CLINICAL STUDIES

Bone Mineral Density and Fractures in Turner Syndrome

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PURPOSE: To determine whether women with Turner syndrome who were treated with estrogen were more likely to have osteoporosis and fractures.

METHODS: Areal bone density at the lumbar spine and femoral neck was measured in 40 adult women with Turner syndrome and 43 age-matched healthy women using dual-energy X-ray absorptiometry. Histories of estrogen treatment and fractures were obtained by structured personal interviews.

RESULTS: Mean (± SD) areal bone density was significantly lower at the lumbar spine (0.87 ± 0.11 g/cm² vs. 0.98 ± 0.10 g/cm², P <0.001) and femoral neck (0.68 ± 0.07 g/cm² vs. 0.83 ± 0.08 g/cm², P <0.001) in women with Turner syndrome than in controls. The diagnostic criterion for osteoporosis (T-score <−2.5) was met by 8 women with Turner syndrome (20%) with scores at the lumbar spine and by 3 (8%) with scores at the femoral neck. All women diagnosed with osteoporosis were less than 150 cm in height. Areal bone density correlated significantly with height (lumbar spine: $R^2 = 0.3, P <0.001$; femoral neck: $R^2 = 0.4, P <0.001$). Adjustments for skeletal size reduced the differences between the groups as well as the number of women diagnosed with osteoporosis (e.g., from 8 to 2 women based on lumbar spine scores). The prevalence and type of fractures were similar in the two groups.

CONCLUSION: The prevalence of osteoporosis and bone fractures is not increased significantly in women with Turner syndrome who are treated with standard estrogen therapy. Women less than 150 cm in height are likely to be misdiagnosed with osteoporosis when areal bone density is measured, unless adjustments for body size are made.


Turner syndrome, which is caused by partial or total monosomy X, is associated frequently with osteoporosis (1). At least two features of Turner syndrome may contribute to defective bone formation: skeletal dysmorphogenesis due to haploinsufficiency of the short-stature homeobox-containing gene, and ovarian hormone deficiency due to gonadal dysgenesis (2). Haploinsufficiency of the short-stature homeobox-containing gene, an Xp pseudoautosomal region gene encoding a transcription factor (3,4), appears to be responsible for structural abnormalities of bone development such as Madelung deformity, as well as short stature (5–7). Studies have reported osteopenia and osteoporosis in two thirds of women with Turner syndrome, which appear to be associated with deficient estrogen treatment (8–13). Additionally, an increased prevalence of fractures has been reported in some (9,11,14) but not all (15,16) studies.

In this study, we sought to determine whether women with Turner syndrome who received standard hormone replacement therapy from the mid-teens or the time of ovarian failure have normal or near-normal bone mineralization, as well as more fractures. To address these issues, we compared bone density and fracture history in women with Turner syndrome and age-matched healthy women.

METHODS

Subjects

Study subjects comprised 40 women with Turner syndrome who were participants in an observational study of genotype and phenotype interaction that was conducted at the National Institute of Child Health and Human Development and approved by the Institutional Review Board. Participants were recruited through nationwide advertising. Women with known causes of osteoporosis or bone disease, or prior use of medications known to affect bone density, were excluded. Most women had been diagnosed at or before puberty and had pubertal induction by age 16 years. They were subsequently treated with standard hormone replacement therapy.
(about 50% were taking oral contraceptives containing 20 to 35 μg of ethinyl estradiol, and the rest were taking 0.625 to 1.25 mg of conjugated estrogens in combination with cyclical or continuous progestins). Two women who had ovarian failure when they were about 25 years old began hormone treatment at that time. Ten had been treated with growth hormone for 1 to 6 years, when they were between the ages of 6 and 15 years; and 2 had been treated with oxandrolone before the age of 11 years. One woman was a current smoker, but smoked less than a pack per week. All women had fewer than three to four alcoholic drinks per week. Three patients were Hispanic and the rest were white. Karyotypes were determined by G-banding of 50 lymphocytes.

Controls were 43 age-matched, healthy, premenopausal women recruited by the National Institutes of Health Normal Volunteer office. They had regular menstrual cycles; did not take medications containing estrogen, progesterone, or testosterone; did not smoke; and used alcohol occasionally in minimal amounts. Three were Asian, 6 were African American, and 34 were white. Histories concerning menstruation, menopause, and fracture occurrence were obtained by structured personal interviews and questionnaires.

