Review Article

Orthopaedic Manifestations in Turner Syndrome

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Abstract

Turner syndrome is one of the most common chromosomal anomalies occurring in live-born females. It has been extensively reviewed in the medical literature, yet little has been discussed regarding the skeletal manifestations that present to the orthopaedic surgeon. It is important for the orthopaedic surgeon to be familiar with the clinical findings and comorbid conditions in Turner syndrome because they may be the first line of diagnosis when a patient presents for short stature, scoliosis, or slipped capital femoral epiphysis. Recent studies have identified the short stature homeobox gene as the main cause of the skeletal differences in patients with Turner syndrome, affecting longitudinal bone growth. Skeletal deformities including short stature, delayed skeletal maturation, angular deformity of the limbs, spinal deformity, and early-onset osteoporosis have been associated with Turner syndrome. This article will review the skeletal manifestations of Turner syndrome and propose guidelines for the treatment and monitoring of these patients.

Level of Evidence: Level V

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Skeletal deformity in Turner syndrome has been extensively described.[1,2] The syndrome is associated with short stature, angular deformities of both upper and lower extremities, coronal and sagittal deformities of the spine, altered bone growth, and early-onset osteoporosis. Studies have previously linked these skeletal differences to intrinsic bone abnormalities and defects in growth hormone.[3] However, more recent research into the genetic changes in patients with Turner syndrome has revealed a deficiency in the short stature homeobox-containing (*SHOX*) gene within the bone regulatory center for longitudinal growth.[4-6]

Patients with Turner syndrome can be seen in any subspecialty area within orthopaedic surgery. They may present to the pediatric orthopaedic surgeon for short stature or scoliosis or slipped capital femoral epiphysis (SCFE) in childhood, the upper extremity orthopaedic surgeon for Madelung deformity, the orthopaedic spine surgeon for thoracic hyperkyphosis, or to the adult general orthopaedic surgeon for fragility fractures later in life. It is important for the orthopaedic surgeon to be familiar with the common orthopaedic manifestations seen in Turner syndrome, the appropriate diagnostic tools, treatment guidelines, and associated comorbidities.

Turner Syndrome in Review

Turner syndrome occurs in approximately 1 in 2,500 to 1 in 3,000 live births.[7] Females carrying a complete or partial deficiency of one sex chromosome are affected. The clinical characteristics can vary widely across multiple systems based on the

chromosomal deficiency present (Table 1, Supplemental Digital Content 1, http://links.lww.com/JAAOS/A336). Diagnosis can occur in utero or well after. Prenatal diagnosis may occur based off of a triple screening, fetal karyotyping, or fetal edema seen on ultrasonography.[8] Approximately one fifth to one third of patients are diagnosed as infants, which is usually secondary to excessive nuchal skin or lymphedema. Another one third are diagnosed in midchildhood as a result of a workup for short stature. The remaining undiagnosed patients usually present in adolescence when they fail to progress through puberty or as adults after multiple failed attempts at pregnancy. Patients presenting with signs of Turner syndrome can be definitively diagnosed by blood sample karyotyping. Physicians working up a patient for Turner syndrome should include the following in their management: echocardiogram with referral to cardiology for abnormal findings, thyroid function and glucose intolerance tests, gonadotropin levels, referral to endocrinology, renal ultrasonography, hearing test, ophthalmologic evaluation, and referral for psychosocial issues, if appropriate.[7,8]

Skeletal Growth

SHOX Gene

Turner syndrome is defined as a partial or total loss of one X chromosome. The most common karyotype is 45 XO. Other defects causing Turner syndrome include mosaicism, isochromosomes, ring chromosomes, and long/short arm deletions.[9] These dosage-specific, haploinsufficient changes of certain X-Y homologous genes have been found to lead to the variety of clinical features observed in Turner syndrome.[4]

The *SHOX* gene is expressed on the short arm of both sex chromosomes. It is responsible for encoding a transcription factor that regulates longitudinal bone growth.[5] In patients with clinically significant short stature without Turner syndrome, heterozygous mutations have been found within the *SHOX* gene. In patients with Turner syndrome, the complete absence of a secondary sex chromosome results in haploinsufficiency of the *SHOX* gene[6] and resultant changes in longitudinal bone growth.

