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EARLY-ONSET OSTEOPOROSIS IN ADULT TURNER SYNDROME: IMPORTANCE OF LIFELONG BONE MONITORING

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Abstract

Introduction: Turner syndrome (TS) is a common sex chromosome disorder associated with gonadal dysgenesis, chronic estrogen deficiency, and increased risk of impaired bone mineral acquisition. Reduced bone mineral density may remain under-recognized during the transition from pediatric to adult care.

Case presentation: We report a 29-year-old woman with TS due to monosomy X (45, X), diagnosed at 17 years of age, who was referred for endocrine evaluation and skeletal assessment. She had short stature (141 cm), low body weight (38 kg; BMI 19.1 kg/m²), delayed puberty, primary ovarian insufficiency, and inconsistent adherence to cyclic estrogen–progestin replacement therapy. Hormonal evaluation showed hypergonadotropic hypogonadism, with elevated FSH and LH and low estradiol.

Thyroid evaluation confirmed autoimmune thyroiditis with stable thyroid function under levothyroxine replacement. DXA demonstrated bone mineral density below the expected range for her age, predominantly at the hip. Lumbar spine L1–L4 BMD was 0.901 g/cm² with a Z-score of −1.4, while total left and right femur Z-scores were −2.4 and −2.6, respectively. Femoral neck Z-scores ranged from −2.3 to −2.5. Vitamin D deficiency was also present. Although small bone size and short stature may contribute to underestimation of areal BMD by DXA, the markedly reduced femoral Z-scores, chronic hypoestrogenism, low body weight, inconsistent hormone replacement therapy, and vitamin D deficiency supported clinically relevant secondary skeletal impairment.

Conclusion: This case highlights the importance of lifelong skeletal surveillance in TS, including early DXA assessment interpreted with Z-scores, optimization of hormone replacement therapy, correction of vitamin D deficiency, adequate calcium intake, and fracture prevention strategies.

Keywords: *bone mineral density; HRT; osteoporosis; Turner syndrome.*

Introduction

Turner syndrome (TS) is one of the most common chromosomal disorders affecting females, with an estimated prevalence of approximately 1 in 2,000–2,500 live female births. It results from the complete or partial absence of one X chromosome and is characterized by a broad and highly variable clinical phenotype involving multiple organ systems (1,2). Common manifestations include short stature, gonadal dysgenesis, delayed puberty, infertility, cardiovascular abnormalities, autoimmune disorders, metabolic dysfunction, neurocognitive features, and skeletal complications (1,2). Although the clinical phenotype may vary according to karyotype and degree of mosaicism, primary ovarian insufficiency remains one

of the most consistent endocrine features of TS and represents a major determinant of long-term morbidity (1,3).

Estrogen deficiency secondary to gonadal dysgenesis has a profound impact on skeletal development and bone metabolism. Adequate estrogen exposure during puberty is essential for normal bone mineralization and attainment of peak bone mass. Consequently, girls and women with TS are at increased risk of impaired bone accrual beginning in adolescence, which may persist into adulthood and predispose to reduced bone mineral density and fragility fractures (1,4). In addition to hypoestrogenism, several other mechanisms contribute to compromised skeletal health in TS, including altered bone geometry, reduced cortical bone thickness, impaired trabecular bone quality, decreased muscle mass, vitamin D deficiency, low body weight, and reduced physical activity (1,4).

Reduced bone mineral density (BMD) and increased fracture risk are well-recognized manifestations of Turner syndrome. Recent reviews have reported that fracture risk in patients with TS may be approximately 1.4–2.2 times higher than in the general population, with hypogonadism and inadequate estrogen exposure representing major contributing factors (4). Vertebral fractures, impaired bone quality, and early skeletal deterioration have been described, even in relatively young patients (4,5). Li et al. reported a severe case of TS-associated osteoporosis with multiple vertebral compression fractures requiring repeated percutaneous vertebroplasty, illustrating the potential severity of skeletal complications in the setting of prolonged estrogen deficiency (5). In addition, Rawat et al. described primary hyperparathyroidism in a young woman with TS who presented with hypercalcemia and renal stones, further emphasizing the need to evaluate endocrine comorbidities that may aggravate skeletal risk (6).

