TRANSITION IN ENDOCRINOLOGY

Treatment of Turner’s syndrome during transition

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Abstract

Transition in health care for young patients with Turner’s syndrome (TS) should be perceived as a staged but uninterrupted process starting in adolescence and moving into adulthood. As a condition associated with high risk of short stature, cardiovascular diseases, ovarian failure, hearing loss and hypothyroidism, TS requires the attention of a multidisciplinary team. In this review paper, we systematically searched the relevant literature from the last decade to discuss the array of problems faced by TS patients and to outline their optimal management during the time of transfer to adult service. The literature search identified 233 potentially relevant articles of which 114 were analysed. The analysis confirmed that all medical problems present during childhood should also be followed in adult life. Additionally, screening for hypertension, diabetes mellitus, dyslipidaemia, and osteoporosis is needed. After discharge from the paediatric clinic, there is still a long way to go.

Introduction

Turner’s syndrome (TS) is the most common chromosomal abnormality affecting approximately one in 2500 live-born females (1). The complete or partial absence of one of the two X chromosomes in a phenotypic female is usually accompanied by short stature, gonadal dysgenesis, lymphedema, and characteristic dysmorphic appearance in the severe phenotype, though it has a minimal impact on stature or secondary amenorrhea in the mild phenotype (2). Monosomy 45,X is prevalent, and the X-chromosome is of maternal origin in 70% of TS patients (3, 4, 5). Structural abnormalities of the sex chromosome can include deletions of the short arm and duplication of the long arm to form isochromosome (isoXq) and undergo ring formation (rX) and deletion in the short or long arm (Xp-, Xq- respectively). Some individuals are mosaic and carry one or more additional cell lines, also with the Y chromosome (45,X/46,XX, 45,X/46,XY). As a result, TS patients are haploinsufficient for some genes. The described karyotype variability reflects the wide clinical spectrum of the syndrome.

Invited Author’s profile:
Aneta Gawlik is a Senior Consultant at the Department of Paediatrics, Paediatric Endocrinology and Diabetes and Assistant Professor at the Medical University of Silesia in Katowice, Poland. Her major research interests include treatment of Turner’s syndrome, disorders of sex development (I-DSD registry), polycystic ovary syndrome. Dr Gawlik is a member of the European Society for Paediatric Endocrinology (ESPE) and participates in the activities of the ESPE Turner Syndrome Working Group.
The phenotype/genotype correlation in TS is poor. However, patients with monosomy X tend to have the most severe phenotype. The results of studies assessing the impact of X origin (maternal/paternal) on TS phenotype are inconclusive (4, 6, 7, 8). The isoX anomaly is often associated with autoimmunity, whilst the ring X karyotype is also associated with psychological and learning difficulties (9, 10, 11).

It is important to remember that all medical problems that first occur during childhood should be followed into adulthood. At different ages, attention should be paid to different medical issues (Table 1). The management of this chromosomal condition involves long-term care by a multidisciplinary team composed of endocrinologists, gynaecologists, cardiologists, geneticists, otolaryngologists, fertility specialists, behavioural health experts, nurse educators and social workers. A coordinated and consistent transition process from paediatric to ongoing adult care is necessary to ensure appropriate treatment, especially regarding hormone replacement therapy (HRT), bone health, hearing loss, cardiovascular issues and autoimmune disorders. Successful transition requires the collaboration of doctors, patients and their families (12).

This review outlines the key issues to be considered for adolescents with TS as they transition into adulthood.

### Methodology

#### Literature search

Publications were identified by a systematic literature search using PubMed and Cochrane Library to identify studies evaluating medical issues in TS published between June 2003 and August 2013.

The search terms used in the Medical Subject Headings (MeSH) included ‘Turner syndrome’(MeSH Terms) AND (‘therapy’(Subheading) OR ‘therapy’(All Fields) OR ‘treatment’(All Fields) OR ‘therapeutics’(MeSH Terms) OR ‘therapeutics’(All Fields)). The terms were combined in various ways to generate a wide search. For the appropriate choice of ‘transition population’ we used additional filters such as ‘age’ and added (‘adolescent’(MeSH Terms) OR ‘young adult’(MeSH Terms)) AND (‘2003/08/26’(PDat): ‘2013/08/22’(PDat) AND English(lang)).

An initial review of all titles and abstracts was performed for relevance. We included only full-length original articles. Case reports and review articles were not included.

The final full ‘search details’ contained ‘Turner syndrome’(MeSH Terms) AND (‘therapy’(Subheading) OR ‘therapy’(All Fields) OR ‘treatment’(All Fields) OR ‘therapeutics’(MeSH Terms) OR ‘therapeutics’(All Fields)) AND (‘adolescent’(MeSH Terms) OR ‘young adult’(MeSH Terms)) AND (‘2003/08/26’(PDat): ‘2013/08/22’(PDat) AND English(lang)).

In addition, we checked the references of eligible articles for further papers that were not captured by our search strategy and corresponded with authors when a full-length article was not directly available online.

### Results

The literature search identified 233 potentially relevant articles. After reviewing titles, abstracts and full-length
texts, 114 articles were selected for closer assessment and then analysed further.

**Growth and growth therapy and consequences**

According to a unique analysis by Bereket *et al.* (13) involving 110 untreated TS patients, the adult height was 18.4 cm below the population average, and karyotype did not seem to affect the adult height. During the last decade many studies showed growth hormone (GH) treatment as safe and effective for growth promotion in TS. Table 2 presents the results of growth therapy and indicates positive, negative and neutral determinants of therapy effectiveness as well as consequences and side effects of hormonal therapy in the analysed articles (4, 5, 7, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50).

The Canadian study provided evidence that GH treatment is acceptable to all patients with TS. Refusal of therapy was not related to health care access, but more often involved parental concerns, fear of injections and of unknown side effects, as well as age at diagnosis and height deficiency (51).

To assess the growth treatment results, it is important to choose the most appropriate growth chart. Gawlik *et al.* (52) presented a simple method of validating growth charts for a specific group of patients, as opposed to the general TS population.

**Puberty induction, HRT and fertility prospects**

Spontaneous gonadotropin levels in TS follow a diphasic pattern in all TS patients: peak in childhood, decline at 6–10 years, followed by another increase (53, 54). Ovarian function in TS patients is associated with specific karyotype. The prevalence of spontaneous puberty was 6% for 45,X and 54% for miscellaneous karyotypes (54). The anti-Müllerian hormone (AMH) seems to be a promising marker of ovarian function in girls with TS, which is helpful in counselling TS patients with regard to their fertility potential (55, 56).

