximum forearm muscle cross-sectional area (CSA) in a group of 21 TS patients. These individuals were 19.5 ± 2.3 yr of age (mean \pm SD; range, 16.2–25.4 yr) and had completed growth after having received GH therapy; all but one were receiving estrogen supplementation. Despite short stature, cross-sectional bone size was normal compared with age-matched healthy controls. However, bone mineral content was decreased, resulting in a low total volumetric bone mineral density. This was due to decreased cortical thickness at both sites of measurement,

whereas trabecular volumetric bone mineral density of the metaphysis was normal. Muscular CSA was normal. The relationship between muscle CSA and external bone size was similar between TS patients and healthy young women. However, TS patients had less bone mineral content and cortical CSA relative to muscle CSA than healthy young women, but similar muscle-bone relationships as healthy prepubertal girls. These findings are compatible with a normal adaptation of external bone size to the mechanical loads imposed by the muscle system and a lack of pubertal effect on the endocortical bone surface, despite estrogen supplementation. Bone strength may not be adequate for the relatively high body weight of TS patients (+0.8 SD score), which could contribute to an increased propensity for fractures. (*J Clin Endocrinol Metab* 86: 5819–5823, 2001)

TURNER SYNDROME (TS) is associated with multiple skeletal abnormalities including short stature, cubitus valgus, Madelung's deformity, and shortness of the fourth metacarpal bone (1). Osteoporosis has been another traditional item on this list since Finby and Archibald (2) reported low bone mineralization on standard x-rays of TS patients four decades ago. Prospective studies on fracture incidence are lacking, but a recent population-based retrospective study concluded that the relative risk of fracture was increased by about 2-fold in TS patients (3). Fracture incidence appeared to be increased already in children and young adults, which was also found in some smaller series of TS patients (4, 5).

The basis for this likely increase in fracture incidence is not entirely clear. Early quantitative densitometric studies seemed to confirm the impression gained from standard x-rays that bone mass was decreased in TS (6–8). However, these and several subsequent studies neglect the fact that bone size might be decreased in TS and that smaller bones can be expected to weigh less, even if they are otherwise completely normal. The finding that (short) TS patients have lower bone mineral content (BMC) or areal bone mineral density than (taller) healthy age-matched controls was therefore considered inconclusive (9).

Recent authors tried to circumvent this size-related prob-

lem either by matching TS patients with healthy controls of the same height or weight (4, 9, 10) or by using mathematical algorithms to estimate three-dimensional volumetric BMD (vBMD) from two-dimensional densitometric results (11). Either way, densitometric results were brought back to normality, and it was concluded that in TS, bone mass is adequate for bone size (4, 9–11).

Nevertheless, both of these approaches to adjust for bone size are only valid if bone shape is the same in TS patients as it is in controls. It is uncertain whether this important condition is met, given the many skeletal abnormalities in TS. It is therefore preferable to study the skeleton of TS patients by methods that can distinguish between effects of size and mass and do not require previous assumptions on bone shape. Peripheral quantitative computed tomography (pQCT) is such a method. Thin tomographic sections of long bones are analyzed, which allows for precise determination of three-dimensional bone density. Further advantages of this technique include the possibility to assess trabecular bone independently of cortical bone and to evaluate various measures of macroscopic bone geometry, which can be combined into indices of bone strength (12, 13).

During childhood and adolescence, bone strength continually has to adapt to increasing mechanical loads. Because the largest physiological loads on bones are created by muscle contraction, bone strength needs to be adapted to muscle force (14, 15). Some insight into this muscle-bone relationship can be gained by performing pQCT analyses at limb sites where the cross-sectional area of muscles (muscle CSA) is at

Abbreviations: BMC, Bone mineral content; CSA, cross-sectional area; pQCT, peripheral quantitative computed tomography; TS, Turner syndrome; vBMD, volumetric bone mineral density.

its maximum. In a single measurement run, both muscle CSA and bone mass and geometry can be evaluated (16).