In utero, the *SHOX* gene is initially expressed in the cells of mesenchymal tissue. As the mesenchyme differentiates in chondrocytes to form a skeletal model, the cells containing the *SHOX* gene condense into the perichondrial layer along the diaphysis of long bones.[4] The *SHOX* gene is most strongly expressed within the mesomelic region of the limbs. In the upper extremity, the radius and ulna are particularly affected with the greatest longitudinal growth defect occurring around the elbow.[4] In the lower extremity, the tibia and fibula are most significantly affected with the greatest longitudinal growth defect occurring around the knee. Haploinsufficiency of the *SHOX* gene can cause bowing and shortening in these regions, leading to mesomelic short stature, cubitus valgus, and genu valgum. *SHOX* gene expression has also been demonstrated in vertebral body epiphyseal plates, with upregulation having been demonstrated in cases of idiopathic and congenital scoliosis.[10] Altered growth patterns in these regions can lead to scoliosis and thoracic kyphosis.

Short Stature

Short stature is the single most common skeletal manifestation in patients with Turner syndrome. The incidence of short stature in these patients ranges from 88% to 100%.[11] All other skeletal anomalies common to Turner syndrome including short metacarpals, cubitus valgus, high-arched palate, micrognathia, and short neck have incidences of less than 60%.[5] Short stature in patients with Turner syndrome is thought to result from growth retardation throughout development. Most patients show mild growth impairment in utero and are delivered short for age. Zero to 24 months seems to be the period most affected by slowed growth. Davenport et al[1] reviewed the growth charts of 62 children with Turner syndrome. They found the greatest retardation of growth to be between zero and 1 year of age. By one and a half years, the patients continued to show growth retardation but pulling away from the mean heights at a lower rate than at less than 1 year of age.[1] Patients also show delayed onset and slow growth during childhood, as well as failure to undergo the normal pubertal growth spurt.[11] Turner syndrome is an important diagnostic consideration for providers when evaluating children younger than 2 years who have fallen off of the height growth curve.

Short stature may be the first physical abnormality found in an undiagnosed patient with Turner syndrome. By age 4 to 8 years, the mean height of girls with Turner syndrome is −2.3 SDs from the norm.[1] On average, individuals with Turner syndrome, not treated with growth hormone, are 20 cm shorter than the average female adult of corresponding ethnic population.[1,11] The final height for most adults with Turner syndrome ranges from 54 to 60 inches tall.[12]

Delayed Skeletal Maturation

Many authors have noted a delay in skeletal maturation when evaluating patients with Turner syndrome. It has been reported that bone age wrist radiographs often appear normal for age in Turner syndrome patients less

than 11 years. However, bone age wrist radiographs will progressively become more delayed as the patient ages. A maximum of 2-year bone age delay can be seen by age 16 years in patients with Turner syndrome, which is believed to be due to a failure in epiphyseal plate closure, possibly secondary to chromosomal deficiency and the absence of pubertal hormone onset.[5,6]

Upper Extremity

The upper extremity can be involved to varying degrees in Turner syndrome (Table 2, Supplemental Digital Content 2, http://links.lww.com/JAAOS/A337). The classic upper extremity findings include bowing and shortening of the forearms, cubitus valgus, brachymetacarpia of the fourth digit, distal radioulnar physeal discrepancy, and Madelung deformity (Figure 1). Although most upper extremity deformities can be treated with observation only, it is important to monitor those that may require surgical intervention.

Cubitus Valgus

Cubitus valgus is an increase in the carrying angle of the elbow and affects approximately 45% of patients with Turner syndrome.[10,13] This can also be accompanied by bowing and shortening of the forearms. This is most commonly asymptomatic and requires no treatment other than observation.

