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REVIEW

Care of the adult woman with Turner syndrome

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ABSTRACT

Turner syndrome (TS) is the most common chromosomal abnormality in females, affecting up to 1/2000 live female births. TS is associated with partial or complete loss of the second X-chromosome in phenotypic females and is associated with increased morbidity and mortality. There are many challenges in providing optimal care for the adult TS women. This review highlights uncertainties that remain in hormone replacement therapy, bone health and cardiovascular optimization and discusses current management recommendations based on the recently published international guidelines and the experience at the TS clinic at Monash Health.

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Turner syndrome; premature ovarian insufficiency; hormone replacement therapy; screening; co-morbidity

Introduction

Turner syndrome (TS) is the most common chromosomal abnormality in females, affecting up to 1/2000 live female births[1]. TS is associated with partial or complete loss of the second X-chromosome in phenotypic females, with loss of the paternally derived X chromosome in 75–80% of cases[2]. The 45X karyotype is the commonest, observed in 40–50% of patients[1,3–5]. Hallmark features of women with TS include short stature and gonadal dysgenesis. However, the phenotype of women can vary immensely (Figure 1). Co-morbidities are related to the underlying genetic abnormality and the potential impact of estrogen deficiency secondary to hypogonadism. Women with a 45X karyotype are likely to develop a more severe phenotype compared with women with mosaicism, with greater morbidity and mortality[1,4,5]. Furthermore, isochromosome Xq karyotype is associated with diabetes mellitus in some, but not all cohorts[4], and a ring X chromosome karyotype may be associated with intellectual disability[6] and metabolic syndrome[4].

The diagnosis of TS is usually made prenatally or in childhood/adolescence, with younger age at diagnosis associated with the 45X karyotype[1]. However, 38% of women were diagnosed in adulthood in one series[1], with premature ovarian insufficiency (POI) or infertility as the initial presenting complaint. In addition, there appears to be a disparity between the expected prevalence (1/2000) versus the observed prevalence, suggesting under/missed diagnosis[1]. TS is associated with increased morbidity and mortality which vary across the life course (Figure 2)[1,5]. The estimated standard mortality rate (SMR) of women with TS is calculated as 2.86 and 3.0 in Danish and UK populations, respectively, with the highest SMR reported in women with a 45X karyotype[1,5].

TS is associated with long-term consequences and co-morbidities that require regular surveillance in adulthood. There are many challenges in providing optimal care for adult TS women including: (1) missed or delayed diagnosis; (2) transitioning from pediatric to adult health-care services; (3) lack of high-quality evidence for optimal management of medical issues faced by TS women including optimal hormone replacement therapy (HRT); and (4) lack of multidisciplinary specialist clinics to provide care[7]. Recently published international management guidelines provide welcome advice to clinicians and highlight persisting uncertainties[8]. Table 1 provides a comprehensive multisystem guideline on screening in adulthood, and below we provide a discussion on the important aspects of care that have been identified from our experiences at our institution.

Diagnosis

TS diagnosis should be considered in any female regardless of age, with characteristic phenotype, growth or pubertal delay, primary/secondary amenorrhea and infertility[8]. TS guidelines[8] recommend a 30-cell karyotype be performed if there is clinical suspicion for TS as it will detect 10% mosaicism with 95% confidence. This may, however, miss the diagnosis in a small percentage of women with a low level of mosaicism[9]. Women aged 50 years and over with a low level of mosaicism for monosomy X (<5%) should not be labeled as having TS[10]. Gonadectomy is recommended if Y chromosome material is detected due to the risk of gonadoblastoma[8]. Delay in