Despite advances in pediatric diagnosis and management, long-term follow-up during adulthood remains challenging. Clinical attention is often directed toward reproductive, cardiovascular, and metabolic complications, whereas skeletal health may be underestimated or insufficiently monitored (1,3). Delayed recognition of TS may contribute to prolonged untreated estrogen deficiency and preventable long-term complications. Recent case reports describing TS diagnosed in late adulthood, including at 61 and 76 years of age, underscore the variable presentation of the syndrome and the potential consequences of missed or delayed diagnosis (7,8).

Current international guidelines recommend lifelong multidisciplinary surveillance in girls and women with TS, including assessment of bone health, optimization of calcium and vitamin D intake, promotion of weight-bearing physical activity, and timely initiation and maintenance of estrogen–progestin hormone replacement therapy to support bone accrual and reduce future fracture risk (1). Recent clinical data have also demonstrated beneficial effects of hormone replacement therapy on BMD in adult women with TS, reinforcing the importance of adequate hormonal management throughout life (9).

This case report describes markedly reduced bone mineral density below the expected range for a women aged 29 with Turner syndrome. The case highlights the importance of continuous skeletal surveillance beyond childhood and adolescence, appropriate DXA interpretation using Z-scores in young women, and timely interventions to preserve bone mass and reduce long-term fracture risk.

Case Presentation

A 29-year-old woman with a previously established diagnosis of Turner syndrome was referred for comprehensive endocrinological evaluation and assessment of skeletal health. Turner syndrome was diagnosed at the age of 17, based on cytogenetic analysis

demonstrating monosomy X, 45,X. Her clinical phenotype included short stature, delayed pubertal development, and primary ovarian insufficiency. The patient's final adult height was 141 cm, with a body weight of 38.0 kg and a body mass index of 19.1 kg/m². Growth hormone therapy had been administered during late adolescence, resulting in an approximate height gain of 5 cm.

The patient had a history of primary hypothyroidism diagnosed in 2013. She reported irregular adherence to levothyroxine therapy for several years, with treatment reinitiated in 2023. At the time of assessment, thyroid function was stable under levothyroxine replacement therapy. Thyroid ultrasonography demonstrated a thyroid gland of normal size, shape, and anatomical position, but with heterogeneous and non-homogeneous parenchyma, anechoic areas suggestive of lymphocytic infiltration, and hyperechogenic reflections consistent with chronic autoimmune thyroiditis. No focal thyroid nodules were identified. The markedly elevated anti-thyroid peroxidase antibody level further supported the diagnosis of autoimmune thyroiditis, a common autoimmune comorbidity in Turner syndrome.

Reproductive history and hormonal evaluation were consistent with primary ovarian insufficiency secondary to gonadal dysgenesis. The patient had delayed pubertal development and had been prescribed cyclic estrogen–progestin hormone replacement therapy; however, adherence had been inconsistent over several years. Biochemical evaluation demonstrated markedly elevated gonadotropin concentrations, with follicle-stimulating hormone of 62 IU/L and luteinizing hormone of 53 IU/L, accompanied by low estradiol concentration of 28 pg/mL.

These findings were compatible with hypergonadotropic hypogonadism, which is characteristic of Turner syndrome.

Transvaginal ultrasonography revealed a hypoplastic uterus with thin endometrium and markedly reduced ovarian dimensions bilaterally, supporting the presence of longstanding gonadal dysgenesis and chronic estrogen deficiency.

Given the well-established association between Turner syndrome and impaired skeletal health, bone mineral density was evaluated using dual-energy X-ray absorptiometry. In view of the patient's young age, premenopausal status, and Turner syndrome as an underlying cause of secondary bone loss, DXA interpretation was primarily based on Z-scores rather than T-scores. Lumbar spine assessment showed a mean L1–L4 BMD of 0.901 g/cm², corresponding to a Z-score of −1.4, with individual vertebral Z-scores ranging from −0.9 to −1.6. A more pronounced reduction in bone mineral density was observed at the hip. Total left femur BMD was 0.617 g/cm² with a Z-score of −2.4, while total right femur BMD was 0.591 g/cm² with a Z-score of −2.6. Femoral neck Z-scores ranged from −2.3 to −2.5 bilaterally, indicating bone mineral density below the expected range for the age. The greatest skeletal deficits were observed in Ward's and trochanteric regions, with Z-scores reaching −3.2 and −2.8, respectively.