In recent years, TS has been diagnosed at younger ages, and puberty has been induced at a physiological age (even in late TS diagnoses), in most instances, successfully mimicking physiological progress (57). Table 3 presents the age of induction, route, dose and consequences of HRT in TS on the basis of the analysed articles (58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75).

Fertility preservation may not be feasible for most patients with TS. However, after careful consideration of increased pregnancy-associated risks, fertility preservation may be offered to young females with mosaic TS (76). TS patients achieved acceptable pregnancy rates after oocyte donation. A high rate of pregnancy-associated hypertensive disorders was observed which have led to a high rate of prematurity and intrauterine growth restriction (77).

**Cardiovascular anomalies/problems**

In the French study, aortic coarctation (CoA), bicuspid aortic valve (BAV) and exceeded aortic diameter (>2 cm/m²) were found in 6.9, 21 and 39% of TS patients respectively. On the basis of data available for only 233 of 336 TS patients, the authors emphasised that cardiovascular monitoring for TS is currently insufficient. BAV remains undiagnosed until later in life (78). Lopez *et al.* analysed a population of adolescents with TS and found BAV in 26%, history of CoA in 17% and hypertension in 40%. The proximal aorta was larger in young individuals with TS when compared with control groups. Further analyses revealed that BAV, GH therapy and 45,X karyotype predicted a larger proximal aorta. Importantly, all of the analyses revealed that TS predicted a larger proximal aorta independent of these characteristics (79).

Some studies confirmed that new imaging techniques, such as MRI, have revealed the presence of vascular anomalies undetected at echo (80). Patients with TS have larger aortic diameters (per body surface) at all thoracic levels of measurement and larger ascending/descending aortic diameter ratios than controls. Those with TS formerly treated with GH have dilated aortas and signs of impaired wall distensibility. The severity of abnormalities seems related to the GH dose, with a beneficial effect of a larger GH dose on the abnormalities (81). According to Bondy *et al.* both ascending and descending aortic diameters were increased in the GH-treated individuals. However, multivariate analysis indicated that this increase is explained by the increase in height without evidence for any additional impact of GH treatment on the cardiovascular system. The ratio of ascending to descending aorta diameters was not altered in the GH-treated group and was actually quite normal (82).

The International Turner Syndrome Aortic Dissection Registry confirmed that aortic dissection occurs in young individuals at smaller aortic diameters than in the general population, or other forms of genetically triggered aortopathy. The absence of BAV or other cardiac malformations appears to markedly reduce the risk of aortic
Table 2  Growth therapy, determinants of therapy effectiveness, consequences and side effects.

<table>
<thead>
<tr>
<th>References</th>
<th>No. total/GH</th>
<th>Duration of GH treatment (c.o.)</th>
<th>Mean/range GH dose (mg/kg per week)</th>
<th>Gain in FH (cm)</th>
<th>FH (c.o.) (cm)</th>
<th>Consequences/side effects of growth therapy</th>
<th>Determinants of FH after GH therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4)</td>
<td>83/62</td>
<td></td>
<td>5.8 (2.4)</td>
<td>0.26</td>
<td>–</td>
<td>150.3 (6.0)</td>
<td>(~) Parental origin of the X chromosome</td>
</tr>
<tr>
<td>(5)</td>
<td>180</td>
<td></td>
<td>0.26</td>
<td>–</td>
<td>150.3 (6.0)</td>
<td>~</td>
<td>(~) Parental origin of the X chromosome</td>
</tr>
<tr>
<td>(7)</td>
<td>33</td>
<td>Ongoing</td>
<td>5.7 (1.6)</td>
<td>7.2</td>
<td>149.0 (6.4)</td>
<td>No difference between GH-treated and untreated in glucose level, HbA1c, T4, TSH. GH-treated: higher incidence in surgical procedures, otitis media, joint disorders, sinusitis; lower incidence – goiter</td>
<td>(~) Baseline hSDS</td>
</tr>
<tr>
<td>(14)</td>
<td>104/61</td>
<td></td>
<td>5.7 (1.6)</td>
<td>0.30</td>
<td>7.2</td>
<td>149.0 (6.4)</td>
<td>(~) Younger age at GH start</td>
</tr>
<tr>
<td>(15)</td>
<td>708</td>
<td>5.0 (2.2)</td>
<td>0.26</td>
<td>8.5</td>
<td>149.9 (6.1)</td>
<td>~</td>
<td>(~) Age and GH treatment duration – 90% of variance; GH dose, number of injections, age at spontaneous puberty onset, type of oestrogens (percutaneous)</td>
</tr>
<tr>
<td>(16)</td>
<td>212</td>
<td>Ongoing</td>
<td>4.0 (1.5)</td>
<td>0.33</td>
<td>–</td>
<td>150 (5.1)</td>
<td>(~) Age at oestrogen introduction</td>
</tr>
<tr>
<td>(17)</td>
<td>49/21</td>
<td></td>
<td>0.33</td>
<td>–</td>
<td>150 (5.1)</td>
<td>~</td>
<td>(~) Low dose of GH – also effective</td>
</tr>
<tr>
<td>(18)</td>
<td>186</td>
<td>5.2 (2.6)</td>
<td>0.33</td>
<td>–</td>
<td>151.7</td>
<td>~</td>
<td>(~) Target height (parental height), baseline hSDS, growth rate in first year</td>
</tr>
<tr>
<td>(19)</td>
<td>242</td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td>~</td>
<td>(~) Age at GH start, duration of therapy</td>
</tr>
<tr>
<td>(20)</td>
<td>119/60</td>
<td></td>
<td>6.5</td>
<td>0.30</td>
<td>5.0</td>
<td>151.0 (6.1)</td>
<td>(~) Taller height at GH start, higher parental height</td>
</tr>
<tr>
<td>(21)</td>
<td>149/67</td>
<td></td>
<td>6.5</td>
<td>0.30</td>
<td>5.0</td>
<td>144.9GH146.8GH+E</td>
<td>(~) Age at GH start</td>
</tr>
<tr>
<td>(22)</td>
<td>987</td>
<td></td>
<td>0.28</td>
<td>–</td>
<td>151.0NAH(median)</td>
<td>~</td>
<td>(~) Advanced age at GH start (22%- diagnosis after 12 years of age)</td>
</tr>
<tr>
<td>(23)</td>
<td>77</td>
<td>6.3</td>
<td>0.27</td>
<td>6.1</td>
<td>153.5</td>
<td>~</td>
<td>(~) Karyotype</td>
</tr>
<tr>
<td>(24)</td>
<td>382</td>
<td></td>
<td>0.36</td>
<td>–</td>
<td>–</td>
<td>~</td>
<td>(~) Height at start, GH duration ΔhSDS</td>
</tr>
<tr>
<td>(25)</td>
<td>76</td>
<td>Ongoing</td>
<td>0.35</td>
<td>–</td>
<td>–</td>
<td>~</td>
<td>(~) Younger age at start, GH duration</td>
</tr>
<tr>
<td>(26)</td>
<td>463</td>
<td></td>
<td>0.29</td>
<td>–</td>
<td>151.6</td>
<td>Ox addition – slowed breast development and delayed the menarche, no influence on bone mineral density</td>
<td>(~) Ox addition (0.06 mg/kg per day p.o.)</td>
</tr>
</tbody>
</table>

