Bone mineral density in middle-aged women with Turner’s syndrome

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Women with Turner’s syndrome have a total (45,X) or partial loss (mosaic) of one of the X chromosomes. Growth retardation with a reduced final height and hypogonadism are the main characteristics of this chromosome aberration. Decreased bone mineral density (BMD) has been reported in girls with Turner’s syndrome but whether this is due to genetic influence or to the chronic estrogen deficiency has not been settled (1-5).

In a study of Turner girls (45,X and mosaic), with a mean age of 16.7 ± 3.5 years, Shore et al. (3) concluded that the osteopenia found in the radius, ulna and humerus could be an independent effect of the chromosome aberration.

This is in contrast to findings by Stepan et al. (5) where women with Turner’s syndrome (aged 21-42 years) were compared to women with gonadal dysgenesis (aged 25-45 years) and the chronic estrogen deficiency was suggested to be the etiological factor for osteopenia in both groups. Naeraa et al. (6) also demonstrated that bone mineral content (BMC) of the spine and the forearm in women with Turner’s syndrome were correlated positively with the duration of estrogen therapy, irrespective of karyotype.

The benefit of estrogen therapy in the menopause to prevent osteoporosis and reduce the risk of fractures is well documented (7-11). The absence of the protective effect of estrogen is more important than risk factors like smoking, low dietary intake of calcium and vitamin D, a low level of physical activity, white race or alcohol consumption. Estrogen inhibits bone resorption and therefore prevents bone loss and may increase BMD in postmenopausal women (12). The major fall in bone density in all sites is related to the menopause, and none of the other risk factors can predict satisfactorily women at future risk for osteoporosis (13). A quantitatively higher bone loss is found in women with early menopause than in women with menopause of later onset and is a risk factor for osteoporosis (14).

Peak bone mass is influenced strongly by genetic factors. The bone mineral status of sons and daughters resembles that of their parents, and daughters of women with osteoporosis are more likely to develop symptomatic bone disease (15). Estrogen status and genetic influence are most important determinants of peak bone mass, which is of great interest when BMD decreases with age. A high peak bone mass will prolong the time interval to reach the fracture threshold. Women with Turner’s syndrome have a genetic aberration and are hypoestrogenic from birth. Several studies have been performed in the young and adolescent Turner girls, but few data are available on the middle-aged women. The question of whether it is the genetic influence or the estrogen


Bone mineral density (BMD), bone mineral content and body composition were determined in 47 middle-aged (mean age 47.9 ± 1.1 years) women with Turner’s syndrome. Bone mineral density was measured in the forearm, femoral neck and total body. The women investigated had a BMD lower than the normal mean. When expressed as Z scores (individual values compared to normal reference data matched for age, weight and sex), the median Z score of the total body was -1.23. When comparing women with the karyotype 45.X and mosaic women, the latter showed a higher BMD in all sites of measurement. Duration of hormonal replacement therapy (HRT) differed significantly between the mosaic and the 45.X women, with a longer duration in the mosaic group (20.7 ± 2 vs 12.1 ± 2.6 years; p < 0.01). The duration of HRT was found to be the more important factor to maintain bone mass, not the karyotype. Bone mineral density increased with years of HRT but not until after > 20 years of HRT could a significant difference be shown between the women with HRT ≤ 20 years and those with HRT > 20 years. No correlation was found between BMD and body weight, body fat or percentage body fat. Whether the osteopenia found in women with Turner’s syndrome is similar to that found postmenopausally or is a specific form related to the chromosome aberration remains to be investigated further. The present data support a relation to estrogen deficiency.

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deficiency that decreases bone mass in Turner women is still unsettled.

In the present study BMD in middle-aged women with Turner’s syndrome was investigated by single photon absorptiometry (SPA) and dual X-ray absorptiometry (DEXA). The results were related to duration of hormonal replacement therapy (HRT).

Patients and methods

Forty-nine middle-aged (37–68 years) women with Turner’s syndrome diagnosed with chromosomal analysis at the Department of Clinical Genetics, Karolinska Hospital, Stockholm, Sweden were recruited to this study of BMD. The clinical characteristics and selection criteria of these women have been described in detail previously (16). Two women were excluded, one severely handicapped due to encephalitis during childhood and one because of a recent hip fracture. Mean age was 47.9 ± 1.1 years and the age distribution is shown in Fig. 1. The study was approved by the Ethical Committee of Karolinska Hospital and all 47 women gave their informed consent. Physical details were recorded in all women, including karyotype, age, height, weight, alcohol and cigarette consumption, age at induced or spontaneous menarche, fractures, years of HRT and ongoing HRT. As HRT was considered, dosages equivalent to 0.625 mg conjugated estrogens together with progestins.