These findings indicate markedly impaired peak bone mass acquisition in a young adult woman with Turner syndrome. The reduced bone mineral density is most likely multifactorial, related to chronic hypoestrogenism, delayed and inconsistent hormone replacement therapy, low body weight, reduced mechanical loading, vitamin D deficiency, and longstanding gonadal dysgenesis. In this clinical context, the skeletal impairment should be interpreted as secondary osteoporosis associated with Turner syndrome rather than primary or postmenopausal osteoporosis.

Body composition analysis demonstrated a low body weight, fat mass of 15.9%, and lean mass of 84.1%. The patient denied smoking, excessive alcohol intake, glucocorticoid or

anticonvulsant use, and there was no reported family history of osteoporosis or fragility fractures. Biochemical assessment showed serum calcium and phosphorus within reference ranges, with normal renal and liver function tests. However, 25-hydroxyvitamin D levels were markedly reduced, ranging from 6 to 14 ng/mL, consistent with significant vitamin D deficiency and representing an additional modifiable contributor to impaired bone health. No additional major contributors to secondary bone loss were identified apart from Turner syndrome–related hypogonadism, low body weight, and vitamin D deficiency. Other endocrine and metabolic parameters were unremarkable. Prolactin was within the reference range. Fasting plasma glucose and fasting insulin levels were normal, without evidence of impaired glucose metabolism or insulin resistance at the time of evaluation. Dehydroepiandrosterone sulfate, total testosterone, and morning cortisol concentrations were also within the expected reference ranges.

Serum growth hormone and insulin-like growth factor 1 levels were appropriate for adulthood following previous growth hormone therapy, with no biochemical evidence of persistent growth hormone deficiency.

Although the patient had been followed endocrinologically for Turner syndrome-associated comorbidities, bone mineral density assessment had not been performed earlier in adulthood. She had no previous history of fragility fractures; however, the presence of markedly reduced bone mineral density at the age of 29 years suggests increased future fracture risk. This case emphasizes that skeletal surveillance in Turner syndrome should extend beyond childhood and adolescence and should be incorporated into lifelong multidisciplinary care. Early DXA assessment, interpretation using Z-scores in young women, optimization of hormone replacement therapy, correction of vitamin D deficiency, adequate calcium intake, and long-

term monitoring are essential for reducing future skeletal complications in this high-risk population.