Brachymetacarpia

Brachymetacarpia, or shortening of the fourth metacarpal, can be identified in 37% of patients with Turner syndrome.[10] This is rarely symptomatic and is often only noted as the fourth metacarpophalangeal joint being shorter than the others clinically or the incidental finding of a short metacarpal on radiograph (Figure 2). Treatment, as with cubitus valgus, is observation.

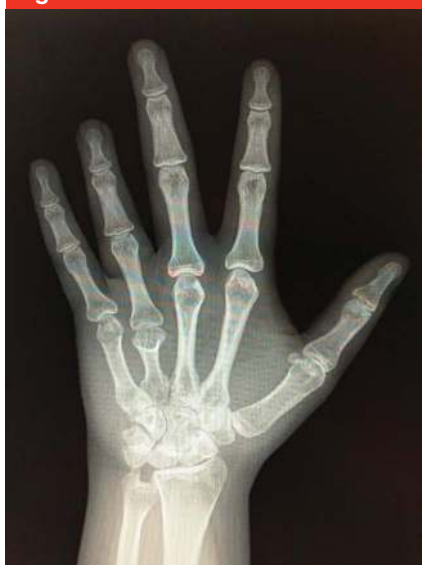
Figure 1

Clinical picture of cubitus valgus, brachymetacarpia, and shortening of the upper limbs in a patient with Turner syndrome.

Madelung Deformity

The most discussed upper extremity difference in Turner syndrome but least common is Madelung deformity (Figure 3, A and B). Madelung deformity is a classic finding of abnormal growth of the volar-ulnar aspect of the distal radius, resulting in increased radial inclination and volar tilt, proximal migration of the carpus, and the appearance of volar subluxation of the wrist on the forearm. This is sometimes accompanied by the finding of Vickers ligament, an abnormally thickened radial-carpal ligament that tethers the volar-ulnar distal radial physis and the lunate[14] (Figure 4). Although routinely discussed as a finding in Turner syndrome, it is identified in only 2% to 7% of patients.[2,10] A more common finding, although still found in a limited number of patients, is an increased ulnar negative variance (Figure 2). This is the opposite finding to Madelung deformity where there is commonly an ulnar positive variance.[2] Initial treatment of Madelung deformity is observation if asymptomatic and not progressing on yearly surveillance posterior-anterior and lateral radiographs of the forearm. If pain does develop, first treatment is rest, bracing, and activity modification. If symptoms continue or progression is noted and the patient is still skeletally immature, an epiphysiolysis and interposition fat graft of the region of growth disturbance at the volar-ulnar aspect of the distal radius physis with or without release of Vickers ligament can restore growth. There is, however, risk of further injury to the physis and possible greater growth disturbance.[14] If the patient is approaching skeletal maturity, and is symptomatic, a dome osteotomy to correct the multiplanar deformity with or without an ulnar shortening osteotomy is recommended.[15] Wrist arthrodesis is recommended as a salvage procedure for severe pain in the skeletally mature.

Figure 2

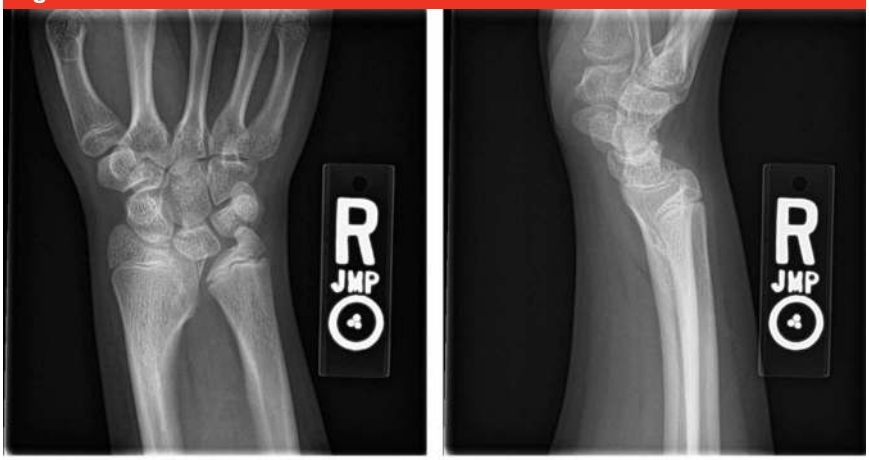


Posterior-anterior radiograph demonstrating brachymetacarpia of the fourth digit and ulnar negative variance at the wrist.

