absence of one X chromosome, mosaicsisms, or its structural abnormalities.\textsuperscript{21}

The classic TS phenotype includes short stature, gonadal dysgenesis with primary amenorrhea and hypergonadotrophic hypogonadism, facial and body dysmorphisms, skeletal abnormalities, cardiovascular and renal malformations, and predisposition to autoimmune diseases, such as thyroid diseases, diabetes mellitus, celiac disease, and vitiligo.\textsuperscript{21} Short stature is always present and is caused by several factors, such as \textit{Short Stature Homeobox (SHOX)} haploinsufficiency and related skeletal dysplasia, intrauterine growth retardation, poor growth in early childhood, absence of the growth spurt, and skeletal dysplasia.\textsuperscript{21}

TS is a state of reduced sensitivity to growth hormone (GH) rather than a GH deficiency, and treatment with high doses of GH can increase growth velocity and final height. In puberty, estrogen therapy should be coordinated with GH use.\textsuperscript{21} However, optimization of bone health in girls with TS also requires maintaining a healthy, active lifestyle with adequate calcium and vitamin D intake.\textsuperscript{22}

Despite only limited reports of a greater number of fractures during childhood or adulthood, osteoporosis historically has been described as a feature in TS. However, data of prevalence of osteoporosis in TS are not uniform and the causes have not been fully elucidated (Table 3).

Several studies have concluded that TS patients have low BMD.\textsuperscript{22} For example, Lisà et al described a reduced bone density in 25\% of TS associated with reduced osteocalcin and alkaline phosphatase values, indicating a reduced osteoblast activity.\textsuperscript{23} However, Benetti-Pinto et al studied BMD by DXA in 38 women and showed a marked decrease in BMD of the lumbar spine (90\%) and femoral neck (55\%). Interestingly, the authors have found a positive correlation with BMD in the lumbar spine and the duration of estrogen therapy but not with the age at which therapy was initiated.\textsuperscript{24}

More recently, Nadeem calculated bone mineral apparent density (BMAD) for correction of misdiagnosed BMD due to short stature and demonstrated that TS patients have lower BMAD values at the lumbar spine compared with an age- and sex-matched general population. According to their study, puberty had a positive impact on BMAD irrespective of the time of its commence. In addition, they noted that it is the stage of puberty, not the age at initiation of estrogen therapy, which is important for BMAD. No influence of karyotype on BMAD was demonstrated.\textsuperscript{25}

However, using new techniques such as high-resolution peripheral quantitative computed tomography (HR-pQCT), Hansen et al evaluated 32 TS patients and 32 controls matched respective to age and body-mass index and showed that TS had compromised trabecular microarchitecture and lower bone strength at the radius and tibia, which may partly account for the increased risk of fracture observed in these patients.\textsuperscript{25}

Nonetheless, other studies have displayed conflicting results. For example Shaw et al conducted a longitudinal study examining BMD at the lumbar spine in 18 girls with TS aged 4-17 years by DXA several times over a 2.5-year period. They reported only one girl with a significant bone density reduction in comparison with controls. No advantage was found for any form of treatment in optimizing bone mineralization.\textsuperscript{27}

Estrogen therapy is very important to avoid a rapid decrease in BMD and to induce maximal peak bone mass in TS adolescents. Bertelloni et al studied 26 young women with TS at final heights. The areal BMD (aBMD) and the vBMD measured by DXA demonstrated that final heights and aBMD were significantly higher in TS treated with estrogen and GH therapy than those in patients treated only with estrogen therapy. Nevertheless, vBMD was higher, though not significantly different between the groups.\textsuperscript{28} These data may suggest that in TS, GH administration improves final height and aBMD, but it does not significantly increase vBMD; aBMD reduction in

\textbf{Table 3. Mechanisms contributing to reduced bone mass in Turner syndrome}

- Turner syndrome related mechanisms
- Puberty delay
- Estrogen deficiency
- Low intake of vitamin D
- Vitamin D receptor gene polymorphisms
- Hormonal factors (i.e., thyroid disorders)
- Autoimmune diseases