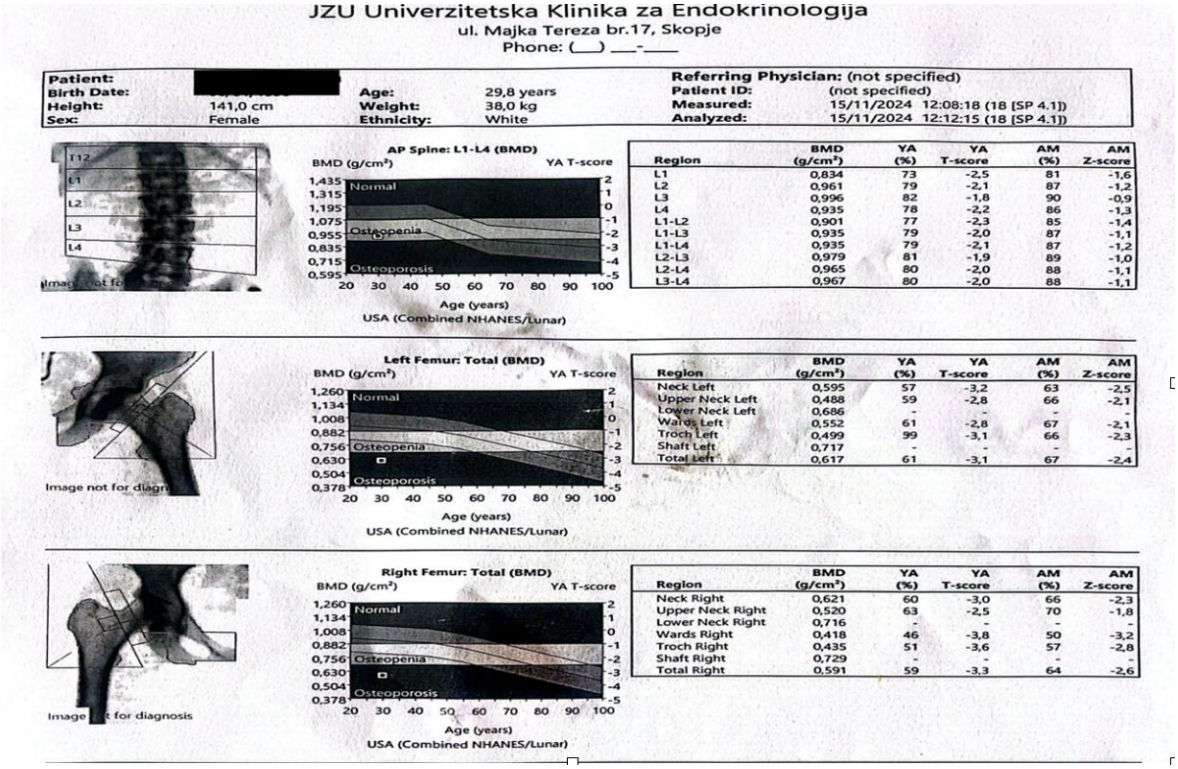

Figure 1. DXA scan showing reduced bone mineral density in a 29-year-old patient with Turner syndrome. Z-scores demonstrated lumbar spine reduction (L1–L4 Z-score −1.4), with more pronounced femoral involvement, including total left femur Z-score −2.4 and total right femur Z-score −2.6, consistent with bone mineral density below the expected range for age.

Discussion

Turner syndrome is a lifelong multisystem disorder in which skeletal health represents an important, but often under-recognized, component of long-term morbidity. Although short stature, gonadal dysgenesis, infertility, cardiovascular anomalies, and autoimmune disorders are commonly emphasized in clinical follow-up, reduced bone mineral density and increased fracture risk are also well-established complications (1,4).

The present case illustrates early-onset impairment of bone health in a young adult woman with Turner syndrome, emphasizing the need for systematic skeletal assessment beyond childhood and adolescence (1,4).

The main finding in this patient was significantly reduced bone mineral density at the age of 29, with the greatest impairment observed at the hip. Because the patient was young and premenopausal, and because Turner syndrome itself represents an underlying cause of secondary osteoporosis, interpretation of DXA findings should primarily rely on Z-scores rather than T-scores (1,4). In this case, lumbar spine BMD was reduced but less severely affected, with an L1–L4 Z-score of −1.4. In contrast, femoral involvement was more pronounced, with total left femur and total right femur Z-scores of −2.4 and −2.6, respectively. These values indicate bone mineral density below the expected range for the age and suggest clinically relevant impairment of peak bone mass acquisition (1,4).

An additional consideration in the interpretation of DXA findings in Turner syndrome is the influence of short stature and small bone size on areal BMD measurements. DXA provides a two-dimensional estimate of bone mineral density and may underestimate volumetric bone density in individuals with smaller bones (4,10,11). Therefore, in patients with Turner syndrome, particularly those with marked short stature, reduced areal BMD should be interpreted with caution and in the context of body size, pubertal history, estrogen exposure, and clinical risk factors. Adjustment methods such as bone mineral apparent density, height-for-age Z-scores, or interpretation according to height age rather than chronological age may provide additional information and help distinguish true skeletal fragility from size-related underestimation of BMD (4,10,11). Nevertheless, in the present case, the markedly reduced femoral Z-scores, chronic hypoestrogenism, inconsistent hormone replacement therapy, low

body weight, and vitamin D deficiency support clinically relevant skeletal impairment rather than a purely size-related DXA artifact.