Spinal Deformity

Spinal deformity, both in the frontal and sagittal planes, seems to occur more frequently in patients with Turner syndrome compared with the general population (Table 3, Supplemental Digital Content 3, http://links.lww.com/JAAOS/A338). There

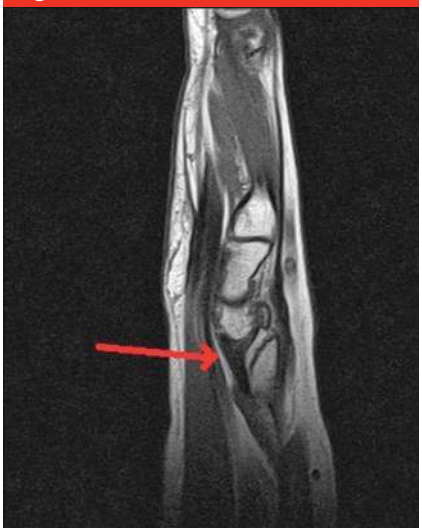
Figure 3



A B

A, Posterior-anterior radiograph of a wrist with Madelung deformity. **B**, Lateral radiograph of a wrist with Madelung deformity.

Figure 4



MRI demonstrating Vickers ligament (arrow) of the volar wrist.

has long been a known presence of irregular vertebral epiphyseal growth rings and anterior vertebral wedging in Turner syndrome.[15-17] Historically, the incidence of scoliosis in Turner syndrome has been estimated to be approximately 10%. However, more recent literature raises this figure to as high as 59%.[3] Thoracic kyphotic deformity has been estimated to be as high as 48%.[19] The presence of these deformities seems to be later in onset compared with the general population, and therefore, the prevalence increases with age, well into the second decade of life. As a result, general screening by physical examination and selective radiography has been recommended up to age 20 years.

Scoliosis

Scoliosis in Turner syndrome is clinically and radiographically similar to idiopathic scoliosis (Figure 5). However, a small percentage has been associated with vertebral body malformations (congenital scoliosis).[10,19] The mean age at presentation for scoliosis in larger studies is typically between 12 and 13 years,[3,10] with onset described as young as age 3 years and as old as age 18 years. The deformities observed are usually mild (Cobb angle $< 20°$). Ricotti et al reported 29 of 29 patients with deformities between 10° and 20°,[3] whereas Day et al[10] reported 8 of 13 patients with curves $<20°$ and the remaining 5 with curves up to 55°. This study did not report on brace or surgical therapies. Kim et al[19] reported an incidence of 5 of 43 patients with scoliosis (11.6%), of which 2 were braced and 3 underwent surgical treatment. Treatment of scoliosis in Turner syndrome should follow standard principles of treatment for adolescent idiopathic scoliosis.