Bone mineral content (BMC) represents the kilograms of bone mineral within the region studied and BMD normalizes the BMC within the projected area of bone (g/cm²).

The BMD of the non-dominant forearm was measured by SPA using an arm scanner (Molsgaard 1100 A) with a 125I radionucler source. Scanning was performed at two sites: ulnartral (trabecular bone) and proximal (cortical bone). Data from only the proximal site were used in the study (17). The precision of the BMD of the forearm was ±0.02 g/cm². Reference values were those provided by the manufacturer.

The BMD of the femoral neck and the total body was measured by DEXA (Lunar Model DPX, Lunar Radiation Corporation). The results were expressed as absolute BMD in g/cm². The accuracy of the measurements was ±0.01 g/cm². In addition, body composition (% fat and BMC in kg) was determined using the DEXA technique.

To assess whether the measurements performed in each individual were normal or reduced, the values were expressed as Z scores compared with appropriate normal reference data matched for age, weight and sex (18). Reference values were those provided by the manufacturer (19, 20). The Z score was determined using the following formula:

\[
\text{BMD patient - BMD (mean age-matched value)} / \text{Standard deviation of the mean age-matched value}
\]

Body mass index (BMI) was calculated from the formula: BMI = Weight/(Body height)² (kg/m²).

Statistical analyses

Conventional statistical methods were used for the calculations of means, standard deviations (sd) and standard errors of means (sem). The significance of the differences was evaluated by the Wilcoxon signed rank test for unpaired observations, analysis of variance and the chi-squared test. The relations between variables were examined by multiple regression and stepwise regression analysis. Results were expressed as the mean ± sem. Owing to a large number of significance tests, the p values were corrected according to the Bonferroni procedure. Thus, a p < 0.01 was considered significant in order to maintain approximately an overall 5% level.

Results

All 47 women were apparently healthy and did not take any medications interfering with BMD except for estrogens and progestins. None of the women had an over-consumption of alcohol and none was smoking regularly. The BMD measurements in different sites demonstrated a wide range. Median Z scores of the femoral neck and total body were -1.2 (range -3.92 to 1.75) and -1.23 (range -2.95 to 2.42), respectively.

45.X women compared to mosaic women

Nineteen of the women had the karyotype 45,X and 28 had different mosaics (45,X/46,X,i(Xq)) in seven, 45,X/46,XX in 15, 45,X/46,XX/47,XXX in three and 45,X/46,XY in three). No differences were found in mean age, mean height, mean weight, % body fat or BMI between 45.X and mosaic women (Table 1). The mean BMD showed higher values in the mosaic group in all sites of
measurements. Significant differences were found in the BMD of the femoral neck (p < 0.003) and total body (p < 0.01) (Table 1).

A significant difference was found in the duration of HRT where the mosaic women had been treated for 20.7 ± 2 years and the 45.X women for 12.1 ± 2.6 years (p < 0.01). Eight of the 45.X women (n = 19) had a history of previous fractures compared to four in the mosaic group (n = 28) (p < 0.03).

### Duration of HRT

When the importance of karyotype, BMI and duration of HRT on BMD were tested simultaneously using multiple regression analysis, the duration of HRT was found to be the more important determinant for BMD (Table 2). The women were divided into classes according to the duration of HRT (0–5, 6–10, 11–15, 16–20 and >20 years). Although BMD was gradually increasing with the duration of HRT, no significant differences in BMD or BMC were found between women treated with estrogens for 20 years compared to those treated for less than 20 years. Significant differences in BMD in all sites of measurement between the women were obtained after >20 years of HRT (Table 3), with a mean total body Z score of −1.62 ± 0.11 in the group treated with hormones for ≤20 years and −0.08 ± 0.24 in the group treated for >20 years.

### Correlation analyses

The Z scores of total body and femoral neck BMD were correlated positively to the duration of HRT (r = 0.63, p<0.0001). There was a good correlation between Z score of the femoral neck and total body (r = 0.63, p<0.0001).