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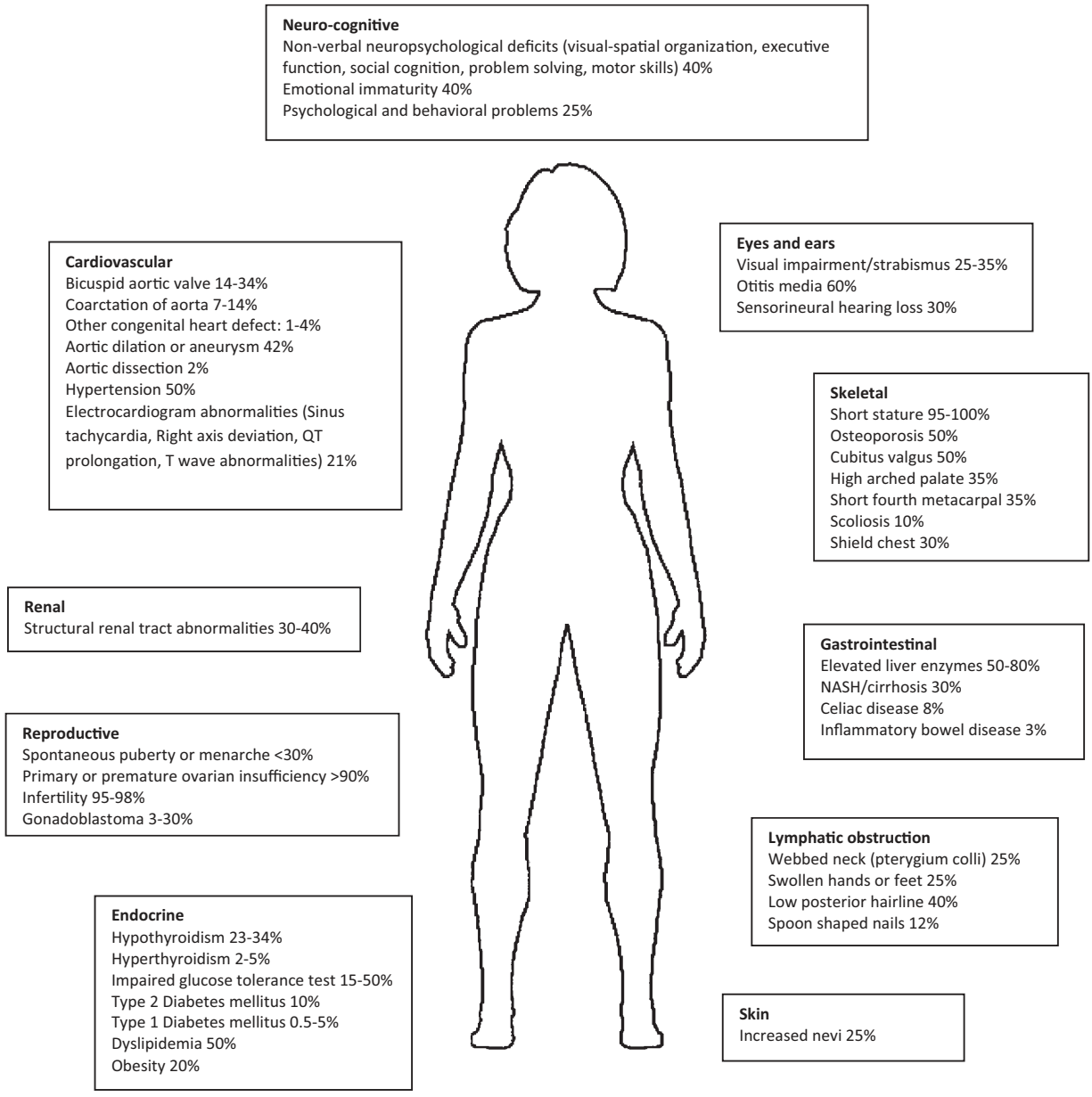

Figure 1. Clinical features associated with Turner syndrome and their approximate prevalence (shown as percent frequency). Data derived from reference 8.

diagnosis may prevent timely institution of growth hormone or HRT and identification of co-morbidities negatively impacting on psychosocial and physical health[11].