With respect to normal bone development, it has been shown previously that postpubertal girls have more bone relative to muscle CSA than prepubertal girls or males (16). This is because during puberty girls develop a relatively smaller marrow cavity than boys, a process that was already observed by radiogrammetry of the second metacarpal (17). It can be hypothesized that these changes during female puberty result from hormonal changes occurring during that period in life. TS might be a good model to test this hypothesis, because the normal pubertal changes usually do not occur in these girls.

In the present study, we used pQCT to evaluate bone mass, density, geometry, and strength of the radius as well as forearm muscle size in a group of young TS patients who had completed growth. The aims were to analyze bone by a method that is not influenced by size-related artifacts and to investigate the muscle-bone relationship in TS.

Subjects and Methods

Subjects

The study population comprised 21 adolescent or adult patients with TS at a mean age of 19.5 ± 2.3 yr (mean \pm SD). Individual clinical characteristics are shown in Table 1. All patients had been treated with GH. The GH treatment period was 4.6 ± 1.7 yr (range, 1.4–8.5 yr), from 11.7 ± 2.1 yr (range, 5.9–13.8 yr) until 16.3 ± 1.3 yr (range, 14.4–19.9 yr). Oral estrogen substitution was started at 13.7 ± 1.2 yr of age with a dose of 0.2 mg estradiolvalerate, after a mean of 0.8 yr of 0.5 mg. The corresponding bone age was 12.2 ± 0.7 yr (range, 10.6–13.2 yr). Three patients entered puberty spontaneously, two of them nevertheless received estrogen supplementation 1.5 yr later for a lack of further pubertal development and marked increase of LH and FSH. All patients but one continue on estrogen treatment. After a mean of 1.6 yr, supplementation was continued with a combined estrogen-gestagen preparation for a mean duration of 4.06 ± 2.1 yr. At the time of this study, the treatment dose for all patients was the same, with a dose of 2 mg estradiolvalerate from d 5–15 and a combination of 2 mg estradiolvalerate with 0.5 mg

norgestrel from d 16–25. E2 levels in the patients varied between 26.3 and 612 pmol/liter due to different times of their cycle. All patients have stopped growing. Final height was 148.6 ± 4.8 cm (range, 139.9–159.4 cm).

All anthropometric and pQCT results were compared with those in a German reference population using identical methodology. These were participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed Study, an observational study investigating the interrelations of nutrition, growth, and metabolism in healthy children. The results in this reference population have been described before (12, 13, 16, 18, 19). The muscle-bone relationship in TS patients was compared with those in prepubertal and postpubertal subgroups from the Dortmund Nutritional and Anthropometric Longitudinally Designed Study. The prepubertal group comprised 64 girls aged 8.5 ± 1.7 yr (range, 6.0–12.6 yr). The postpubertal group was made up of 58 females aged 16.1 ± 2.4 yr (range, 11.0–22.0 yr).

Height was measured in a standing position, using a digital telescopic wall-mounted stadiometer (Ulmer stadiometer, Prof. E. Heinze, Ulm, Germany). Weight was determined to the nearest 0.1 kg using an electronic scale (Seca 753 E). The stage of sexual development was determined by physical examination using the grading system defined by Tanner for pubic hair and breast development (20). Forearm length was measured at the nondominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. The study was approved by the ethics committee of the university, and informed consent was obtained from all patients and/or their parents.

pQCT

Two sites of the nondominant radius were analyzed by pQCT (XCT-2000 scanner, Stratec Inc., Pforzheim, Germany), the distal metaphysis (4% site) and the proximal diaphysis (65% site), as described in detail before (12, 18, 19). Measurement at the metaphyseal site was carried out at the location of the radius for which distance to the distal radial articular surface corresponded to 4% of forearm length. The diaphyseal measurement was performed at a site for which the distance to the ulnar styloid process corresponded to 65% of forearm length. This site of measurement was chosen to analyze the forearm at its maximum circumference. At both sites, a 2-mm-thick single tomographic slice was sampled at a voxel size of 0.4 mm.