The BMD of the proximal wrist and total body were

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**Table 1. Data in 45.X and mosaic women.**

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>45.X (N = 19)</th>
<th>Mosaic (N = 28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 ± 1.9</td>
<td>46.8 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148.8 ± 1.3</td>
<td>151.0 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.6 ± 2.4</td>
<td>54.8 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 0.9</td>
<td>24.0 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>% Body fat</td>
<td>35.1 ± 1.8</td>
<td>36.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration HRT (years)</td>
<td>12.1 ± 2.6</td>
<td>20.7 ± 2.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ongoing HRT, N (%)</td>
<td>5 (26)</td>
<td>17 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI: Body mass index</td>
<td>23.7 ± 2.3</td>
<td>17 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Age-matched %</td>
<td>1.12 ± 0.04</td>
<td>1.24 ± 0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>
| BMC prox. wrist (g/cm²) | 0.75 ± 1.4    | 0.79 ± 1.7      | <0.01
| % Age-matched   | 84.6 ± 3.1    | 91.1 ± 2.4      | NS  |
| BMD prox. wrist (g/cm²) | 58.4 ± 105.5 | 67.6 ± 119.5    | <0.003
| BMD femoral neck (g/cm²) | 0.69 ± 0.06  | 0.83 ± 0.03     | <0.003
| Z score         | −1.65 ± 0.22  | −0.74 ± 0.21    | <0.01
| BMD total body (g/cm²) | 0.94 ± 0.02  | 1.04 ± 0.02     | <0.01
| Z score         | −1.44 ± 0.19  | −0.53 ± 0.23    | NS  |
| BMC (kg)        | 1.68 ± 0.07   | 1.98 ± 0.08     | NS  |

* Values are means ± SEM with ranges in parentheses. BMI: body mass index; HRT: hormonal replacement therapy; BMD: bone mineral density; BMC: bone mineral content.

**Table 2. Results from the regression analysis of bone mineral density on body mass index (BMI), karyotype and years of hormonal replacement therapy (HRT) in 47 women with Turner’s syndrome.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SEM</th>
<th>p</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>81.21</td>
<td>5.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.12</td>
<td>0.22</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>45.X/mosaic</td>
<td>2.82</td>
<td>2.23</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Years of HRT</td>
<td>0.44</td>
<td>0.01</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Women with Turner’s syndrome on hormonal replacement therapy (HRT) for ≤ 20 years and >20 years.**

<table>
<thead>
<tr>
<th></th>
<th>≤ 20 years HRT</th>
<th>&gt;20 years HRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 ± 1.7</td>
<td>46.1 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148.5 ± 1.0</td>
<td>152.0 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.7 ± 2.3</td>
<td>54.2 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 0.9</td>
<td>23.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>% Body fat</td>
<td>37.3 ± 1.6</td>
<td>38.3 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration HRT (years)</td>
<td>12.1 ± 2.6</td>
<td>20.7 ± 2.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ongoing HRT, N (%)</td>
<td>5 (20)</td>
<td>17 (77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Years since HRT</td>
<td>23.9 ± 2.0</td>
<td>8.2 ± 1.6</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>BMD prox. wrist (g/cm²)</td>
<td>1.08 ± 0.03</td>
<td>1.32 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Age-matched BMD</td>
<td>81.6 ± 2.1</td>
<td>96.03 ± 3.29</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>BMD femoral neck (g/cm²)</td>
<td>0.69 ± 0.02</td>
<td>0.86 ± 0.03</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Z score</td>
<td>−1.66 ± 0.18</td>
<td>−0.47 ± 0.22</td>
<td>&lt;0.0006</td>
</tr>
<tr>
<td>BMD total body (g/cm²)</td>
<td>0.93 ± 0.01</td>
<td>1.07 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Z score</td>
<td>−1.62 ± 0.11</td>
<td>−0.08 ± 0.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMC (kg)</td>
<td>1.68 ± 0.06</td>
<td>2.07 ± 0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractures, N (%)</td>
<td>8 (32)</td>
<td>4 (18)</td>
<td>NS</td>
</tr>
</tbody>
</table>
correlated negatively to age \( (r = -0.57, p<0.0001; r = -0.39, p<0.006) \). The total body BMD in the women with ongoing HRT \( (N = 22) \) demonstrated only a slight decrease in BMD with age \( (r = -0.08, \text{NS}) \).

The BMC was correlated positively to the BMD of the proximal wrist \( (r = 0.61, p<0.0001) \) and the femoral neck \( (r = 0.77, p<0.0001) \) and to duration of HRT \( (r = 0.44, p<0.0002) \). The BMC was correlated negatively to age \( (r = -0.31, p<0.03) \) and years since HRT \( (r = -0.50, p<0.01) \) (Fig. 2).

No correlation was found between body weight or BMI and BMD in the different sites of measurement, or between percentage body fat and duration of HRT. Age at initiation of HRT demonstrated no correlation to BMD.