No side effects
Table 2 Continued

<table>
<thead>
<tr>
<th>References</th>
<th>No. total/GH</th>
<th>Duration of GH treatment (c.o.)</th>
<th>Mean/range GH dose (mg/kg per week)</th>
<th>Gain in FH (cm)</th>
<th>FH (c.o.) (cm)</th>
<th>Consequences/side effects of growth therapy</th>
<th>Determinants of FH after GH therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(27)ᵇ</td>
<td>92</td>
<td>–</td>
<td>0.35</td>
<td>–</td>
<td>151.4 (6.7)</td>
<td>More frequent virilisation in higher dose of Ox (0.06 mg/kg per day) compared with lower doses (0.03 mg/kg per day)</td>
<td>(+) Ox addition (0.05 mg/kg per day), late puberty induction</td>
</tr>
<tr>
<td>(28)ᵇ</td>
<td>82</td>
<td>0.32</td>
<td>155.6–156.7</td>
<td>–</td>
<td>–</td>
<td>(+) Ox addition (better with lower dose 0.03 mg/kg per day)</td>
<td>(~) Ox + late puberty – no addictive result</td>
</tr>
<tr>
<td>(29)</td>
<td>62</td>
<td>Ongoing</td>
<td>0.33</td>
<td>–</td>
<td>147.3</td>
<td>(+) Ox addition</td>
<td></td>
</tr>
<tr>
<td>(30)</td>
<td>?</td>
<td>–</td>
<td>4.28</td>
<td>–</td>
<td>–</td>
<td>(+) Higher parental height</td>
<td></td>
</tr>
<tr>
<td>(31)</td>
<td>158</td>
<td>5.6 (2.3)</td>
<td>0.31</td>
<td>–</td>
<td>151.4</td>
<td>(~) Spontaneous menarche</td>
<td></td>
</tr>
<tr>
<td>(32)</td>
<td>54/35</td>
<td>–</td>
<td>0.30</td>
<td>7.3</td>
<td>–</td>
<td>(~) Comments: similar benefit from GH in patients with SHOX and TS</td>
<td></td>
</tr>
<tr>
<td>(33)ᵇ</td>
<td>43</td>
<td>Ongoing</td>
<td>0.29</td>
<td>–</td>
<td>–</td>
<td>(~) Maternal origin of X chromosome</td>
<td></td>
</tr>
<tr>
<td>(34)</td>
<td>175/115</td>
<td>Ongoing</td>
<td>0.3–0.33</td>
<td>–</td>
<td>–</td>
<td>(~) Exon 3 deleted/full-length GH receptor polymorphism on height velocity</td>
<td></td>
</tr>
<tr>
<td>(35)</td>
<td>120</td>
<td></td>
<td>?</td>
<td>–</td>
<td>145.2 (10.9)</td>
<td>(~) GHR-exon 3 genotype</td>
<td></td>
</tr>
<tr>
<td>(36)ᵇ</td>
<td>46/23</td>
<td>5.0 (2.1)</td>
<td>0.30–0.38</td>
<td>–</td>
<td>–</td>
<td>(~) Autoimmune pathologies</td>
<td></td>
</tr>
<tr>
<td>(37)ᵇ</td>
<td>67/39</td>
<td>4.2 (3.2)</td>
<td>0.21–0.35</td>
<td>–</td>
<td>–</td>
<td>(~) History of GH use: lower total body and abdominal fat mass</td>
<td></td>
</tr>
<tr>
<td>(38)ᵇ</td>
<td>102/76</td>
<td>Ongoing</td>
<td>0.21–0.35</td>
<td>–</td>
<td>–</td>
<td>(~) No influence on body proportions, except for hand length</td>
<td></td>
</tr>
<tr>
<td>(40, 41)ᵇ</td>
<td>82/30</td>
<td>3.7 (1.5)</td>
<td>0.42</td>
<td>–</td>
<td>146.2</td>
<td>(~) Ox addition (0.06 mg/kg per day): increases sitting height, reduces subcutaneous fat mass. Ox in lower dose (0.03 mg/kg per day): decreases biiliacal distance. Both Ox doses: increase muscle mass</td>
<td></td>
</tr>
<tr>
<td>(42)ᵇ</td>
<td>112</td>
<td>0.32</td>
<td></td>
<td>–</td>
<td>–</td>
<td>(~) GH reduces insulin sensitivity, GH cessation – insulin sensitivity returns to pre-therapy values. Oestrogens worsen the indices of insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>(43)</td>
<td>46</td>
<td>6.3 (2.5)</td>
<td>0.33</td>
<td>–</td>
<td>156.0 (5.5)</td>
<td>(~) Metabolic consequences 5 years after GH therapy: higher total cholesterol, higher HDL, insulin sensitivity lower, β-cell function and fasting insulin remained higher, atherogenic index – constant</td>
<td></td>
</tr>
<tr>
<td>(44)</td>
<td>39</td>
<td>8.7 (2.0)</td>
<td>0.31–0.63</td>
<td>–</td>
<td>162 (6.9)</td>
<td>(~) GH has no effect on cardiac dimension</td>
<td></td>
</tr>
<tr>
<td>(45)</td>
<td>86/67</td>
<td>4.4</td>
<td>0.35</td>
<td>–</td>
<td>145.7 (9.4)</td>
<td>(~) No benefits and adverse effects on HRQOL</td>
<td></td>
</tr>
<tr>
<td>(46)</td>
<td>33/21</td>
<td>–</td>
<td>0.30</td>
<td>–</td>
<td>148.9</td>
<td>(~)</td>
<td></td>
</tr>
</tbody>
</table>

Reference: European Journal of Endocrinology
dissection. Aortic dissection can also occur in TS without cardiac malformations or hypertension. Individuals after 18 years of age with an ascending aortic size index > 2.5 cm/m² should be considered for an aortic operation to prevent aortic dissection (83). Sharma et al claim that aortic dilation is seen in individuals with TS, both with and without risk factors. Aortic dilation in those without risk factors was accompanied by decreased aortic distensibility, suggesting an intrinsic abnormality in elastic property of the ascending aorta. Individuals with aortic dimensions in excess of the 95th percentile with decreased distensibility should be followed closely, both clinically and echocardiographically (84).