**Imaging**
Areal bone density was measured using a dual-energy X-ray absorptiometer (Hologic QDR-4500A; Hologic, Inc., Bedford, Massachusetts) with fan beam technology. Lumbar spine (anteroposterior and lateral, L2-L4) and proximal femur (hip) scans were performed according to the manufacturer’s procedures. Daily scans of an anthropomorphic spine phantom over a 6-month period yielded a coefficient of variation of 0.36%. All scans were reviewed by experienced physicians to ensure that analyses were correct and that measurements did not include areas of vessel calcification, degenerative arthritis, or overlap with the iliac crest or ribs. To obtain T- and Z-scores, bone density values were compared with normative data for the anteroposterior lumbar spine (17), the width-adjusted lumbar spine (Hologic, Inc.), and the femoral neck (18).

**Corrections of Areal Bone Density**
We corrected areal bone density values to adjust for differences in bone size. For lumbar spine data, we used bone mineral apparent density to derive bone volume, based on the area of the projected vertebral anteroposterior image (19). The formula assumes that the vertebral body is a symmetric cube. Calculation of bone mineral apparent density at the femoral neck is based on a similar assumption (20). Normative data for determining these T- and Z-scores were provided by L. Joseph Melton III, MD (Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota) (21). Width-adjusted bone mineral density (22) was also used to estimate the volume of the vertebra, assumed to be an elliptical cylinder, using the anteroposterior and lateral projected areas. Other adjustments were made using body surface area (23), which decreases the dependence of areal bone density measurement on height (body size). This method assumes a proportionality of the bone size to the body size through the measure of body surface area.

**Statistical Analysis**
Comparisons between groups were performed by one-way analysis of variance with post hoc Bonferroni test. Where the distribution was not normal or the variance was not equal, analysis of variance on ranks with the Dunn test was used. Proportions were compared by Z-test with Yates correction.

The associations of height, weight, age, and the diagnosis of Turner syndrome with areal bone density were analyzed by multiple forward stepwise regression analysis, and by best subset regression. As a criterion for the best subset, the highest adjusted $R^2$ was used. All $P$ values $<$0.05 were considered statistically significant. Analyses were performed using SigmaStat 2.03 software (Jandel Scientific, San Rafael, California).

**RESULTS**
Women with Turner syndrome were similar in age to controls (mean $[± SD]$, 34 ± 11 years vs. 32 ± 8 years, $P = 0.55$). However, they were shorter ($146 ± 7$ cm vs. $164 ± 6$ cm, $P <0.0001$) and had a higher body mass index (median $[range]$, 26 [18 to 43] years vs. 23 [18-31] years, $P = 0.002$). The karyotypes in women with Turner syndrome were similar to those reported previously (24). These women had timely diagnoses and reported a high compliance rate with estrogen therapy; 39 of the 40 women took hormone treatment consistently during the entire prescribed period and 1 adhered to treatment for 80% of the time. Less than one third had received growth hormone during childhood, for average treatment duration of 4 years.

**Areal Bone Density**
Areal bone mineral density values at the lumbar spine and femoral neck were lower in women with Turner syndrome than in controls (Table 1, Figure 1). However, linear regression analysis showed a significant positive correlation between lumbar and femoral areal bone density and height for all subjects (Figure 2). According to the areal bone density results, only women less than 150 cm in height met the criteria for osteoporosis ($T$-score $<-2.5$; Figure 2).

Forward stepwise regression and best subset regression analyses revealed that height significantly affected areal bone density at the lumbar spine ($adjusted R^2 = 0.26$, $P <0.001$), whereas the diagnosis of Turner syndrome,
age, and weight did not \((P > 0.05)\). The same type of analyses showed that variation in femoral neck bone density was best predicted by the combination of diagnosis of Turner syndrome, weight, and age \((\text{adjusted } R^2 = 0.49)\), with the diagnosis of Turner syndrome \((P < 0.001)\) and weight \((P < 0.001)\) being significant contributors.

### Adjusted Bone Density Measurements

Volumetric adjustments using bone mineral apparent density and width-adjusted bone mineral density eliminated differences between groups for lumbar spine scores (Table 1, Figure 3). Body surface area adjustments eliminated significant differences in lumbar spine Z-scores between women with Turner syndrome and controls (Figure 3), although a small difference remained for the absolute value of the corrected areal bone density (Table 1).