At the metaphyseal site, total CSA, BMC, total BMD, trabecular BMD, and Strength-Strain Index were calculated by the manufacturer's software. Cortical thickness and Strength/Weight Index were derived math-

TABLE 1. Clinical characteristics of study population

Patient no.	Karyotype	Age at start of estrogen supplementation (yr)	Age at pQCT study (yr)
1	45,X/46,X del(X)	14.8	18.5
2	45,X	13	17
3	45,X/46, Xi(Xq)	13	17.7
4	45,X/46 X del(X)	14	18.7
5	45,X	13.2	20.1
6	45,X/46 X idic (Y)	13.5	16.5
7	45,X	13.2	18.9
8	45,X	12.1	17.5
9	45,X/46XY	15.7	21.5
10	45,X	11.3	18.1
11	45,X	14.9	23.3
12	45,X/46,XX	15.8	25.4
13	45,X/46,XX/47.XXX	Spontaneous puberty, secondary ovarian failure	19
14	45,X	13.8	18.1
15	45,XO 46 X, del(X)	13.7	21.1
16	45,X	12.5	16.2
17	45,X	Spontaneous puberty, secondary ovarian failure	23
18	45,X	12.6	20.9
19	45,X	14.9	19.6
20	45,X	14.5	19.5
21	45 XO, 46, r(X) p11.1q28	Spontaneous puberty	18

ematically as described (13). BMC represents the mass of mineral per millimeter of slice thickness. Total BMD is defined as the mean mineral density of the total cross-section (21). The Strength-Strain Index reflects the combined strength of trabecular and cortical bone. Strength/Weight Index gives an indication of the balance between distal radius strength and the mechanical challenges to which the bone is exposed in case of a fall on the outstretched hand. It is calculated by dividing Strength-Strain Index by the product of forearm length and weight (13).

At the diaphyseal site, the total CSA of the radius and the cortical CSA were determined by detecting the outer and inner cortical bone contour at a threshold of 710 mg/cm³. Voxels peripheral of the outer edges of the bone with an absorptiometric density between 20 and 60 mg/cm³ were interpreted as representing muscle. Total CSA, cortical CSA, total BMC, total BMD, and muscle CSA were calculated by the manufacturer's software. Cortical thickness, relative cortical CSA, and marrow CSA were derived from these primary measures as described (19).

Statistical analysis

Results in TS patients were converted into age-specific SD scores using the formula: SD score = [(test result for a patient) – (age-specific mean in reference population)] / (age-specific SD in reference population).

To evaluate whether a parameter was significantly different from the result in controls, the difference of the mean SD score to zero was assessed. A significant difference was assumed when the 95% confidence interval of the mean SD score did not include zero. For comparisons between two groups, *t* tests were used. Throughout, a *P* value below 0.05 was considered significant. All statistical analyses were performed using the SPSS software package (version 6.0 for Windows, SPSS, Inc., Chicago, IL).

Results

Anthropometric data and pQCT results of the study group are shown in Table 2. As expected, body height was clearly decreased when compared with the age-matched healthy population. However, height was slightly above the mean (0.49 ± 0.87 SD score) when compared with German reference data for TS (22). The weight SD score (compared with healthy subjects) was far less decreased than the height SD score, and