One study demonstrated that CoA stenting is a safe and effective procedure at midterm follow-up in a small cohort of patients with TS. Taking into account the cases reported thus far, it appears that stenting is not inferior to other treatment methods (surgery, balloon angioplasty) with regard to morbidity and mortality (85).

The study of Zuckerman-Levin et al confirmed that subjects with TS have resting tachycardia and hypertension. These may be related to sympathetic dysregulation. TS patients are associated with increased resting noradrenaline levels and a compromised response to sympathetic stimulation: they have a sympathetic tolerance for physical stress and an inertia for sympathetic stimulation (86).

Gravholt et al conducted a cross-sectional study and characterised the activities of the haemostatic system in TS patients. They described a significant proportion of individual TS females having high levels of von Willebrand factor, factor VIII, fibrinogen and C-reactive protein (15–40%) and an increased frequency of the Leiden mutation, with important associations with carotid intima-media thickness and blood pressure, suggesting that a subset of TS may have an unfavourable haemostatic balance, which may contribute to the increased risk of premature ischaemic heart disease and possibly increase the risk of deep venous and portal vein thrombosis (87). As suggested by another study, it is advisable to perform a complete thrombophilia screening in TS patients before starting HRT (88).

**Autoimmune disorders**

Thirty-six percent of young women with TS had positive autoantibodies to thyroid peroxidase and/or to thyroglobulin, 4% had positive autoantibodies to tissue transglutaminase (tTG) and 2% had positive autoantibodies to both of them (35). Median age of developing thyroid

<table>
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<th>Table 2 Continued</th>
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</thead>
<tbody>
<tr>
<td><strong>Determinants of FH after GH therapy</strong></td>
</tr>
<tr>
<td><strong>Consequences/side effects of growth therapy</strong></td>
</tr>
<tr>
<td>(+) Positive; (−) negative; (+) neutral</td>
</tr>
<tr>
<td>150.9 (5.6)</td>
</tr>
<tr>
<td>151–158</td>
</tr>
<tr>
<td>(−) Negative</td>
</tr>
</tbody>
</table>

GH, growth hormone; Ox, oxandrolone; E, oestrogens; FH, final height; hSDS, height SDS; HRQOL, health-related quality of life; NAH, near adult height; mpH, midparental height.

a Randomised trial. 
b With control group.

determinations/fh after gh therapy
Table 3  Puberty induction by oestrogen replacement therapy in young Turner's syndrome patients – consequences.

<table>
<thead>
<tr>
<th>References</th>
<th>No. total/ERT</th>
<th>Mean (s.d.) age of ERT start (years)</th>
<th>Form of ERT</th>
<th>Dose (range)</th>
<th>Comments/consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>(58)(a)</td>
<td>12</td>
<td>14.0 (1.7)</td>
<td>CE, TE</td>
<td>0.3–0.625 mg/day(\text{CE}) 0.025–0.0375 mg/day(\text{TE})</td>
<td>TE vs CE: TE after 1 year faster bone accrual (spine), faster increase of uterine size</td>
</tr>
<tr>
<td>(59)(a,b)</td>
<td>10</td>
<td>17.7 (0.4)</td>
<td>OE, TE</td>
<td>0.5–2.0 mg/day(\text{OE}) 0.0375–0.075 mg/day(\text{TE})</td>
<td>TE – oestradiol and oestrone concentration closer to normal, better suppression of FSH, LH. Higher doses of TE – more physiological. Oestrogens – no influence on IGF1, minimal on cholesterol</td>
</tr>
<tr>
<td>(60)</td>
<td>56</td>
<td>12.7 (0.7)</td>
<td>OE</td>
<td>5–10 (\mu g/kg) per day</td>
<td>Breast development is comparable with normal with a 2-year delay. Uterine dimensions are subnormal at the age 20 years. Hormone levels – not useful in a clinical setting</td>
</tr>
<tr>
<td>(61) IGLU study</td>
<td>75</td>
<td>14.7</td>
<td>EE, CE, EV, OC</td>
<td>–</td>
<td>Uterine sizes normal in 45,XX/46,XX. 45,X – smaller uterine dimensions (26% – uterine length below – 2 s.d., 18% – uterine volume below – 2 s.d.)</td>
</tr>
<tr>
<td>(62)(b)</td>
<td>41/30</td>
<td>13.0 (1.4)</td>
<td>OE</td>
<td>0.10–1.75 mg</td>
<td>Uterine volume (US, MRI) in matured TS is lower compared with controls despite therapy. Breast development delayed in TS</td>
</tr>
<tr>
<td>(63)</td>
<td>57</td>
<td>14.6 (2.4)</td>
<td>OE, EE, TE</td>
<td>5–20 (\mu g/kg) per day</td>
<td>Uterine volume suboptimal in adult TS</td>
</tr>
<tr>
<td>(64)</td>
<td>86/73</td>
<td>15.7 (4.1)</td>
<td>CE, OC, OE, TE</td>
<td>–</td>
<td>Normal uterine size in adults, regardless of karyotype and GH treatment</td>
</tr>
<tr>
<td>(65)</td>
<td>18/13</td>
<td></td>
<td></td>
<td></td>
<td>Normal uterine size with adult dimensions (US), regardless of karyotype</td>
</tr>
<tr>
<td>(66)</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td>Normal uterine size with adult dimensions (US), regardless of karyotype</td>
</tr>
<tr>
<td>(67)(a)</td>
<td>48</td>
<td>14.3 (1.4)(\text{ID}) 13.4 (1.0)(\text{FD})</td>
<td>OE</td>
<td>5–15 (\mu g/kg) per day(\text{ID}) 0.2–0.5 mg/day(\text{FD})</td>
<td>ID&amp;FD of OE – normal pubertal development, well tolerated, does not interfere with GH treatment</td>
</tr>
<tr>
<td>(68)</td>
<td>23</td>
<td>13.6</td>
<td>TE</td>
<td>0.1–1.5 mg/day</td>
<td>TE (gel) – gradual development of puberty, well accepted by patients, individualised pubertal induction, no influence on height</td>
</tr>
<tr>
<td>(69)</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>Oestrogens before vs after 13 years – no difference in final height</td>
</tr>
<tr>
<td>(70, 74)</td>
<td>14</td>
<td>–</td>
<td>OE</td>
<td>4 mg/day</td>
<td>Increasing dose of OE reduces IMT, increase HDL decreases glucose. Possible long-term effects of high dose of oestrogens. Exogenous oestrogens – improvement of liver function</td>
</tr>
<tr>
<td>(71)</td>
<td>12</td>
<td>CE</td>
<td></td>
<td></td>
<td>No adverse effects on metabolic and coagulation parameters, significant increase in HDL and bone density</td>
</tr>
<tr>
<td>(72)</td>
<td>11</td>
<td>13.4 (0.5)</td>
<td>OE, TE</td>
<td>0.5–1 mg/day(\text{OE}) 0.025–0.05 mg/day(\text{TE})</td>
<td>OE vs TE: no adverse effect on whole-body metabolism (protein turnover, lipolysis, lipid oxidation rates), no differences in lipids, fibrinogen, insulin concentration, IGF1. Authors emphasised the short length of follow-up</td>
</tr>
<tr>
<td>(73)</td>
<td>9</td>
<td>CE, TE</td>
<td></td>
<td></td>
<td>TE vs CE: no difference with regard to BMI, waist-to-hip ratio, insulin tolerance. TE use – tendency to increase total lean mass</td>
</tr>
<tr>
<td>(75)(b)</td>
<td>14</td>
<td>21.3 (3.1)</td>
<td>EE+MT</td>
<td>20 (\mu g/day)(\text{EE}) +1.5 mg/day(\text{MT}) vs 20 (\mu g/day)(\text{EE})+placebo</td>
<td>Androgen insufficiency – role in TS-impaired body composition, neurocognition, quality of life</td>
</tr>
</tbody>
</table>