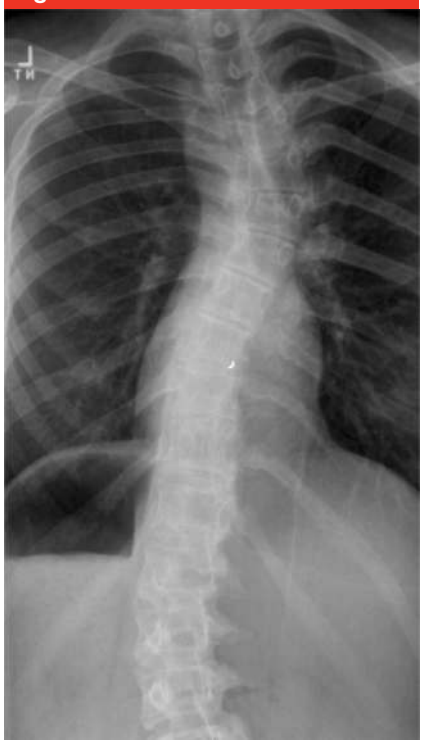
Hyperkyphosis

The anterior vertebral wedging and irregular vertebral epiphyseal growth rings result in a Scheuermann-like disease in Turner syndrome.[18] The incidence of thoracic hyperkyphosis has been reported to be between 35% and 48%. The prevalence has been shown to increase with age, suggesting a late-onset presentation (40% of hyperkyphosis presents after age 14 years).[32] Elder at al[18] specifically studied the incidence of thoracic hyperkyphosis in Turner syndrome. Their study showed that 40% (10/25) of patients had an anterior to posterior thoracic curvature exceeding 40°. Most of these patients demonstrated vertebral body wedging (Figure 6), leading the study to conclude that these two entities may go hand in hand.

Human Growth Hormone

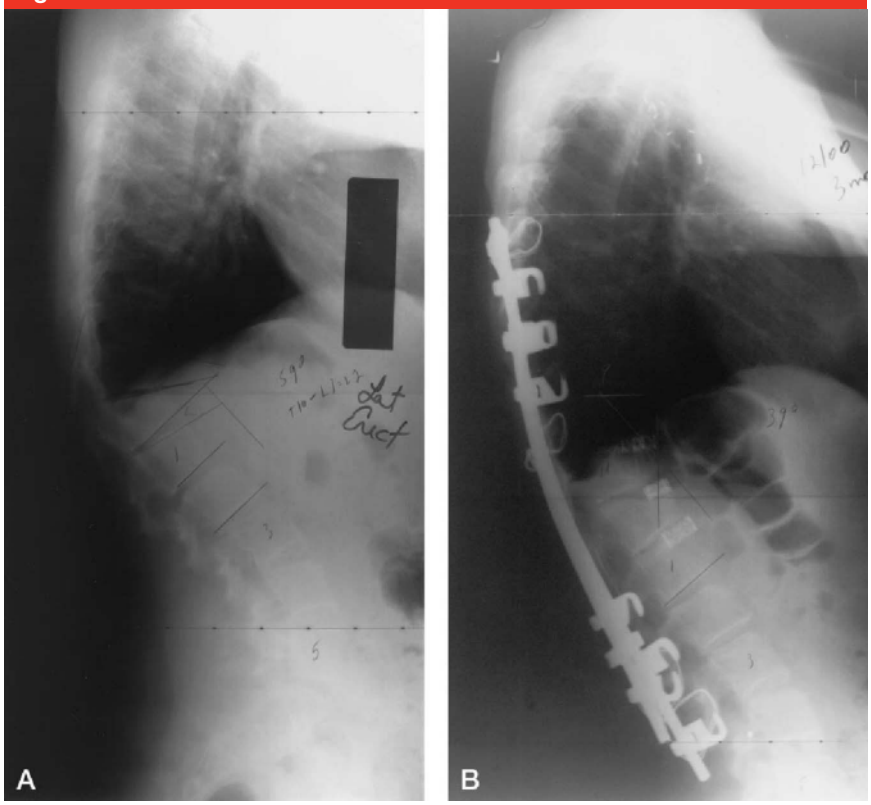
The association between growth hormone therapy and the incidence of scoliosis in Turner syndrome is controversial. Previous reports have suggested that the use of human growth hormone (HGH) supplementation may accelerate preexisting scoliosis.[20-22] Day et al[10] studied a group of Australian patients with Turner syndrome and short stature being treated with HGH. These authors found that 5 of their 13 patients had scoliosis progression during treatment. Their cohort was found to have an increased incidence of scoliosis at 29% compared with previous reports of approximately 10%. The authors concluded that either scoliosis was more common in Turner syndrome than previously believed or that HGH may lead to an

Figure 5



Scoliosis in Turner syndrome occurs at a much greater rate than the general population and generally has the appearance of idiopathic scoliosis. The deformities tend to be small and to present slightly later in life. Most cases do not require intervention. (Reprinted with permission from Day G, Szvetko A, Griffiths L, et al: *SHOX* gene is expressed in vertebral body growth plates in idiopathic and congenital scoliosis: Implications for the etiology of scoliosis in Turner syndrome. *J Orthop Res* 2009;27:807-813.)