A difference was found in percentage age-matched BMC of the wrist and the incidence of fractures \( (p<0.02) \) (Fig. 3), but there was no correlation between duration of HRT and fractures.

### Discussion

Peak bone mass is a major determinant of bone mass and fracture risk in later life and is influenced by a combination of genetic, mechanical, nutritional and hormonal factors. Women with Turner’s syndrome have a chromosome aberration and are hypoestrogenic, both factors that might influence BMD in a negative way.

In this study we have not had a control group because it is difficult to find a group of Swedish women with a mean body height of <150 cm without other endocrine conditions. Bone mineral density is known to be underestimated in shorter individuals, which is why the osteopenia found in women with Turner’s syndrome might not be real for technical reasons. So far, the clinical significance of reduced BMD in women with Turner’s syndrome is uncertain. There are some reports of an increase in fractures, but no reports of back pain. None of the present women complained of back pain but among the 45.X women eight had a history of previous fractures. We did not find any correlation between fractures and duration of HRT, but the women with fractures had a lower mean percentage age-matched wrist BMD. The mean age for the investigated group of women with Turner’s syndrome was 47.9 years and thus it is too early for definite conclusions about fracture risks later in life.

The minimal effective dose of estrogen for prevention of postmenopausal bone loss has been defined. Oral doses of 0.625 mg of conjugated estrogens, 1–2 mg of estradiol and 0.05 mg of transdermal 17β-estradiol all have been found effective in preventing osteoporosis (21–23). While some of the present women were on HRT, none had been treated with growth hormone, which is known to enhance bone mineral. In a recent study by Neely et al. (24), girls with Turner’s syndrome (mean age 14.3 years) receiving growth hormone did not differ in BMD when compared to controls, but still whole-body BMC was significantly lower in girls with Turner’s syndrome. When reassessed after 1 year, the percentage increases in mean BMD were greater in girls on estrogen therapy than in those untreated.

We found differences in BMD between women with the karyotype 45.X and the mosaics in all sites of measurements but still the duration of HRT was found to be more important.
In the Framingham study, recent use of estrogen appeared to be protective to fractures in women under the age of 65 years (10). Christiansen et al. (9) in 1981 found that even temporary HRT after the menopause had a lasting beneficial effect on bone mass. A reduced rate of fractures and spinal osteoporosis was reported in women who had received oestrogens for some years after the menopause. Ross et al. (25) found prepubertal girls with Turner’s syndrome (<13 years old) to have normal BMD for height age, but significantly decreased BMD of the wrist for chronological age, bone age and BMI. They also had significantly more wrist fractures than normal girls and it was suggested that this could be due to structural abnormalities of bone or an increased incidence of falls. In fact Smith et al. (4), with data from 11 adult women (aged 18–57 years; median age 36 years), suggested that the osteoporosis in women with Turner’s syndrome was different that in postmenopausal women and therefore considered long-term estrogen therapy not to be justified. Kurabayashi et al. (26) found that BMD improved slightly with HRT but as the mean age was 27.5 years one would expect that it was too early to draw any conclusions about the effect of HRT on bone metabolism. Our results are in line with those found by Naeraa et al. (6), who investigated 50 women with Turner’s syndrome (mean age 31.7 years) and found the BMC of the forearm and the spine to be correlated positively to duration of estrogen therapy, irrespective of karyotype.

In healthy women, endogenous estrogen production is maintained for a period of 35–40 years. In women with Turner’s syndrome with lack of ovarian function we found that >20 years of HRT was required to be effective and maintain BMC and BMD. These data emphasize the need to offer these women long-term HRT.

Among the middle-aged women with Turner’s syndrome many have been diagnosed late and subsequently have been replaced with estrogens later than normal girls entering puberty. In addition, many of the women with Turner’s syndrome had stopped their HRT early in life because they were over treated and suffered from side effects.

Weight and BMI are known to correlate to BMD in all sites (19, 27–29) but in this study we found no correlation between weight, body fat, percentage body fat or BMI and BMD. This might be explained by the lack of appropriate reference material for comparison.

We found middle-aged women with Turner’s syndrome to be osteopenic. Whether this is an osteopenia similar to that found in ageing and postmenopausal women or a specific form related to the chromosome aberration or an underestimation of their BMD due to short body height remains to be investigated. Data support a relation to estrogen deficiency. Duration of HRT rather than karyotype seems to be the important factor in reducing bone mass loss. Women with Turner’s syndrome should be offered long-term HRT to reduce osteopenia and probably decrease the incidence of fractures later in life. Such long-term HRT also might enhance the quality of life and prevent cardiac disease.

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References


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