ERT, oestrogen replacement therapy; CE, oral conjugated oestrogens; OC, oral contraceptives; OE, oestradiol (oral); TE, transdermal oestradiol; EE, ethinyl oestradiol; EV, oestradiol valerate; MT, methyl testosterone; ID, individualised dose; FD, fixed dose.

*Randomised study.

\(b\)Study with control group.

ERT, oestrogen replacement therapy; CE, oral conjugated oestrogens; OC, oral contraceptives; OE, oestradiol (oral); TE, transdermal oestradiol; EE, ethinyl oestradiol; EV, oestradiol valerate; MT, methyl testosterone; ID, individualised dose; FD, fixed dose.

*Randomised study.

\(b\)Study with control group.
autoantibodies was 14.1 years and they appeared mainly after the age of 13 (89). The incidence of positive autoantibodies grew with age. More than half of the adults with TS had thyroid autoantibodies, and the prevalence of hypothyroidism was 31%. About one-third were considered to have Hashimoto’s thyroiditis: 70% of TS women with hypothyroidism were receiving l-thyroxine (90).

TS may be associated with changes in lymphocyte subpopulations. Compared with healthy young women, the percentage of CD3+CD4+ cells were significantly reduced, whilst the percentage of CD19–CD138+, CD4+CD25+FoxP3+ and CD4+CD8–IL17A+ cells were significantly increased in TS patients. Oestrogen therapy did not affect the percentage of lymphocyte subpopulations (91).

Despite the fact that raised liver function tests are common in women with TS, there was no evidence of excessive hepatic autoimmunity in TS women; the incidence of positive antismooth muscle antibodies in patients with TS and in the general population was comparable (2.2%) (74).

### ENT problems

Hearing impairment was rated as the most serious problem associated with TS (48, 92). In the population of young women with TS (mean age 17.3 years), about half had a history of recurrent otitis media and in 20% there were some auricular anomalies. Otoscopic examination identified eardrum abnormalities in 45% of patients, with myringosclerosis as the most common condition. Audiologic analysis revealed conductive hearing loss (CHL) in 10% and sensorineural hearing loss (SNHL) in 17%. Further analyses did not confirm any association with karyotype or craniofacial anomalies (93). In younger patients, CHL occurred in 38% and persistent secretory otitis media in 55%. SNHL frequency was similar (94).

More than 60% of patients with TS showed high-frequency (8 kHz) sensory neural hearing loss. The hearing thresholds at high frequencies were correlated with age (more apparent in 45,X) and height (95).

In the Canadian randomised study, GH treatment predisposed to ear disorders, otitis media and ENT surgical procedures, which can be explained by an increase of tonsils and adenoids during GH use. There were no differences in auditory acuity between GH and control patients (14). According to Ostberg et al., oestrogen and GH therapy had no impact on adults’ hearing loss in TS, independent of age. They confirmed that the prevalence of SNHL increases with age. CHL was associated with ENT history and karyotype, so the only possible intervention to reduce hearing loss in women with TS is assiduous treatment of ENT problems during childhood (96).

The findings of Hamelin et al. (32) regarding a putative X-linked imprinting effect on SNHL suggest that a gene (genes) expressed from the maternal origin X-chromosome may prevent the gradual decline in hearing. Also oestrogens may have an effect on hearing loss in TS patients (92).

The TS phenotype includes important voice and speech problems. Monosomic and isochromosome TS patients have more voice problems and also more high-pitched voices than mosaic patients. Most TS women, despite their karyotype or age, exhibit a higher frequency of pitched voice than non-TS women (49, 97).

Menke et al. found that the addition of oxandrolone to GH increases voice deepening in a dose-dependent way. Although most voice frequencies have remained within the normal range, they may occasionally become lower than −2 S.D., especially on GH plus oxandrolone at a dose of 0.06 mg/kg per day (97).

### Y-chromosome mosaicism

Patients with TS, in particular those with 45,X or a marker chromosome at conventional cytogenetic analysis, may benefit from molecular screening analysis to detect the presence of Y-chromosome material (98, 99). An unselected series of 171 patients with TS diagnosed cytogenetically was studied for Y-chromosome markers (SRY and Y-centromeric DYZ3 repeats). Y-chromosome material was found in 14 patients (8%). Of the 14 patients, 12 were gonadectomised and in four (33%) gonadoblastoma was detected under 16 years of age. According to the authors, the epidemiological studies in the past underestimated the risk of gonadal neoplasms in this group of patients (98). A different study confirmed the association of Y fragments with gonadoblastoma at an early age; however, the presence of Y material was not combined with virilisation (99).

### Bone

The Danish national survey, based on questionnaires from 322 TS patients and 1169 controls, confirmed an increased risk of early fractures in TS, especially in those without ovarian function and with positive family history of fracture and osteoporosis (100). Trabecular bone mineral density (BMD) of the spine appears normal, but cortical bone strength of the extremities is reduced in TS. This observation was in agreement with the
documented increased incidence of long bone fractures. Zuckerman-Levin et al. (101) recommended quantitative ultrasonography for the detection of frail cortical bones in TS patients. A cortical bone deficit in girls with TS characterised by low cortical area, thin cortex and probably decreased cortical volumetric BMD (vBMD) was also confirmed in the next publication. Early commencement of GH therapy, as well as oestrogen replacement, was associated with higher cortical vBMD (102).