TABLE 2. Results in 21 patients with TS

	Result	SD score
Height (cm)	149 ± 5	-2.8 ± 0.7 ^a
Weight (kg)	54.8 ± 11.6	-0.6 ± 1.1 ^a
BMI (kg/m ²)	24.9 ± 5.6	1.3 ± 2.0 ^a
Forearm length (mm)	223 ± 12	-2.9 ± 1.0 ^a
Radial metaphysis		
Total CSA (mm ²)	295 ± 54	0.0 ± 1.3
BMC (mg·mm ⁻¹)	95 ± 24	-0.9 ± 1.6 ^a
Total vBMD (mg·cm ⁻³)	320 ± 54	-1.0 ± 1.0 ^a
Trabecular vBMD (mg·cm ⁻³)	191 ± 33	0.0 ± 1.0
Cortical thickness (mm)	0.71 ± 0.21	-1.4 ± 1.1 ^a
Polar Strength-Strain Index (mm ³)	131 ± 57	-2.1 ± 0.7 ^a
Strength/Weight Index (mm ³ ·kg ⁻¹ ·m ⁻¹)	10.6 ± 3.9	-1.8 ± 0.9 ^a
Radial diaphysis		
Total CSA (mm ²)	112 ± 26	0.0 ± 1.7
BMC (mg·mm ⁻¹)	70 ± 13	-2.0 ± 1.1 ^a
Total vBMD (mg·cm ⁻³)	637 ± 99	-1.4 ± 1.3 ^a
Cortical thickness (mm)	1.90 ± 0.41	-1.6 ± 1.2 ^a
Cortical CSA (mm ²)	59 ± 12	-1.3 ± 1.2 ^a
Relative cortical CSA (%)	54 ± 12	-1.4 ± 1.5 ^a
Marrow CSA (mm ²)	54 ± 24	1.2 ± 2.0 ^a
Polar Strength-Strain Index (mm ³)	211 ± 67	-0.9 ± 1.3 ^a
Muscle CSA (mm ²)	2757 ± 399	-0.3 ± 1.1

Values are mean ± SD.

^a A significant difference of SD score mean values from 0.

therefore body mass index was increased. Forearm length was decreased, in accordance with the short stature.

pQCT at the radial metaphysis

Although total radial CSA was normal, BMC was decreased, resulting in a low total vBMD (Table 2). Trabecular vBMD was normal, and therefore the decrease in total vBMD must result from a low amount of cortical bone. Indeed, cortical thickness was clearly decreased. The consequence was an even larger decrease in polar Strength-Strain Index and in Strength/Weight Index.

pQCT at the radial diaphysis

Similar to the distal site, total radial CSA was normal at the proximal diaphysis, and BMC was decreased (Table 2). Consequently, total vBMD was low, due to a decrease in cortical thickness and cortical CSA and a correspondingly increased marrow CSA. The combined effect of these findings was a low polar Strength-Strain Index.

Muscle-bone relationship

TS patients had lower BMC relative to muscle CSA than healthy females of pubertal stage 5 (Fig. 1). BMC was below the predicted value (*i.e.* the regression line for healthy subjects) in 18 of the 21 TS patients. This can be explained by the finding that TS patients have a lower cortical CSA for a given muscle CSA than postpubertal controls (Fig. 1). However, the relationship between external bone size (total CSA) and muscle CSA was similar between these two groups.

When TS patients were compared with prepubertal girls, the situation was different (Fig. 1). For all three bone parameters, results in TS patients were distributed evenly around the regression line for healthy prepubertal girls.

Effect of puberty and estrogen supplementation

Exclusion of patients with spontaneous pubertal development (patients 13, 17, and 21) did not change the significance of any of the results presented in Table 2. However, the only study participant with sustained endogenous estrogen production (patient 21) had the highest diaphyseal BMC and cortical CSA of the entire study population (Fig. 1). In contrast, patients with secondary ovarian failure after initial spontaneous pubertal development (patients 13 and 17) had results similar to other TS patients (Fig. 1).

In the 18 subjects who had not shown signs of spontaneous pubertal development, the duration of estrogen therapy was not associated with any of the pQCT parameters after adjustment for chronological age.