Figure 6



Hyperkyphosis is common in Turner syndrome. **A**) Preoperative and **B**) postoperative, Schmorl nodes and anterior wedging may be seen. (Reprinted with permission from Elder DA, Roper MG, Henderson RC, Davenport ML: Kyphosis in a Turner syndrome population. *Pediatrics* 2002;109:e93.)

increased prevalence of scoliosis. Ricotti et al[3] reported that patients with scoliosis tended to be taller than those without scoliosis and that those patients with scoliosis were more likely to be on HGH at baseline. However, in this study, all cases of scoliosis were felt to be minor in degree. In summary, HGH may promote progression of preexisting scoliosis in patients with Turner syndrome, but for most patients, the increase in deformity is minor and surgical intervention is rarely necessary.

Lower Extremity

The lower extremity may be involved in Turner syndrome to varying degrees (Table 4, Supplemental Digital Content 4, http://links.lww.com/JAAOS/A339). The greatest deficits in longitudinal growth are seen within the tibia and fibula proximally around the knee. The most commonly reported lower extremity finding in Turner syndrome is genu valgum. Less commonly, tarsal coalitions and brachymetatarsia have been described.

Genu Valgum

In 1973, Beals[12] reported that 7 of 11 patients (63%) in his series of Turner syndrome had knee abnormalities. Altered chromosomal make up of perichondrial cells around the knee may cause longitudinal growth impairment and adaptive changes in the epiphysis resulting in deformity. The proximal tibia is the most common site of physeal/epiphyseal changes found in patients with Turner syndrome. Patients have been observed to have medial projections from the metaphysis, depression of the medial plateau, or superior or inferior beaking of the medial boarder overlying the epiphysis. The overlying medial femoral condyle becomes enlarged, which can result in a lateral shift of the tibia.[12] Thus, creating an almost Blount type deformity without genu varum.[23]

Genu valgum is a normal physiologic finding in children between ages 3 and 4 years with an average angle of 2° to 20°.[24] Most children in the

general population will correct this femoral-tibial angle to less than 12° by age 7 years. In patients with Turner syndrome, chromosomal deficits in the perichondrium cause longitudinal growth impairment and may lead to the development of genu valgum that does not correct.[5] Mild or moderate genu valgum is most commonly asymptomatic and requires no treatment other than observation. However, in patients with severe genu valgum (mechanical axis of the lower extremity passing through or beyond the lateral cortex of the tibial plateau) or moderate genu valgum with pain (mechanical axis passing through the lateral half of the lateral femoral condyle), surgical treatment may be warranted.[24] For the skeletally immature patient with more than 1 to 2 years of growth remaining, hemiepiphysiodesis using any variety of guided growth techniques is indicated.[25] In the skeletally mature patients or skeletally immature patients with less than 1 to 2 years of growth remaining, a varus producing proximal tibial or distal femoral osteotomy may be more appropriate.[25]

Brachymetatarsia

Brachymetatarsia, or a shortened fourth or fifth metatarsal, has been suggested as a rare finding in patients with Turner syndrome.[26] Cosmetic differences may be noted in the metatarsal phalangeal joint alignment and shortening of the fourth or fifth toes. It is rarely symptomatic and most often is only found incidentally on foot radiograph. The treatment, as with brachymetacarpia, is observation.