The volumetric transformation of femoral neck areal bone density values using bone apparent mineral density and the body surface area correction reduced, but did not eliminate, the differences between groups, although both corrections eliminated the height dependency (Table 1).

All normalization methods at both sites of measurement resulted in a reduction in the diagnosis of osteoporosis (Table 1), with no significant differences between groups.

### Bone Fractures

The prevalence of fractures was similar in both groups, and most fractures involved the appendicular skeleton (Table 2). A past history of fractures was not associated with differences in mean current bone density measurements at the lumbar spine \((0.90 \pm 0.10 \text{ g/cm}^2)\) with history of fracture vs. \(0.90 \pm 0.12 \text{ g/cm}^2\) without history of

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**Table 1. Transformations of Areal Bone Density to Adjust for Bone Size**

<table>
<thead>
<tr>
<th>Age</th>
<th>Turner Syndrome</th>
<th>Control</th>
<th>Difference between Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{Number (% or Mean } \pm \text{ SD)})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lumbar spine*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anteroposterior areal bone density (\text{g/cm}^2)</td>
<td>0.87 ± 0.11</td>
<td>0.98 ± 0.10</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>8 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone mineral apparent density (\text{g/cm}^3)</td>
<td>0.14 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>2 (5)*</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lateral areal bone density (\text{g/cm}^2)</td>
<td>0.70 ± 0.09</td>
<td>0.79 ± 0.09</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>11 (28)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Width-adjusted bone mineral density (\text{g/cm}^3)</td>
<td>0.22 ± 0.03</td>
<td>0.23 ± 0.02</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>5 (12)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Areal bone density/body surface area (\text{g/cm}^2)</td>
<td>0.94 ± 0.12</td>
<td>1.00 ± 0.10</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>2 (5)*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Femoral neck*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Areal bone density (\text{g/cm}^2)</td>
<td>0.68 ± 0.07</td>
<td>0.83 ± 0.08</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>3 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone mineral apparent density (\text{g/cm}^3)</td>
<td>0.15 ± 0.02</td>
<td>0.16 ± 0.02</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>3 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Areal bone density/body surface area (\text{g/cm}^2)</td>
<td>0.73 ± 0.1</td>
<td>0.83 ± 0.1</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* Criteria for osteoporosis: T-score <−2.5.
† \(P <0.05\) for comparison with areal bone density.

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**Figure 1.** Areal bone density of the lumbar spine (anteroposterior) and femoral neck in women with Turner syndrome (hatched boxes) and controls (gray boxes). The boxes represent the 25th and 75th percentiles, the bars represent the 10th and 90th percentiles, and the dots represent the 5th and 95th percentiles. The horizontal line in the box is the median. \(P <0.005\) for both sites.
DISCUSSION

In our study of bone density in women with Turner syndrome who had undergone estrogen therapy and age-matched, healthy controls, uncorrected areal bone density measurements suggested that lumbar spine areal bone density was significantly lower, and osteoporosis was significantly more common, in women with Turner syndrome. However, these values were influenced by height and bone size, with the shortest women with Turner syndrome subject to misdiagnosis. Correction of areal bone mineral density data to adjust for bone size eliminated the difference between groups, including the diagnosis of osteoporosis for most women with Turner syndrome. In contrast, adjustment for bone size reduced, but did not eliminate, the between-group difference in bone mineral density values for the femoral neck, suggesting that women with Turner syndrome may have reduced bone mineralization at the femoral neck, despite standard estrogen treatment. Finally, bone fractures were not increased in the women with Turner syndrome, suggesting that neither osteoporosis nor increased fragility is a major problem in young adult women with Turner syndrome who are treated with estrogen.

Some earlier studies have reported increased fractures in patients with Turner syndrome. Using single photon absorptiometry, Ross et al (14) found that radial bone mineral density was similar in girls with Turner syndrome aged 3 to 14 years and in height-matched controls (14). However, the incidence of wrist fractures was increased in children with Turner syndrome. This finding may be explained partially by ascertainment bias due to obtaining information on Turner syndrome–related fractures by personal interview, whereas control data were obtained from medical records or registries. A British study of women who were similar in age to our patients reported a similar fracture prevalence for Turner syndrome of about 50%, but a much lower rate of about 5% for controls (9). This low rate may reflect underreporting for the small control group in that study. A study based on Danish registry data reported an approximately twofold increased incidence of fractures in adults with Turner syndrome (25). These data, which were collected for older adults almost 2 decades ago, most likely included many women who had not been treated with estrogen and therefore suffered from osteoporosis related to prolonged hypogonadism. Another study evaluated women (aged 15 to 57 years) with a cumulative total of 770 years at risk, and found that the number of fractures of the distal radius corresponded to the normal premenopausal rather than postmenopausal fracture incidence (15). Thus, women with Turner syndrome who receive inadequate estrogen treatment may be at increased risk of osteoporotic fractures, whereas there is no convincing evidence that estrogen-treated women are at an increased risk.