Several mechanisms may explain the reduced bone mineral density observed in this patient. The most important factor is chronic estrogen deficiency due to primary ovarian insufficiency, which is one of the hallmark endocrine features of Turner syndrome (1,12). Estrogen plays a central role in pubertal bone mineralization, epiphyseal maturation, maintenance of bone mass, and regulation of bone remodeling (9,12,13). Inadequate estrogen exposure during adolescence and early adulthood may prevent optimal acquisition of peak bone mass, thereby increasing the risk of premature osteoporosis and future fragility fractures (8,9,12,13,14). In the present case, delayed pubertal development and inconsistent adherence to estrogen–progestin hormone replacement therapy likely contributed substantially to skeletal impairment.

Low body weight may have further aggravated bone loss. The patient had a BMI of 19.1 kg/m^2 and low body weight, which may reduce the mechanical loading of bone and negatively affect bone strength. Mechanical loading is an important determinant of bone formation, and reduced lean mass or low body mass may contribute to lower bone mineral density, particularly in patients already exposed to chronic hypoestrogenism (11,12,14).

Therefore, the skeletal phenotype in this case is likely multifactorial, resulting from the combined effects of gonadal dysgenesis, inadequate estrogen exposure, low body weight, reduced mechanical stimulation, and vitamin D deficiency.(1,4,11,14)

Vitamin D deficiency represented an additional modifiable risk factor in this patient. Although serum calcium and phosphorus were within reference ranges, 25-hydroxyvitamin D levels were markedly reduced. Vitamin D deficiency may impair calcium absorption, contribute to secondary alterations in bone metabolism, and further compromise bone

mineralization. In a patient with Turner syndrome and already reduced bone mass, correction of vitamin D deficiency is essential as part of comprehensive bone-protective management (1).

Another important aspect of this case is the presence of autoimmune thyroiditis. Autoimmune thyroid disease is frequently associated with Turner syndrome and in this patient, it was supported by elevated anti-thyroid peroxidase antibodies and ultrasound features compatible with chronic autoimmune thyroiditis (1). At the time of evaluation, thyroid function was stable under levothyroxine replacement therapy. Although uncontrolled hyperthyroidism or excessive levothyroxine replacement may negatively affect bone metabolism, this was not evident in the present case. Nevertheless, regular monitoring of thyroid function remains important, as both thyroid dysfunction and overtreatment may influence skeletal health over time (1).

The gynecological and hormonal findings further support the role of longstanding gonadal dysgenesis. Elevated FSH and LH levels with low estradiol confirmed hypergonadotropic hypogonadism, while transvaginal ultrasonography demonstrated a hypoplastic uterus with thin endometrium and markedly reduced ovarian dimensions. These findings are consistent with chronic estrogen deficiency and provide a pathophysiological explanation for impaired bone mass acquisition (1,13). They also reinforce the importance of continuous and adequate hormone replacement therapy in women with Turner syndrome, not only for induction and maintenance of secondary sexual characteristics, but also for preservation of skeletal health (8,9,12-14).

This case also highlights an important gap in adult follow-up. Although the patient had regular endocrinological care for Turner syndrome-associated comorbidities, bone mineral density assessment had not been performed earlier in adulthood.

The absence of previous fragility fractures may have contributed to the underestimation of skeletal risk. However, osteoporosis and low bone mass may remain clinically silent until a fracture occurs (1,4,5). Therefore, relying only on symptoms or fracture history may delay diagnosis and intervention. Early DXA screening and periodic reassessment are necessary, especially in patients with delayed puberty, poor adherence to hormone replacement therapy, low body weight, vitamin D deficiency, or other risk factors for reduced bone mass (1,10).

