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Bone density and fractures in Turner syndrome

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Abstract. Apparent demineralization of the skeleton has been noted in females with Turner syndrome (TS) since the first descriptions of the disorder. Studies, using quantitative methods to measure areal bone mineral density (BMD) in TS, have often been confounded by small skeletal size and variable exposure to estrogen. Recent studies taking bone size into account suggest that BMD at skeletal sites of predominantly trabecular bone, e.g., the lumbar spine and ultra distal radius, is normal in women that have used estrogen consistently. However, these women have significantly lower than normal BMD at skeletal sites with predominantly cortical bone, e.g., the radial shaft and femoral neck. It is unknown whether the reduction in cortical BMD is an intrinsic feature of TS perhaps related to haploinsufficiency for SHOX or another X-linked gene, or due to deficient estrogen exposure during childhood and adolescence, and whether this cortical bone deficit increases fracture risk. Current recommendations to begin low dose estrogen treatment in the early teens may clarify these issues. Wide use of bisphosphonates to treat low BMD in young women with TS is not warranted since these agents have little if any effect on cortical bone while trabecular bone has excellent response to estrogens. © 2006 Elsevier B.V. All rights reserved.

Keywords: Turner syndrome; Bone mineral density; Osteoporosis; Fracture; DEXA; Estrogen replacement therapy

1. Introduction

Henry Turner first noted that the bones of girls and women with “infantilism, congenital webbed neck and cubitus valgus” although grossly normal in appearance seemed “demineralised” on roentgenograms [1]. Subsequent observations confirmed that girls with Turner syndrome (TS) had hypomineralized appearing bones on hand radiograms [2,3].

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Quantitative methods for estimation of bone mineral density (BMD) such as radiogammametry [4], single and dual-photon absorptiometry [5,6], and dual energy X-ray absorptiometry (DEXA) [7] have showed 20–25% reduction of BMD at various skeletal sites according to some [7–9] but not all studies [10,11]. There has been controversy regarding the age when BMD deficit becomes apparent in TS, to what extent size-based artefact related to areal densitometry explains low BMD findings, whether there is increased fracture risk and whether the low BMD in TS is due to prolonged hypoestrogenism or intrinsic bone mineralization defect.

2. Factors affecting bone density in Turner syndrome

There are at least two mechanisms to explain the low BMD and the increased fracture rate in TS: bone dysmorphogenesis and chronic estrogen deprivation. Bone dysmorphogenesis is manifested as various degrees of Madelung's deformity of the wrists, cubitus valgus and scoliosis. It is postulated that haploinsufficiency for the SHOX gene is the major cause for these abnormalities, in addition to short stature [12]. Almost all karyotypes associated with TS are monosomic for the SHOX containing, terminal Xp region. Haploinsufficiency for the SHOX gene may result in low production of a homeobox regulatory protein, which is a key regulator of skeletal growth and development. SHOX haploinsufficiency may thus adversely impact bone mineralization and quality. Apart from SHOX haploinsufficiency, or other X-chromosome associated gene(s) haploinsufficiency, the early estrogen deprivation, as early as pre-pubertal age, as a result of ovarian failure and delayed introduction of estrogen replacement therapy (ERT) may lead to low bone mineral accrual during adolescence, which persists later in life, especially if adequate ERT is not given.

3. A selective deficiency of cortical bone in Turner syndrome

Several recent studies suggest that girls and women with TS have a selective cortical bone deficit [13–15]. This is detected by DEXA scan and by quantitative computer-assisted tomography (QCT). Skeletal sites that are built-up of predominantly cortical bone such as femoral neck and 1/3 proximal radius consistently show osteoporosis or osteopenia on DEXA scans even after correction for size [13,15]. The cortical bone deficiency contributes to the demineralised appearance of skeletal X-rays in girls with TS but is most evident in adulthood. In a cross-sectional study of 41 women with TS, age 32 ± 8 years all of which had been taking standard ERT, we measured BMD by DEXA at 1/3 proximal radius (predominantly cortical bone) and ultradistal radius (predominantly trabecular bone) of the same arm [13]. The cortical bone density (1/3 proximal radius) Z-score was low, -1.75 ± 0.75 , and 12% of these women fulfilled criteria for osteoporosis, i.e. T-score < -2.5 . At the same time, their trabecular BMD (at the UD-radius) was on average in the normal range and only 2.4% had DEXA readings in the osteoporosis range (Fig. 1). There was no correlation between estrogen exposure and cortical BMD [13].