Determining the prevalence of osteoporosis in Turner syndrome is complicated by confounding factors of small bone size and variability in estrogen treatment. Earlier studies that used areal bone density without adjusting for bone size reported reduced bone mineral density (9,12,13,26,27). A recent Danish study that attempted to address these confounding factors initially reported lower areal bone mineral density measurements for the lumbar spine and femoral neck (24), similar to our find-
ings. However, after volumetric corrections, the difference in femoral neck density disappeared, but the difference in lumbar spine density remained (24). These authors also found that in multivariate analysis, the diagnosis of Turner syndrome was not associated with lumbar spine or femoral neck bone mineral density.

The three forms of volumetric/bone size correction that we used—bone mineral apparent density, width-adjusted bone mineral density, and body surface area—eliminated or reduced the difference between groups for lumbar spine areal bone density, resulting also in fewer diagnoses of osteoporosis. Corrections for bone size in the case of the femoral neck reduced, but did not eliminate, the difference in areal bone density between groups. These findings are consistent with the multiple regression analyses that showed height to be the only significant contributor to variation in bone density at the lumbar spine, whereas the diagnosis of Turner syndrome was found to predict a reduction in bone density at the femoral neck, independently of height. The femoral neck contains a greater proportion of cortical bone compared with the lumbar spine, and evidence suggests that cortical bone is selectively reduced in Turner syndrome. For example, direct volumetric measurement of the radius using quantitative computer tomography showed that young women with Turner syndrome, all of whom had appropriate estrogen treatment, had reduced cortical bone content of the radius, whereas trabecular bone content was normal (28). In addition, it is notable that the mean Z-scores for areal lumbar spine and femoral neck bone density in both groups fell below the normal mean provided by the manufacturer (Figures 1 and 3), high-

**Table 2.** Characteristics of Fractures in Women with Turner Syndrome and in Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Turner Syndrome (n = 40)</th>
<th>Control (n = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of first fracture (years)</td>
<td>14 (3–34)</td>
<td>16 (4–38)</td>
<td>0.6</td>
</tr>
<tr>
<td>Women with at least one fracture episode</td>
<td>23 (58)</td>
<td>17 (52)</td>
<td>0.65</td>
</tr>
<tr>
<td>Women with &gt;1 fracture episode</td>
<td>8 (20)</td>
<td>5 (15)</td>
<td>0.6</td>
</tr>
<tr>
<td>Total fracture episodes</td>
<td>(n = 37)</td>
<td>(n = 25)</td>
<td>0.06</td>
</tr>
<tr>
<td>Appendicular bone fractures</td>
<td>30 (82)</td>
<td>21 (83)</td>
<td>0.9</td>
</tr>
<tr>
<td>Fractures during sport or play</td>
<td>16 (43)</td>
<td>23 (71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fractures during daily activities</td>
<td>11 (31)</td>
<td>7 (21)</td>
<td>0.35</td>
</tr>
<tr>
<td>Fractures during car accident</td>
<td>5 (14)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Other fracture</td>
<td>4 (11)</td>
<td>9 (28)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Figure 3.** Effect of volumetric transformations and body surface area adjustments on lumbar spine areal bone density Z-scores in women with Turner syndrome (hatched boxes) and controls (gray boxes). The boxes represent the 25th and 75th percentiles, the bars represent the 10th and 90th percentiles, and the dots represent the 5th and 95th percentiles. The horizontal line in the box is the median. The asterisks (*) indicate \( P < 0.001 \) for comparison between women with Turner syndrome and controls. BMAD = bone mineral apparent density; WA/BMD = width-adjusted bone mineral density.
lighting the importance of a contemporaneous control group for this type of study.

In summary, it appears that women with Turner syndrome who have received standard hormone replacement do not have significant reductions in bone mineral density of the spine, and have only modest reductions at the hip. Those who are less than 150 cm in height are likely to be misdiagnosed with osteoporosis. The current bone density does not seem to correlate with a history of bone fractures.

REFERENCES