Gonadal dysgenesis

TS is associated with accelerated loss of oocytes resulting in primary amenorrhea or POI[12]. In an Italian cohort, spontaneous puberty was only observed in 32% and menarche in 16% of girls with TS, predominantly in those with a mosaic karyotype[13]. The presence of ovarian follicles on biopsy in 47 TS girls was associated with mosaic karyotype, spontaneous puberty or menarche and normal serum follicle stimulating hormone (FSH)/anti-Müllerian hormone (AMH)[14]. The AMH level may predict ovarian function; a longitudinal study of 101 Danish TS patients indicated that AMH <4 pmol/l in pre-pubertal girls predicted failure to enter puberty or AMH <5 pmol/l in adolescents ($<$ 2 standard deviations) predicted imminent POI[15]. AMH ≤ 3 pmol/l was a sensitive marker of POI in TS adolescents/adults (95% sensitivity and specificity)[15]. HRT containing estrogen (and progestogen for endometrial protection) is necessary for almost all TS patients for either (1) pubertal induction (breast/uterine development and to attain peak bone mass); or (2) management of POI (Table 1). Methodological problems of reported studies, including heterogeneous populations, small sample sizes, variable HRT regimens, use of surrogate markers for endpoints and increased risk of bias, limit conclusions. Thus, the optimal age of initiation, dose, route, type and duration of HRT remain unclear and more research is needed. A recent meta-analysis, which included 12 randomized, controlled trials (RCTs) and 13 cohort studies involving 771 girls, adolescents or young adults with TS, reported greater increases in lumbar bone mineral density

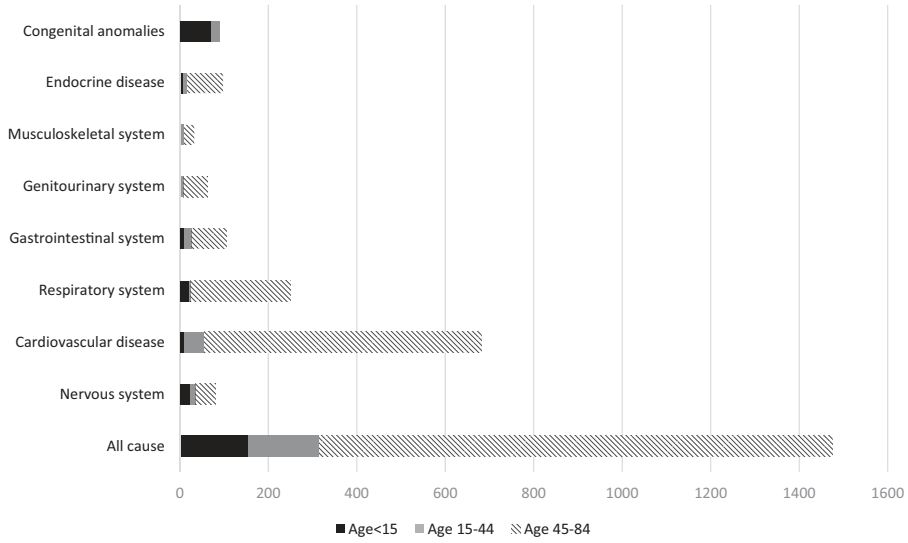

Figure 2. Causes of mortality in a cohort of women with TS according to age. Results are expressed as absolute excess risk (calculated by subtracting the expected from the observed numbers of deaths, dividing by person-years at risk, and multiplying by 100 000) derived from reference 5. Absolute excess risk of mortality due to selected causes varies at different ages. Cardiovascular and respiratory diseases are associated with the highest risk in women aged >44 years.

(BMD) with estradiol compared with oral estrogens (ethinylestradiol and conjugated equine estrogens) and increases in high density lipoproteins (HDL) with oral estrogens compared with transdermal estradiol[16]. There are no studies comparing different progestogens in women with TS, although studies in postmenopausal women indicate potential advantages with micronized progesterone[17].