Other General Orthopaedic Concerns

Coalitions

Bony coalitions can be a fairly common finding in patients with Turner syndrome. Sternal coalitions are the most common. Phalanx coalitions, carpal coalitions, tarsal coalitions, and vertebral coalitions have also been described.[12] Most of the coalitions are incidental findings and are rarely symptomatic. Vertebral coalitions, however, may result in significant progressive, congenital scoliosis and should be followed for ongoing surveillance. Tarsal coalitions causing pain are treated nonsurgically with activity modification and casting. If the pain is unrelieved by nonsurgical measures, surgical management including resection of the coalition and possible tissue interposition should be considered.

Developmental Dysplasia of the Hip

It has been proposed that infants with Turner syndrome may have an increased risk of developmental dysplasia of the hip (approximately 5% of patients).[8,11] However, there has been little research to support this theory. Orthopaedic recommendations for hip evaluation in infants with Turner syndrome remain equal to those of the general population. Evaluation of the hips using Ortolani and Barlow physical examinations, assessing for Galeazzi sign and measurement of hip range of motion, is recommended at all well-baby checks by the primary care practitioner. Breech presentation, family history of hip dysplasia, and instability by examination at birth are indications for a screening ultrasonography.[27]

Bone Mineral Density

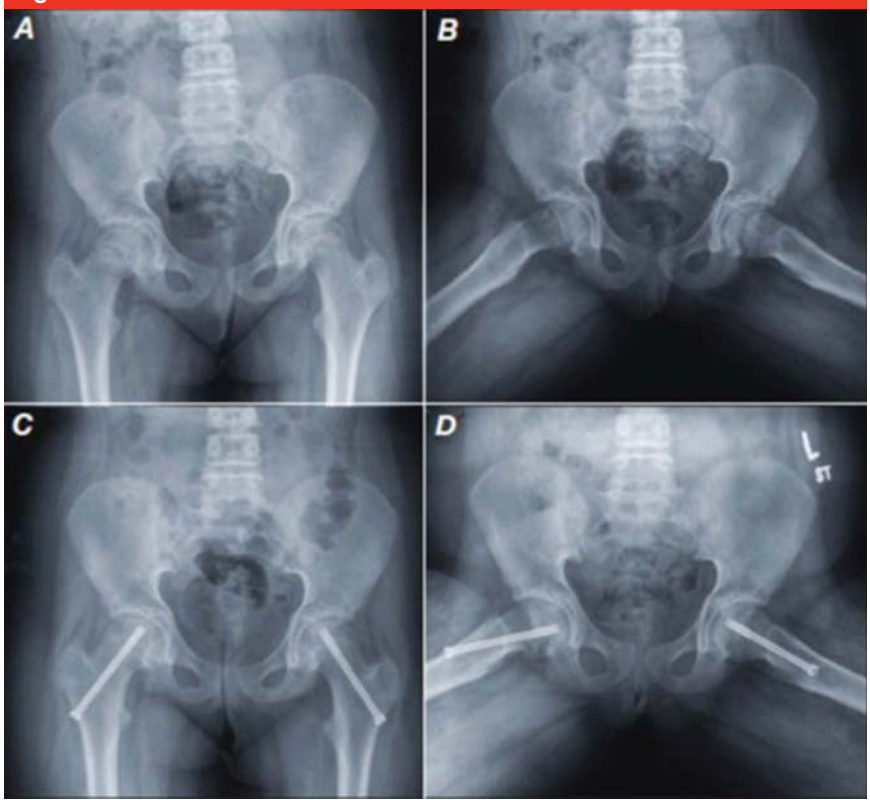
Many studies have reviewed data on osteoporosis in patients with Turner syndrome. Although controversial, bone mineral density (BMD) and bone fragility are considered lifelong comorbidities in patients with Turner syndrome.[28] At a young age, patients with Turner syndrome have been found to have a lower cortical bone density but normal trabecular bone density compared with age-matched norms.[28] It has been hypothesized that these differences are due to a combination of estrogen deficiency and sex chromosome abnormality.[29] Gravholt et al[30] published a study reviewing the medical morbidities of 594 females with Turner syndrome using the Danish National Registry. They reported 2.66 times the relative risk (1.37–4.64, 95% confidence interval) of potential osteoporotic fractures (fractures of the spine, femoral neck, and radius/ulna) in patients with Turner syndrome compared with age-matched norms. A decreased bone cortical density, along with differences in bone geometry (ie, size, shape, and microarchitecture secondary to continuous remodeling), may predispose these patients to fragility fractures.[28,29] Other common comorbidities such as obesity, decreased physical activity, sensorineural hearing deficits, and low vitamin D may also contribute to the higher risk. More recent studies have focused on the evaluation of the elevated risk of fragility fractures in patients with Turner syndrome. An increased risk of fracture was seen only in those older than 45 years. However, all younger study subjects had previously been treated, since childhood, with hormone replacement therapy compared with the older subjects who had not. Hormone factors were seen to be of great importance in the development of peak bone mass and the maintenance of BMD in these patients.[31]