Some studies report normal cortical BMD in pre-pubertal girls with TS [16,17] thus raising the possibility that ovarian hormone (estrogen and/or androgen) deficiency may be involved in the pathogenesis of the cortical bone deficit. In girls with normal karyotype, the

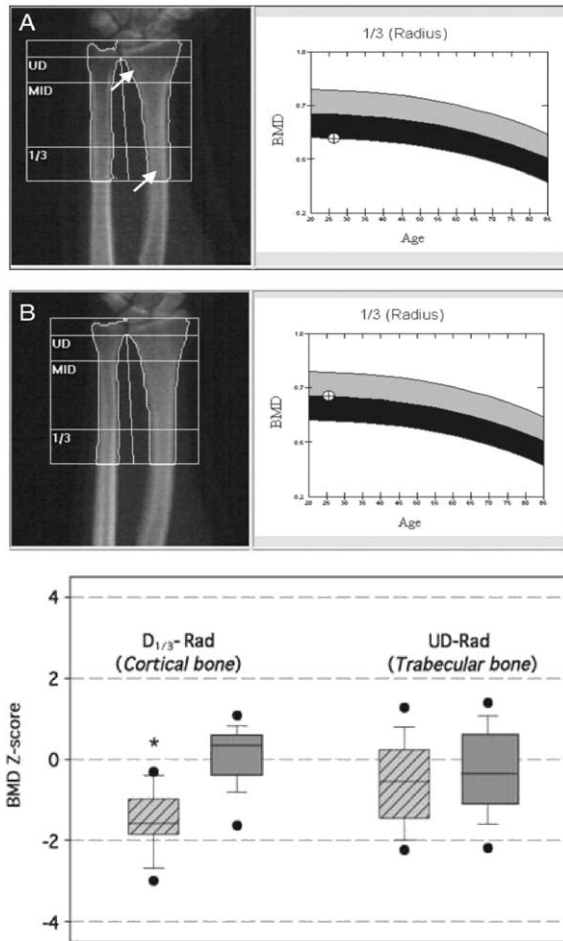


Fig. 1. Panel A: 27-year-old woman with TS. The arrow points the 1/3 radius (cortical bone). The circle on the nomogram is the 1/3 radius BMD. The crossed arrow points the ultradistal radius (trabecular bone). The cross on the nomogram is UD radius BMD. Panel B: 26-year-old woman with premature ovarian failure (POF) and normal karyotype. 1/3 radius Z-score is plotted as a circle. Panel C: Hatched boxes designate TS ($n=41$, mean age 32 ± 8 years). Gray boxes designate POF ($n=35$, mean age 33 ± 5 years). Boxes represent 25th and 75th percentiles, the bars 10th and 90th, and the dots 5th and 95th, the horizontal bars—the medians. $*P < 0.0001$ (J Clin Endocrinol Metab 88:5717–22, 2003).

elevation of the estrogens during puberty and immediately before puberty leads to increased endosteal bone apposition in addition to increased periosteal bone formation, thus substantially increasing the cortical bone thickness. Girls with TS who do not experience spontaneous puberty and who start taking estrogen replacement therapy relatively late may never have the chance of reaching a normal cortical thickness. Once established, however, this cortical bone deficiency does not seem to be influenced by later ERT therapy [13,14]. It is possible that the selective cortical bone deficit in TS is insensitive to the estrogen effect

and that this is part of a bone dysmorphogenesis caused by X-chromosome gene(s) haploinsufficiency, e.g., SHOX. For example, one study found increase in fracture incidence, despite normal bone density in pre-pubertal girls with TS [17] hence the possibility for an intrinsic defect in bone strength.

4. Trabecular bone density is normal in estrogen-treated women with Turner syndrome

Unlike the skeletal sites with predominantly cortical bone, the sites with predominantly trabecular bone are quite sensitive to estrogens even in post-adolescent years in women with TS [18]. In one study, 3 years of treatment with subcutaneous estradiol implants resulted in normalization of BMD in 19 young women with TS [19]. Bone biopsies showed that the increased bone density was due to increased trabecular bone volume. The cortical bone did not change. This study showed that estrogens not only prevent bone loss, but when given in high enough dose might lead to gain of bone mass. In another study, we compared the BMD at lumbar spine, measured by DEXA and by QCT, of two groups of women with TS. The first group included 34 women who were compliant with their ERT (taking the medication >75% of the prescribed time); the second group included 16 women with TS at a similar age who did not take ERT for several years or more [18]. The average Z-scores of the compliant group were in the normal range and none had osteoporosis, while 38% of the non-compliant group had osteoporosis.