Pubertal induction

The recommended starting age for HRT is 11–12 years old, commencing with low-dose estrogen therapy and up titrated gradually every 6 months to mimic normal physiological levels, with the aim of completing feminization over a 2–3-year period[8]. When short stature is a concern, consideration may be given to commencing growth hormone treatment prior to or with concurrent low-dose estrogen therapy[18]. Delayed initiation of estrogen therapy may negatively impact bone health, breast and uterus development and psychosocial well-being. A progestogen should be added after the first vaginal bleed or after 2 years of estrogen therapy to minimize the risk of endometrial hyperplasia due to unopposed estrogen therapy[8]. Titration of HRT is important and the ethinylestradiol combined oral contraceptive pill (OCP) or early introduction of progestogen should be avoided as abnormal breast development may occur[19].

As per the recent 2017 international guidelines, transdermal estradiol is the preferred estrogen for pubertal induction[8]. Benefits of this include better bioavailability, improved end-organ effects and lack of a hepatic first-pass effect compared to oral estrogen therapy. In a study of 704 girls with TS on growth hormone therapy, girls using transdermal estradiol achieved 2 cm greater height than those on oral estradiol[20]. Limited data suggest that estradiol is superior to the ethinylestradiol combined OCP or conjugated estrogens for uterine development[21,22]. Two studies looking at BMD suggest greater acquisition of bone at the lumbar spine with transdermal versus oral estrogens[22,23].

Maintenance hormone therapy in adulthood

Previous studies in women with TS suggest that HRT is associated with improvement in aspects of cognitive function (processing speed, motor functions and memory)[24,25], improvement or maintenance of BMD[16,26], positive effects on liver function[27,28], lower blood pressure[29], reduction in visceral adipose tissue, increment in muscle mass[29], reduction in hyperinsulinemia and improvement in vascular function[30]. The recent clinical practice guidelines[8] evaluated data from five RCTs[22,23,31–33] and concluded that use of transdermal estradiol was associated with a decrease in HDL cholesterol but had no effect on low density lipoprotein, triglycerides or total cholesterol. There were no reported differences in insulin or glucose levels[23,32,33], body mass index or waist-to-hip ratio[34,35]. Higher blood pressures were associated with the ethinylestradiol combined OCP compared with transdermal estradiol in a mixed population of women with POI[36]. No difference in BMD[37] was observed in a 5-year RCT ($n = 20$) of low-dose (2 mg) versus high-dose (4 mg) oral estradiol. Nevertheless, HRT is not contraceptive and the oral contraceptive pill may be necessary for menstruating adolescents/women with TS who require contraception. There are no data regarding the newer estradiol-containing OCPs in women with TS.

Despite methodological limitations and the use of surrogate markers for cardiovascular and fracture endpoints, TS guidelines[8] recommend ongoing HRT (preferably transdermal estradiol with a progestogen) through adulthood until the expected age of menopause (approximately 51 years of age). As with HRT use in natural menopause[38], the type, dose and duration of HRT need to be individualized to each woman and risk/benefits need to be re-evaluated as circumstances change. Evidence suggests that TS women have a reduced

Table 1. Summary of recommendations for surveillance and management of adult women with Turner syndrome. Data are derived from references 7 and 8.