Cleemann et al. evaluated BMD together with bone formation and resorption markers, both in TS adolescents treated with GH and in TS subjects after GH therapy. The results were compared with a healthy control group. BMD increased in parallel with age in TS patients receiving optimal oestradiol (E2) therapy and GH, and in controls. Young TS patients undergoing pubertal induction and still receiving GH had lower z-score BMD than older TS patients receiving HRT, where a near-normalised BMD was achieved. Patients previously receiving GH showed signs of increased bone resorption (103).

Continuous oestrogen therapy increases BMD in TS patients. The maximum BMD negatively correlated with the age at which adult-dose oestrogen therapy was initiated, and younger patients, <18 years of age, responded well to this therapy. Thus, adult-dose oestrogen therapy should be started by at least 18 years of age (104). Similar positive effects of HRT were also observed by others (71).

By contrast, one earlier study indicated that GH administration in childhood and adolescence as well as HRT in adulthood did not increase bone mineralisation in TS patients. One explanation could be a delayed start of oestrogen therapy (mean age 20.4 years) (105).

BMD can be maintained at most sites in well-informed young to middle-age individuals with TS, by encouraging them to maintain a healthy lifestyle including regular oestrogen therapy and higher intake of calcium and vitamin D (106).

The cross-sectional study revealed higher risk of developing scoliosis in TS and the age at risk was protracted further with respect to healthy subjects. This risk appeared to be influenced by the patient’s height and, indirectly, by GH therapy (107).

Liver enzymes

The prevalence of liver abnormalities in girls and adolescents with TS was much lower and more strictly related to hormonal therapies than in TS adults. Both autoimmunity and obesity were not frequently involved in the aetiology of TS liver dysfunction. Liver damage was either mild or moderate, and its severity was not conditioned by karyotype. Its natural history may be characterised in some cases by a slight deterioration of intrahepatic cholestasis, with no negative repercussions on liver synthetic function (108).

Psychological and educational issues

Young adult women with TS have normal health-related quality of life (HRQOL), suggesting that they adjust well to their challenges in life (46). GH and oestrogen treatment is hypothesised to have a positive influence on HRQOL in young TS women (109).

In comparison to healthy females, patients with TS did not report more behavioural and emotional problems, except for attention problems; indeed, they reported fewer problems on some subscales (somatic complaints, thought problems, delinquent behaviour). TS patients did not differ from the non-TS female group in their bodily satisfaction. However, they perceived themselves as less socially competent (particularly patients with a 45,X karyotype). BMI was significantly related to the appraisal score of the body attitude scale, whereas height was not related to any of the evaluated psychosocial parameters (110).

By contrast, another study showed a lower quality of life, higher tension-anxiety scores and impaired cognitive functions in TS girls after GH therapy than that of age-matched controls (111). According to NIH study, TS women reported a higher rate of lifetime depression (112). Social isolation was more commonly reported in the whole TS cohort than in the general population (47). During adolescence, TS girls were at risk of psychological problems with lower self-esteem and higher state of anxiety levels (113).

To optimise self-esteem, social adjustment, and the initiation of sexual activity in patients with TS, puberty should be induced at a physiologically appropriate age. Psychological support and counselling should be offered to patients, focusing particularly on those from families with a low socioeconomic status (114).

The addition of androgen replacement in TS girls has a positive effect on arithmetic performance (115). Another trial showed that oxandrolone did not cause evident psychological virilising side effects in behaviour, aggression, romantic and sexual interest, mood and gender role in GH-treated girls with TS. Problem behaviour is frequently present in untreated girls with TS, but seems to decrease during therapy. However, total and internalising problem behaviour remains increased (116).
The issue of diagnostic disclosure in TS patient was analysed by Sutton et al. Thirty percent of study participants spontaneously mentioned that their health care providers or parents had withheld all or part of their TS diagnosis. Moreover, some of them were not informed of the infertility component of their diagnosis (117). Gravholt et al. (100) conducted a study to assess risk factors of bone fractures and unexpectedly found 45/322 participants were unaware of their TS diagnosis.

Complex health care during transition in studies

Little attention has been given to follow-up during transition phase between paediatric and adult care. Devernay et al. conducted the first large study assessing the adequacy of medical follow-up in a population-based cohort of 568 women with TS during the transition period. Only 20 of them (3.5%) had undergone medical follow-up assessment in line with recent international recommendations. Follow-up was grossly insufficient for most assessments, leaving TS women at risk of undetected diseases. Only 21% of patients without known heart diseases had undergone echocardiography, and only 17% without known otological conditions had undergone audiometry assessments during the last years. Lipids determinations were the most frequently performed tests (68%), followed, in decreasing order of frequency, by determinations of blood glucose (54%), thyroid hormones (36%) and liver enzymes (16%). It was found that being followed by an endocrinologist rather than another type of physician had the greatest impact on the quality of follow-up (118). The results from a recently published questionnaire study also showed that medical follow-up in the transition phase was still inadequate and that none of the patients had undergone all the recommended investigations. Moreover, the most striking finding was the fact that several GPs were not aware of TS diagnosis in their patients (119). Verlinde et al. confirmed that a multidisciplinary approach to young adults with TS is needed in order to optimise health and psychological status. Although about 40% of these young women reported health problems, almost 13% did not consult any physician. According to one study, 14% did not take oestrogen replacement therapy (120), whilst in another, only half of young adults with TS used HRT (121).

The first study evaluating medical care in a large cohort of adolescents with TS found changes in medical practice since the establishment of the international guidelines in 2007. However, screening for associated comorbidities was still deficient in >50% of patients. Before 2007, none of the patients had screening performed for celiac disease, dyslipidemia or liver dysfunction and none had routine electrocardiography or cardiac magnetic resonance imaging. Since 2007, 63% were screened for celiac disease, 54% for liver abnormalities, and 38% for dyslipidemia. Echocardiography was performed in 23% and cardiac magnetic resonance was performed in 39% (122). The questionnaire received from paediatric endocrinologists also confirmed discrepancies between the guidelines and transitional paediatric service (123).

Discussion

Adolescence is a difficult time for any child with a chronic disorder. The teenagers with TS are already confronting a variety of problems, including those relating to growth and pubertal management. They may have other ongoing or changing physical problems, such as cardiovascular or hearing abnormalities. As well as physical problems, they may have associated learning or behavioural difficulties which can affect peer relationships. All these areas need to be encompassed in any service providing care for the adolescent and young adult with TS.