The case also underscores the importance of terminology in young women with Turner syndrome. In postmenopausal women, osteoporosis is commonly classified using T-scores. However, in premenopausal women and younger individuals, particularly those with secondary causes of bone loss, Z-scores are more appropriate for interpretation (10). Therefore, the skeletal impairment in this patient should be described as bone mineral density below the expected range for the age and secondary osteoporosis associated with Turner syndrome, rather than primary postmenopausal osteoporosis. This distinction is clinically relevant because it directs attention to the underlying mechanism, namely, impaired peak bone mass acquisition due to estrogen deficiency and other Turner syndrome-related factors (1,4,10).

From a therapeutic perspective, management should focus on correcting modifiable risk factors and preventing future fractures. Optimization of estrogen–progestin hormone replacement therapy is central, provided there are no contraindications (1,8,9,12-14). Adequate replacement may help maintain bone mass and reduce further skeletal deterioration. Correction of vitamin D deficiency, ensuring sufficient calcium intake, optimizing nutrition, and encouraging regular weight-bearing and muscle-strengthening physical activity are also essential (1). In addition, follow-up DXA assessment should be planned to evaluate the skeletal response to treatment and monitor progression.(1,10)

Pharmacological anti-osteoporotic therapy in young women requires individualized consideration. In this patient, the first priority should be optimization of hormone replacement therapy and correction of vitamin D deficiency, because the underlying cause is mainly hypoestrogenism-related impaired bone accrual (1,8,9,12-14). Antiresorptive or anabolic therapy may be considered only after careful evaluation of fracture risk, persistence of very low BMD despite correction of reversible factors, presence of fragility fractures, or additional risk factors. The patient's reproductive potential, long skeletal retention of some medications, and long-term safety considerations should be taken into account before initiating such treatment.(1)

Overall, this case demonstrates that clinically significant skeletal impairment may be present in young adults with Turner syndrome even in the absence of fragility fractures.(1,4,5) It reinforces the need for lifelong multidisciplinary care, with bone health assessment integrated into routine adult follow-up (1). Timely DXA evaluation using Z-scores, consistent hormone replacement therapy, correction of vitamin D deficiency, adequate calcium intake, lifestyle measures, and regular monitoring are essential to reduce long-term fracture risk (1,8,10). The case therefore contributes to the growing recognition that skeletal surveillance should be considered a core component of adult Turner syndrome management, rather than an optional or secondary concern.

Conclusion

This case highlights early-onset skeletal impairment in a young woman with Turner syndrome, most likely resulting from longstanding hypoestrogenism, delayed and inconsistent hormone replacement therapy, low body weight, vitamin D deficiency, and impaired peak bone mass acquisition. The markedly reduced femoral Z-scores demonstrate

bone mineral density below the expected range for the age and support the interpretation of secondary osteoporosis in the context of Turner syndrome.

The case emphasizes that bone health assessment should be an integral component of lifelong multidisciplinary follow-up in patients with Turner syndrome, extending beyond childhood and adolescence into adult care. DXA interpretation in young women should primarily rely on Z-scores rather than T-scores, particularly when secondary causes of bone loss are present. Although small bone size related to Turner syndrome and short stature may contribute to underestimation of areal BMD by DXA, the markedly reduced femoral Z-scores, together with chronic hypoestrogenism, inconsistent hormone replacement therapy, low body weight, and vitamin D deficiency, support clinically relevant secondary skeletal impairment.

Early recognition of reduced bone mineral density, optimization of estrogen–progestin replacement therapy, correction of vitamin D deficiency, adequate calcium intake, and promotion of weight-bearing physical activity are essential strategies to preserve bone mass and reduce future fracture risk.

Declarations

Ethics approval and consent to participate: According to institutional policy, ethics committee approval is not required for single case reports. Not applicable. All procedures were performed as part of routine clinical practice.

Conflict of interest: The authors declare that they have no conflicts of interest related to this manuscript.

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Availability of data and materials: All data generated or analyzed during this study are included in this article. Additional anonymized data are available from the corresponding author upon reasonable request.

Authors' contributions: M.T.S. contributed to study design, data collection, and manuscript preparation. I.M.S. contributed to data interpretation and manuscript revision. A.G.V. contributed to clinical evaluation and manuscript revision. All authors approved the final manuscript.

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