5. Areal bone density and diagnosis of osteoporosis in women and girls with Turner syndrome

Some studies have reported decreased BMD in women with TS despite adequate ERT [9,15,20]. For the predominantly trabecular bone sites, this finding might be explained in part by the inherent tendency of DEXA to under estimate BMD of persons with short stature [21]. Since DEXA measures areal bone density, bigger bones project more density on the measured surface than the smaller bones. The peak and age specific BMD reference values are derived from women who are on average 15–20 cm taller than women with TS. Thus, T- and Z-scores would be systematically lower in smaller individuals [22]. This problem could be resolved by the use of a size independent method, such as QCT [23]. It measures volumetric bone density, is not size dependent, and has the added benefit of evaluating cortical and trabecular bone density separately [24]. However, it is expensive and uses a lot of radiation. In addition, the ability of QCT scan to predict fractures is uncertain.

Another option to overcome the size-related artefact is to transform DEXA areal BMD into volumetric bone density [25]. Accepted methods include calculation of bone mineral apparent density (BMAD) by using bone mineral content and projected bone area, and width-adjusted BMD (only for lumbar spine), by using lateral bone mineral content and lateral and AP projected areas [26]. This abolishes the size dependence, especially for DEXA measurements of the lumbar spine. For example, the AP L1–L4 areal BMD (by DEXA) of 40 women with TS was 12% lower than the areal BMD of 43 healthy control women ($p < 0.001$) [22]. Moreover, 20% of the women with TS had osteoporosis by the WHO criteria, compared to 0 from the control group ($p = 0.003$). The mean age of both

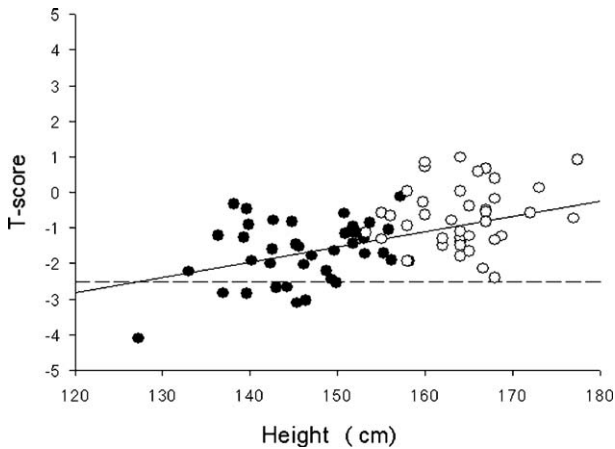


Fig. 2. Association of lumbar spine areal BMD *T*-scores with height in women with TS (solid circles) and controls (open circles). The dashed line represents the *T*-score threshold (-2.5) for diagnosis of osteoporosis (Am J Med 115:259–264, 2003).

groups was similar (34 ± 11 years for TS, 32 ± 8 years for controls, $p=0.55$) but the controls were significantly taller (164 ± 6 cm versus 146 ± 7 cm, $p<0.00001$). After correction for size by transforming the areal BMD into the volumetric BMAD, the difference between the two groups was reduced to 3% ($p=0.18$) [22]. Only 5% of the women with TS fulfilled the *T*-score criteria for osteoporosis by volumetric BMAD, compared to 20% by areal BMD method ($p<0.05$). The same was valid for other size corrections of the areal BMD, such as width-adjusted BMD and body surface area adjusted BMD [21]. Almost all women who fulfilled the *T*-score criteria for osteoporosis by areal BMD measurement were <150 cm in height (Fig. 2) [22].

Estimation of BMD by DEXA in children with TS is even more problematic due to variation in pubertal status in addition to height disparity during the pubertal years. In these cases, height or bone age rather than calendar age can be used to calculate *Z*-scores [17].