		Screening frequency				
Co-morbidity	*Assessment*	*Diagnosis/initial visit*	*Annual*	*2–5-yearly*	*Pre-pregnancy*	*Management*
Cardiovascular disease	ECG	✓			✓	• Consider 24-h HM if ECG abnormal
	TTE/CMR	✓	Yearly TTE if: • ASI >2 cm/m^2 • aortic root >3 cm • existing CHD	✓	✓ (CMR)	• Treat CVD risk factors • Adjust exercise regimen if aortic dilatation • Cardiologist review
Hypertension	Blood pressure	✓	✓		✓	• Strict BP control • Aim systolic BP <120mm Hg if BAV • Beta-blockers or ARB preferred
Metabolic	Weight/BMI	✓	✓		✓	• Maintain healthy weight range (BMI <25 kg/m^2) and encourage healthy diet and exercise
	Fasting lipids	✓	✓		✓	
	FBG or HBA1C	✓	✓		✓	• oGTT as required • Treat dyslipidemia and diabetes mellitus
Renal	U&E, eGFR	✓	✓		✓	• Treat urinary tract infections, hypertension and diabetes mellitus
	Urinalysis	✓	✓ if structural abnormalities		✓	
	Renal ultrasound	✓			✓	
Thyroid	TFTs	✓	✓		✓	• Treat thyroid disorders
	Thyroid antibodies	✓			✓	
Hearing	Audiogram	✓	✓ if abnormal	✓ if normal		• Refer to ENT specialist as required
Vision	Optometrist	✓		✓		• Refer to ophthalmologist as required
Osteoporosis	C/P/M	✓	✓		✓	• Optimize calcium intake, vitamin D and weight-bearing exercise
	25-OH vitamin D	✓	✓		✓	• Estrogen replacement until ~51 years
	DXA scan	✓		✓		
Gastrointestinal	LFTs	✓	✓	✓	✓	• Liver US and refer to liver specialist if persistent/ progressive increase in liver enzymes • Consider changing to transdermal estradiol
	Celiac antibodies	✓		✓	✓	
Gynecological	Breast exam	✓	✓		✓	• Pubertal induction if required
	Pelvic/vaginal US	✓	✓As required		✓	• Estrogen replacement until ~51 years
	Pap smear if sexually active	✓		✓	✓	• Potential advantages with estradiol and transdermal preparations. Add progestogen if uterus present • Assess for sexual function problems • Discuss contraception needs/fertility options • Mammogram and Pap smear according to national screening guidelines
	Mammogram if ≥50 years	✓		✓		
Psychological	Clinical assessment	✓	✓			• Assessment of overall function • Referral to psychologist/ psychiatrist • Support group referral • Academic support referral • Vocational guidance referral
Other	Skin assessment for nevi/lymphoedema	✓	✓			• Referral to dermatologist/ lymphoedema clinic as required
	Dental	✓	✓			• Annual dental review

ECG, electrocardiogram; TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance imaging; ASI, aortic size index; CHD, congenital heart disease; HM, holter monitor; CVD, cardiovascular disease; BP, blood pressure; BMI, body mass index; BAV, bicuspid aortic valve; ARB, angiotensin receptor blocker; FBG, fasting blood glucose; HBA1C, glycosylated hemoglobin; oGTT, oral glucose tolerance test; UEC, serum urea and electrolytes; eGFR, estimated glomerular filtration rate; TFTs, thyroid function tests; ENT, ear/nose/throat specialist; C/P/M, serum calcium/phosphate/magnesium; 25-OH vitamin D, 25-hydroxy-vitamin D; DXA, dual-energy X-ray absorptiometry; LFTs, liver function tests; US, ultrasonography.

risk of breast cancer[39] and long-term HRT does not appear to increase breast cancer risk[40].

Androgen levels are decreased in women with TS[41], with potential negative impacts on sexual function[42], neuro-cognition, quality of life, BMD and body composition. Although benefits have been observed in women with natural menopause[38], there is a paucity of data regarding testosterone therapy in women with TS. A RCT in 14 TS women showed improvements in lipid profile, BMD, body composition, aspects of neurocognition, quality of life and sexual desire with addition of methyl-testosterone to HRT versus placebo[43].

Pregnancy

Most TS women are infertile and this can negatively impact quality of life[44]. Spontaneous pregnancy occurs in up to 7.6% of TS women; spontaneous menarche and mosaic karyotype are correlated with spontaneous pregnancy[45]. Spontaneous pregnancies are associated with an increased risk of miscarriage and chromosomal or congenital abnormalities[45–48]. Counselling regarding fertility options, such as oocyte preservation, is recommended for girls >12 years due to the risk of POI[8]. Assisted reproductive technology (ART) with donor oocyte/embryo is usually required for women with TS to achieve pregnancy. Alternatively, surrogacy or adoption may be considered.