This article reviews the present status of TS comorbidities and health care during the transition time. The analysis was based on 114 studies from the last decade, presenting results coming from adolescents (13–18 years) and young adults (19–24 years).

Growth in transition time

Short stature affects ~95% of women and girls with TS. Without medical intervention, these patients attain a mean adult height of 143 cm, which is ~18–20 cm below the healthy female population (13, 124). The goal of growth-promoting therapy is to attain a normal final adult height. The results of a Canadian study support GH supplementation to school-age girls with TS and provide an accurate estimate of the results. Still, the benefits of GH supplementation need to be balanced against the costs of the therapy and the daily injections over a period of many years (14). Most TS patients begin GH in childhood, whilst the transition time is mainly for the assessment of treatment results as well as the possible side effects. Factors predictive of taller adult height are tall height at GH therapy onset, tall parental heights, better first year responsiveness to GH, long duration of therapy and a high GH dose (18, 22, 23, 24, 25). The significance of age at therapy onset is not evident and the optimal time for therapy initiation has not been established. Therapy may
continue until a satisfactory height has been attained or until there is little growth potential left (bone age > 14 years and growth velocity < 2 cm/year) (14). Although GH therapy has a safety profile in TS, when administered at higher doses, IGF1 levels are often above normal ranges. Elevated levels of IGF1 should be avoided in view of the potential long-term adverse effects. Also careful monitoring for benign intracranial hypertension, scoliosis, slipped capital femoral epiphysis, body proportion, abnormal glucose tolerance and reduced insulin sensitivity is recommended (41, 43, 50, 107).

In older girls, or those with extremely short stature, a nonaromatisable anabolic steroid, such as oxandrolone, can be considered. Although both oxandrolone and late induction of puberty have been shown to increase final height, simultaneous administration of both does not improve the outcome (27). Higher doses of oxandrolone are likely to result in virilisation and rapid bone age maturation, thus lower doses (0.03 mg/kg per day) are recommended (28).

Puberty/fertility in transition time

TS and its treatment may have an impact on puberty, sexual function and reproductive potential as well as the possible side effects and safety. Although up to 30% of girls with TS undergo some degree of spontaneous pubertal development (125, 126), and 2–5% may achieve spontaneous pregnancy (127), ultimately, over 90% have follicular atresia resulting in gonadal failure.

Gonadotropin concentrations show a biphasic pattern, with elevated concentrations during the first years of life and then again at the expected age of puberty (53, 54). AMH concentrations correlate with a specific karyotype and ovarian dysfunction, and seem to be a promising marker of ovarian function (55, 56).

The optimal oestrogen formulation, dosage, route of administration, as well as the time of adding progestin treatment, still remain controversial. The overall goal of oestrogen treatment is to replicate the pace of puberty development comparable to young peers. Delayed puberty does not affect final height outcome (15, 18, 69); however, recent data have shown a positive effect of introducing oestrogen at the age 14 rather than at 12 (27). Nevertheless, if GH therapy is initiated early enough, puberty can be induced at an age-appropriate time. If there is no spontaneous puberty and the FSH levels are elevated, HRT should be initiated around the age of 12–14, with initial low-dose oestrogen monotherapy. It is advisable to delay the addition of progestin by at least 2 years, so as to enable normal breast and uterine development. In order to maintain feminisation and prevent osteoporosis, oestrogen replacement is usually required until the time of normal menopause (Table 4) (2).

Still, recent studies have shown that a considerable percentage of TS patients discontinue therapy in adult life (120, 121).

Although oral oestrogens are the most widely used, transdermal E₂ (both patch and gel) seems a more physiological alternative. It results in better BMD, faster

### Table 4 Hormone replacement therapy in Turner’s syndrome: suggestions (2).

<table>
<thead>
<tr>
<th>Age</th>
<th>Suggestions</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–11</td>
<td>Puberty assessment/FSH/AMH</td>
<td>t/d</td>
<td>Decision about low-dose E₂ (?), 6.25 μg/day</td>
</tr>
<tr>
<td>12–13</td>
<td>No puberty/elevated FSH/check AMH</td>
<td>t/d</td>
<td>Adult: 0.25 mg/day/depot E₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.o.</td>
<td>Adult: 2–4 mg micronised E₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.m.</td>
<td>Adult: 0.2–0.4 mg/month depot E₂</td>
</tr>
<tr>
<td>12.5–15</td>
<td>Gradual increase in E₂ dose over 2 years to adult dose</td>
<td>t/d</td>
<td>Adult: 20 μg EE₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.o.</td>
<td>Adult: 1.25–2.5 mg CEE</td>
</tr>
<tr>
<td>14–16</td>
<td>After 2 years or when breakthrough bleeding occurs – add cyclic progesterone</td>
<td>p.o.</td>
<td>Adult: 200 mg/day (cyclic)</td>
</tr>
<tr>
<td>14–30</td>
<td>Full dose of oestrogen</td>
<td>t/d</td>
<td>Adult: 100–200 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.o.</td>
<td>Adult: 2–4 mg micronised E₂</td>
</tr>
<tr>
<td>30–50</td>
<td>Lower dose of oestrogen but providing full protection against osteoporosis</td>
<td></td>
<td>Adult: 20 μg EE₂</td>
</tr>
<tr>
<td>&gt;50</td>
<td>As in other postmenopausal women</td>
<td></td>
<td>Adult: 1.25–2.5 mg CEE</td>
</tr>
</tbody>
</table>

AMH, anti-Müllerian hormone; E₂, oestradiol; EE₂, ethinyl oestradiol; CEE, conjugated equine oestrogens; t/d, transdermal.
increase of uterine growth (58), greater suppression of gonadotropins (59) and better final height (15). Moreover, patients receiving transdermal E2 have lower oestrone concentrations than those using oral oestrogen, because the latter undergoes first pass metabolism in the liver. Transdermal therapy is often preferred for the initial stages of pubertal development as patches can be cut and the dosage can be gradually increased.

Oestrogen treatment, both oral or transdermal, contraceptive pills and HRT improve liver function (74), increase HDL and may be cardioprotective (71). Regardless of the form, route and dose of oestrogens, the possibility to achieve mature uterine size during HRT seems controversial (60, 61, 62, 63, 64, 65, 66).

Recent studies have raised the issue of high risk of venous thromboembolism events (deep-vein thrombosis, pulmonary embolism, cerebral sinus thrombosis and superficial venous thrombophlebitis) during HRT (128). Moreover, Gravholt et al. (87) reported higher levels of procoagulant factor and inflammatory markers in TS patients. Accordingly, screening for thrombophilia-related disorders is required (88). Thrombosis prevention should be discussed with the patient and their family.