Discussion

In this pQCT study, we found several salient features of the radius in TS patients. First, bone shape was abnormal. The length of the radius was markedly decreased, whereas the total CSA of the bone was normal at both the metaphysis and the diaphysis. Second, bone mass and density were decreased, because the cortex was thinner than in healthy subjects. Third, the muscle-bone relationship of TS patients receiving estrogen supplementation resembled that of pre-

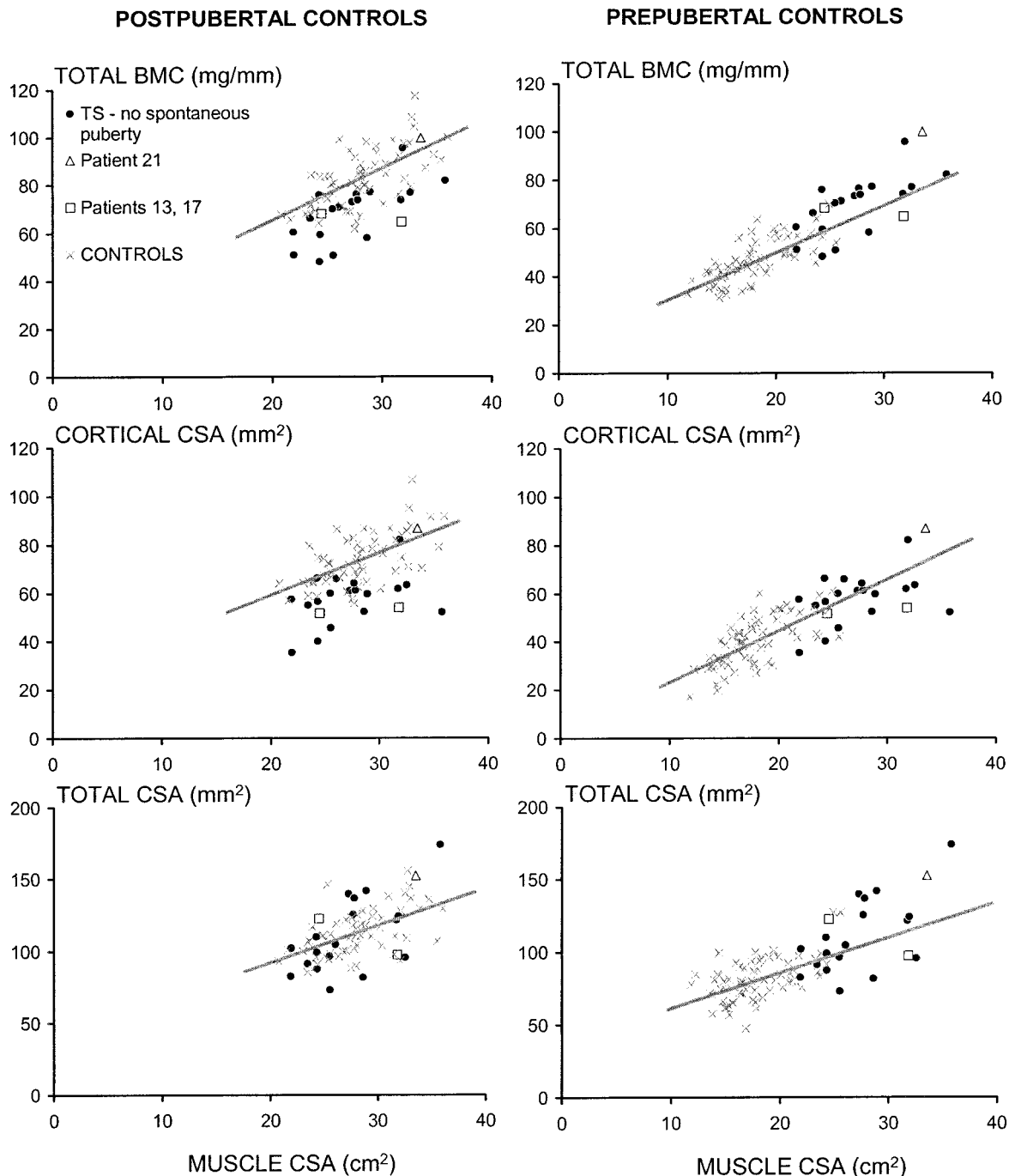


FIG. 1. Muscle-bone interrelationship at the proximal forearm. The regression lines for results in healthy subjects are indicated. *Left*, results in TS patients are compared with those in healthy adolescents and young women at pubertal stage 5. *Right*, results in TS patients are compared with those of healthy girls of pubertal stage 1.