TS women seeking fertility should be counseled regarding the fertility options and the obstetric and neonatal risks associated with each[8]. Obstetric complications include: increased risk of miscarriage, maternal cardiovascular complications (pre-eclampsia, hypertension, postpartum hemorrhage, aortic dilatation/dissection), gestational diabetes, pre-term and cephalo-pelvic disproportion requiring Cesarean section[47,49]. Significantly, aortic dissection may occur in up to 2% of pregnant women with TS (compared with general maternal mortality of 1/10 000) with an 86% maternal mortality rate[49,50]. Adverse neonatal outcomes include a three-fold increased risk of intrauterine growth retardation and preterm delivery[49]. Contraindications to pregnancy (spontaneous or ART) include previous aortic surgery or dissection, significant cardiac valve abnormality, aortic coarctation, aortic dilatation with aortic size index >2.5 cm/m^2, uncontrolled hypertension and portal hypertension[8,50]. Although cardiac imaging (magnetic resonance or echocardiogram) and a cardiologist assessment prior to ART with repeat imaging during pregnancy are recommended[8], <50% of women underwent cardiac imaging before pregnancy in one study[47]. Single embryo transfer is recommended due to the greater risks with multiple pregnancies[50]. Management of pregnant women with TS should be undertaken by a multidisciplinary team including maternal–fetal medicine specialists and cardiologists with expertise in managing women with TS[8,50].

Cardiovascular disease

Monitoring for cardiovascular disease (CVD) in TS is often suboptimal[7,51] which has important implications as CVD is the main cause of mortality in TS women (Figure 2), especially in pregnancy. CVD affecting women with TS includes both congenital and acquired diseases[52]. Multiple factors contribute to CVD in TS including (1) abnormal autonomic neural, arterial and lymphatic development associated with genetic abnormalities; (2) estrogen deficiency[53]; and (3) co-morbidities such as diabetes mellitus[5,54], dyslipidemia and obesity[52].

Up to 70% of TS females have congenital heart disease (CHD) (Figure 1) and the presence of bicuspid aortic valve (BAV) should prompt karyotype assessment for TS[8]. The most common abnormality is BAV, occurring in 15–34% of TS patients (compared with 1–2% in the general population)[52]. BAV is a risk factor for valvular dysfunction, aortic dilation, aortic dissection and infective endocarditis. Coarctation of the aorta, the second most common form of CHD, occurs in up to 17% of patients (compared with 0.04% in the general population) and may coexist with BAV and abnormal aortic phenotype. Other identified abnormalities include: partial anomalous pulmonary venous drainage, transverse aortic arch, atrial septal defects, ventricular septal defects, persistent arterial duct, interrupted inferior vena cava with azygous continuation, and pulmonary valve stenosis[52].

Acquired cardiac diseases, including aortic dissection, myocardial infarction and stroke, are more common in TS women compared to the general population and contribute significantly to morbidity and mortality (Figure 2). Aortic dissection occurs in up to 1–2% of women with TS[55], the peak incidence occurring in the third to fifth decades of life[55]. Risk factors for developing aortic dissection include 45X karyotype, aortic dilation, BAV, coarctation of the aorta, hypertension and pregnancy[52,56]. However, aortic dissection can occur in the absence of CHD or hypertension[57,58]. Thus aortic caliber monitoring is recommended (Table 1)[8]. Cardiac magnetic resonance imaging is the gold standard for measuring aortic size and detecting BAV, as transthoracic echocardiography may underestimate aortic diameter[59]. However, echocardiography is more widely available without the contraindications of cardiac magnetic resonance imaging. As women with TS are of smaller stature, aortic size index (ASI) is proposed as a measure of aortic diameter that adjusts for body surface area[55,58]. Potential pitfalls of the use of ASI occur in women who are obese or underweight. Consideration for aortic surgery is recommended[8] in females >16 years of age with an ASI >2.5 cm/m^2. Although important for cardiovascular health, exercise may need to be modified in the setting of aortic dilation. Guidelines[8] suggest that intense weight training should be avoided if ASI >2.0 cm/m^2 and competitive sports avoided if ASI >2.3 cm/m^2.