Spontaneous pregnancy among TS patients is reported in 2% of cases (127). For the vast majority of young TS women, IVF with donor oocytes is recommended. A thorough evaluation of various organ systems should be carried out to assess the risk of potential pregnancy-related complications. A check of cardiovascular and renal system, thyroid function and glucose tolerance is recommended. In TS women, the risk of aortic dissection or rupture during pregnancy may be ≥2%, and the risk of death during pregnancy can be even 100-fold higher (129). In order to reduce the risk of hypertensive disorders during pregnancy, single embryo transfer should be proposed (77). The potential to use cryopreserved ovarian tissue and immature oocytes harvested before ovarian regression is being studied. This would give the patient the possibility of pregnancy with her own oocytes.

Cardiovascular abnormalities in transition

Both clinical (78, 80, 122) and questionnaire studies (118, 119) revealed that cardiovascular monitoring for TS was insufficient. All girls and women with TS require comprehensive cardiovascular evaluation to diagnose congenital heart diseases and hypertension and to exclude long-term consequences of childhood GH treatment on aortic structures or function. A body-surface area-adjusted aortic size index > 2.0 cm/m² warrants a prompt referral to an experienced cardiologist and close follow-up; if > 2.5, an aortic operation should be considered. However, the ideal timing for interventions to protect TS individuals at risk is unknown. The fact that death due to aortic dissection occurs in many younger TS women who have symptoms for > 24 h before they seek medical attention emphasises the need to increase awareness of the critical significance of chest pain in young TS women (83). Aortic dissection can occur in TS without cardiac malformations or hypertension (83, 84).

Hypertension affects almost half of young adults with TS, and should therefore be closely monitored and treated vigorously (2). It may be related to hyperactive sympathetic nervous system (SNS) and elevated catecholamines, and may be treated with sympathetic drugs (e.g. β antagonists or α2 agonists). Nevertheless, given the possible β hypersensitivity and increased sympathetic tone found in TS patients, these drugs should be initiated with caution and in smaller than usual dosage. Treatment targeting the overactive SNS may be useful to prevent later cardiovascular complications in these patients (86).

Autoimmune diseases during transition

Due to the increased risk of developing overt diseases, screening for autoimmune disorders should be continued throughout life. Specific manifestations include autoimmune thyroid diseases (Hashimoto thyroiditis and Graves’ disease), celiac disease, inflammatory bowel disease, alopecia areata and diabetes mellitus. According to a Danish study, autoantibodies were present in 58% of all patients (range: 6–60 years), whereof 18% had autoantibodies targeting more than one organ (130). In the analysed studies, TS patients in transition time had a higher prevalence of autoimmune thyroid disorders (35, 89, 90). The health care for TS adolescents includes a yearly TSH; in patients with subclinical hypothyroidism, autoantibody assessment or ultrasound should be considered (89). Impaired glucose tolerance and diabetes are also more frequent in TS. According to a French study, blood glucose was one of the most common medical follow-up assessments in the young population (118). By contrast, screening for celiac disease by measuring tissue tTg IgA antibodies was the least common test (119).

Hearing problems

Regular otological examination is essential, as ~17% of adolescents and 60% of adults with TS experience SNHL.
(93, 95). In younger patients, CHL was more common (94). Recent guidelines have recommend screening at least every 2–3 years in all asymptomatic patients, and more frequently in those with established hearing loss or new symptoms of hearing problems (2).

**Bone health**

Fractures are more common in TS, but only in older patients without optimal oestrogen treatment and with positive family history (100). The BMD increases with continuous oestrogen therapy and correlates negatively with the age at which adult-dose oestrogen therapy was initiated (71, 104). A low BMD in young women may result from oestrogen replacement noncompliance, tobacco use, excessive alcohol use, possible celiac disease or vitamin D deficiency (2).

Scoliosis screening in TS patients should be extended up until the age of 20. It is recommended that all TS patients, with or without minor scoliosis, perform physical activity with regular medical check-ups (107).

**Psychosocial issues/HRQOL**

Adolescent and adult women with TS report significantly higher levels of shyness and social anxiety, lower self-esteem and social isolation (47, 114). They tend to leave the parental home and become sexually mature later than their peers; they are also less likely to marry. It remains unclear whether this delayed sexual activity reflects the hormonal influence on behaviour or the timing of puberty. Most probably, the developmental process is affected by treatment with GH and oestrogens that potentially influence the TS girl's self-perception (2). Therefore, puberty should be induced at a physiologically appropriate age to optimise self-esteem and social adjustment (114). Generally, young adults with TS have normal HRQOL (46); however, cardiac or otological problems or induction of puberty after 15 years of age is associated with lower results (48). The impact of GH therapy on HRQOL is inconclusive (109, 111).

Mathematics-learning disabilities are an important and persistent problem in TS. Standard cognitive remediation can be supported by an effective and safe pharmacological intervention, such as replacing deficient levels of androgen. However, the treatment of TS girls with androgen to improve cognitive function should be considered with caution. The optimal dose and duration of treatment, as well as the optimal age of treatment initiation for neural and cognitive development, are still unknown (115).

**Concluding remarks**

The main objective of a physician managing a TS patient is to maximise her lifelong functioning and potential by providing high-quality and developmentally appropriate health care services. It is vital that the services continue uninterrupted throughout the transition period, i.e. as the patient moves from adolescence to adulthood. It is important to remember that once the young woman with TS is discharged from the paediatric clinic, there is still a long way to go.

The transition period should be initiated as a staged process. At the age of 12–13 years, care should be shifted from the parent to the TS teenager. The adolescent patients should be informed about all aspects of adult TS life, risk of complications and the need for regular follow-up and preventive health care. TS is a condition associated with high risk of short stature, cardiovascular diseases, ovarian failure, osteoporosis, hearing loss, diabetes mellitus and hypothyroidism and as such requires the attention of a multidisciplinary team (Table 1). Accordingly, upon transfer to an adult care clinic, the young woman with TS should undergo a comprehensive medical evaluation including screening for hypertension, diabetes, dyslipidemia and osteoporosis. Most importantly, all medical problems present during childhood should be followed in adult life, with special attention being paid to congenital cardiovascular disorders, such as thyroid and celiac diseases and hearing loss.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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**Author contribution statement**

A Gawlik designed the purpose of the review, did the literature search and selection, and wrote the manuscript. E Malecka-Tendera collaborated equally in the literature search and selection, and in paper revision.

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