Despite the limitations, DEXA scan still remains the best tool to estimate BMD in TS. However, it should be used judiciously and always in the context of the small size of this group of patients. This may become less of an issue in the not too distant future, as with GH treatment the average height of adults with TS may be over 150 cm, which does not usually create size-based artefacts. One of the correction methods should be considered in any case where the height is <150 cm or the BMD is quite low, before a decision for a therapeutic intervention is made. It should be kept in mind that normative data for calculation of *T*- and *Z*-scores for BMAD is not readily available and fracture risk estimation is impossible based on *T*- and *Z*-scores derived from volumetric or BSA corrections.

6. Fracture risk in Turner syndrome

Fracture risk is increased in women and girls with TS [17,27,28]. It is not clear whether the fractures are related to osteoporosis or to intrinsic bone weakness. Fracture incidence in TS seems to have two peaks. According to two Scandinavian studies, the peak incidence is

after age of 45, and family history of low impact fractures seems to be a major risk factor. According to one study from USA, there is an increased fracture incidence among children with TS despite normal bone density [17]. One small study recently failed to detect increased fracture risk among younger women with TS [22]. These discrepancies could be explained with the possibility that different mechanisms lead to fractures in the different age groups.

It appears that many women with TS who are currently in the menopausal age have not been treated adequately with estrogens. Thus, they have higher incidence of osteoporosis hence higher risk of fragility fractures. Occasionally, young women can develop fragility fractures too, if they do not take regularly ERT and develop osteoporosis [18]. However, most of the fractures at young age and childhood seem to occur during accidents and sports activities. Problems with spatial orientation, balance and coordination may be major contributors to this phenomenon. However, it seems likely that, in addition, bone dysmorphogenesis due to haploinsufficiency of X-chromosome gene(s) may contribute to cortical bone deficiency and/or to an intrinsic bone weakness. In such case, girls or young women with TS may be prone to break bones at a smaller impact force than individuals with normal karyotype regardless of BMD.

7. Growth hormone therapy and BMD in Turner syndrome

When growth hormone (GH) is used as a replacement therapy in GH deficient states, it clearly has a beneficial effect on bone mass acquisition and mature BMD [29]. However, most girls with TS are not growth hormone deficient and the effect of GH therapy on BMD is unclear. Furthermore, whether GH treatment may reduce fracture rate in TS is even less clear. Up to this moment, there are no data from placebo controlled trials which evaluate the role of GH on the bone. One study [30], using pQCT to evaluate BMD showed that girls with TS had normal bone density scores before starting GH therapy, and increased their bone density score at the conclusion of the GH therapy. This effect persisted after discontinuation of GH. The problem with this study was the lack of placebo controlled group. Several small retrospective studies failed to show an effect of history of growth hormone therapy on the BMD of young adults [31–33]. These studies are flawed with lack of randomisation of the groups and hence the potential for a selection bias. Despite the lack of reliable data, GH treatment is a standard of care for girls with TS and it is unlikely that placebo controlled trials will be designed. However, one possibility is that with the heightened awareness of the paediatricians for growth delay, more girls with TS will be diagnosed in a very early age. In that case, GH therapy can be started early and estrogen replacement can be started at appropriate age, allowing for a normal bone mineral acquisition.

8. Prevention and treatment of osteoporosis in Turner syndrome

Measures to prevent osteoporosis and fractures should be addressed starting in childhood [8,34]. ERT should be initiated in a timely fashion and continued until the age of natural menopause [35]. An oral calcium intake of 1200–1500 mg/day and vitamin D is recommended as well as weight bearing exercise [36]. The effect of GH on bone mineral

density is unclear. However, the introduction of GH early in life allows for a more physiological timing of ERT which might be beneficial for maximal bone mass acquisition.

A baseline measurement of bone mineral density with a DXA scan should be performed in women with Turner's syndrome at the transition to adult care [35]. This should be repeated at age 40–45 as it may help guide future decisions regarding ERT. Bone density measurements should be done more frequently if there are risk factors for osteoporosis, e.g., glucocorticoid treatment, loss of height, low impact fracture or lack of consistent ERT. The bone density should be interpreted with caution, correcting for size if height is <150 cm. Treatment with bisphosphonates should be decided on an individual basis and should not be routinely recommended to young women with TS. Bisphosphonates are contraindicated in those women contemplating pregnancy. This being said, if there is deterioration of the bone mineral density over time conventional therapy for osteoporosis with a bisphosphonate should be strongly considered.

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