Slipped Capital Femoral Epiphysis

Patients with Turner syndrome are at an increased risk of SCFE. A patient presenting out of the normal age ranges (<10 years or >16 years) should raise suspicion for an undiagnosed syndrome or endocrinopathy.[32] SCFE has been estimated to be six times more common in patients with

an endocrinopathy than in those who do not. The most common endocrinopathies in children with SCFE are hypothyroidism, panhypopituitarism, growth hormone abnormalities, and hypogonadism. Along with children with Down syndrome and renal osteodystrophy, patients with Turner syndrome are predisposed to SCFE secondary to the comorbid endocrinopathies, high risk of obesity, delayed skeletal maturation, and treatments with HGH. Any child or adolescent with Turner syndrome complaining of prolonged hip or knee pain should be evaluated radiographically with orthogonal views of bilateral hips for SCFE (Figure 7). Surgical stabilization with percutaneous screw fixation is recommended in hips with a SCFE. Prophylactic stabilization with percutaneous screw fixation of the contralateral hip is also recommended in any patient with a coexisting endocrine disorder.[16,32–34]

Figure 7



Preoperative (**A** and **B**) and postoperative (**C** and **D**) posterior-anterior and frog lateral radiographs demonstrating SCFE in a patient with Turner syndrome. Although the incidence of SCFE is increased in patients with Turner syndrome, treatment should follow standard principles. SCFE = scoliosis or slipped capital femoral epiphysis. (Reprinted with permission from Nasrallah MP, Der-Boghossian AH, Haidar RK: Slipped capital femoral epiphysisin a patient with Turner syndrome receiving growth hormone therapy. *Endocr Pract* 2012;18:e135-e137.)

Summary

The skeletal manifestations of Turner syndrome have been extensively reviewed in the past literature, but several topics remain controversial. Haploinsufficiency of the *SHOX* gene is thought to be the primary driver to skeletal deformity in Turner syndrome. The combination of sex chromosomal abnormality and estrogen deficiency most likely leads to the short stature and delayed skeletal maturation in these patients. Patients with Turner syndrome have a higher incidence of scoliosis and thoracic kyphosis, which should be followed by an orthopaedic spine surgeon for congenital curves or idiopathic curves >20°. The upper and lower extremity abnormalities found in Turner syndrome may be evident on clinical examination but rarely require surgical treatments unless they become symptomatic. Hormone replacement therapies used in the treatment of young patients with Turner syndrome may provide benefit for future bone health and decreased fragility fractures in the future. Practitioners should be aware of the lower BMDs and increased risk of fragility fractures in patients with Turner syndrome at younger ages if they have not been treated with hormone replacement therapy. The skeletal manifestations seen in patients with Turner syndrome should be followed concordantly between the orthopaedic surgeon and endocrinologist.

Although Turner syndrome is the most common chromosomal anomaly in live-born females, it continues to be a rare primary diagnosis seen in the orthopaedic clinic. Although most of these skeletal manifestations remain nonsurgical, the orthopaedic surgeon may be the first provider to see an undiagnosed patient. It is important for the orthopaedic surgeon to be aware of the common conditions seen in patients with Turner syndrome and know the standards of care to properly manage them in a multispecialty discipline.

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