pubertal rather than postpubertal females. In addition, it might come as a surprise that there was no deficiency of trabecular bone. However, trabecular vBMD of the distal radius does not change during development in females, and therefore abnormalities in skeletal development are not necessarily reflected by trabecular vBMD (18).

Why do TS patients have a radius of normal cross-sectional size, although this bone is short? One might explain this finding by an intrinsic bone abnormality affecting the shape

of the radius. The current study does not provide evidence to refute this hypothesis. However, in our view it is more likely that the relatively large total CSA in TS patients is not an abnormality at all. TS patients had a normal muscle CSA, and therefore it is likely that their radius was exposed to similar mechanical loads as the radius of healthy individuals. In that perspective, the relatively large total CSA in TS patients is the expression of an adequate adaptational response of periosteal osteoblasts to muscle force. This is also suggested by

the fact that the relationship between muscle CSA and total CSA of the radius was similar in TS patients and in controls.

Despite normal external cross-sectional bone size, BMC was decreased in TS patients. The reason for this was the decrease in cortical CSA, with a correspondingly increased marrow CSA. These findings are in total agreement with radiogrammetric studies of the second metacarpal (23). Again, it is possible that an intrinsic bone abnormality contributes to the decreased amount of cortical bone. Nevertheless, our data are also compatible with a functional hypothesis: hormonal changes during female puberty normally result in endocortical apposition and contraction of the marrow cavity. Postpubertal girls and women have a greater amount of bone relative to their muscle size than prepubertal girls or men (16). During normal puberty in girls, the surge in estrogen levels appears to sensitize bone next to marrow to the effects of mechanical stimulation, thus leading to endocortical apposition (24). In our TS patients, endocortical apposition apparently did not occur. The muscle-bone relationship of TS patients resembled that of prepubertal rather than of postpubertal females, although they were receiving estrogen supplementation. Thus, estrogen supplementation apparently did not bring about the bone changes that normally occur during puberty in girls.

These observations are in accordance with the recent findings from Carrascosa *et al.* (25), who reported that bone mass was normal in those TS patients who had undergone puberty spontaneously, but not when puberty was induced. Among other possibilities, this might be explained by the fact that estrogen supplementation does not mimic the natural estrogen cycle (16, 25). Route-dependent effects of estrogen on growth factors may also play a role (26, 27). In that respect, it is interesting to note that the only study participant with sustained endogenous estrogen production had the highest BMC value at the radial diaphysis. It would be interesting to specifically study the findings in a larger group of such patients.

The reduced amount of cortical bone in TS patients resulted in decreased bone strength as reflected by the low Strength-Strain Index. However, whether a bone will break in a given situation depends not only on bone strength but also on the mechanical forces to which the bone is exposed. This balance between distal radius strength and factors challenging the stability of the bone (bone length and body weight) is reflected by the Strength/Weight Index (13). This index is clearly decreased in TS patients, because body weight is relatively high. Thus, bone strength in TS patients is not adequately adapted to the relatively high body weight, which might contribute to increased fracture risk in a fall or similar incident. These considerations obviously do not exclude the possibility that increased fracture risk could also be explained by increased propensity to falls or a subtle disorder in neuromuscular coordination.

In conclusion, this study shows that radial bone mass is decreased in TS despite normal cross-sectional bone size, because cortical thickness is reduced. These findings are compatible with a normal adaptation of external bone size to the mechanical loads imposed by the muscle system and a lack of pubertal effect on the endocortical bone surface. Reduced bone strength and relatively high body weight may contribute to increasing the propensity for fractures in TS patients.

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