Hypertension is common (Figure 1); however, there is limited knowledge regarding treatment targets and which antihypertensives to use. As in the general population, lifestyle measures to treat hypertension are important[60]. The ethinylestradiol combined OCP should be avoided due to the potential adverse effect on blood pressure[36]. Beta blockers and/or angiotensin receptor antagonists are recommended: (1) if ASI ≥2.3 cm/m^2; (2) to maintain blood pressure ≤120/80 mmHg if co-existing BAV; or (3) hypertensive with blood

pressure ≥140/90 mmHg[8]. However, angiotensin receptor antagonists are teratogenic and should not be used during ART or pregnancy[60]. Addressing secondary causes of hypertension (renal abnormalities and coarctation of the aorta) may be necessary.

An increased mortality rate from cerebrovascular disease and coronary artery disease (SMR 3.9 and 2.8, respectively) is observed in TS women[5]. Increased frequency of traditional risk factors such as hypertension, diabetes mellitus, obesity, dyslipidemia and the effect of estrogen deficiency on endothelial function are potential contributory factors[53,61]. However, evidence is lacking regarding the impact of HRT on CVD morbidity and mortality in women with TS. Surrogate CVD markers (lipid profile, body composition, glucose metabolism and blood pressure) show variable benefit with HRT, as discussed previously. A healthy lifestyle and cardiovascular risk minimization are important in TS women (Table 1).

Bone health

Women with TS are at increased risk of fractures, the relative risk of fracture varying from 1.16 to 2.16[54,62]. Fractures appear predominantly to occur in the forearm in childhood[63], and dramatically increase after age 45[64,65]. The mechanism for skeletal fragility in TS is likely multifactorial and has been attributed to inherent skeletal dysplasia or defect related to the underlying chromosomal abnormality; acquired low BMD and osteoporosis; vitamin D deficiency and a higher propensity to fall due to visuospatial cognitive dysfunction, hearing or visual impairment, and impaired balance associated with TS[65–67]. Other co-morbidities that are prevalent in the TS population, such as abnormal liver or thyroid function, celiac disease and inflammatory bowel disease, may also contribute to skeletal fragility.

Low BMD, measured by dual energy X-ray absorptiometry (DXA), is common in adult women with TS[68,69], with estrogen deficiency a major modifiable risk factor. Estrogen is a key hormonal regulator of bone health, with an important role in bone mass accrual during skeletal growth, skeletal homeostasis in adulthood, and accelerated bone loss during menopause[70]. In TS, high rates of primary amenorrhea due to gonadal failure contribute to suboptimal accrual of peak bone mass; as such, HRT is key to ensuring optimal bone health in TS women with gonadal failure. Indeed, a delay in pubertal induction with HRT in TS girls with primary amenorrhea has been associated with low bone density at the hip and spine[26]; in TS cohorts with adequate HRT, fracture rates were similar to those in control populations[71]. A recent meta-analysis showed that HRT significantly increased lumbar spine BMD, with results suggesting that physiological estradiol was more beneficial than other synthetic metabolites[16]. Currently, the optimal HRT dose for bone health outcomes remains unclear.

Exogenous growth hormone therapy (GHT), which is now standard treatment in TS for short stature, has been shown to have beneficial effects on skeletal health in some studies[72,73]. Combination therapy with both HRT and GHT may lead to higher spinal BMD than HRT alone[73]. In contrast, other studies did not find a relationship[74–76], and an effect on fracture outcomes has not been shown.

The assessment of osteoporosis and fracture risk in TS women is challenging. DXA-derived BMD is a two-dimensional measurement which can underestimate BMD in individuals with short stature (height <150 cm) and smaller bone size[77]. Studies that have adjusted for height or bone size in TS cohorts have demonstrated a reduction in BMD in some TS cohorts[26,74,75,78], but not others[63,72,79]. Other non-invasive measurements of bone are peripheral quantitative computed tomography (pQCT), and high-resolution pQCT scans, and the few TS studies using these modalities have shown cortical deficits in the forearm[78,80–82], and compromised trabecular micro-architecture at the radius and tibia[83].

Preventative measures to optimize bone health include healthy lifestyle measures, weight-bearing exercises, adequate dietary intake of calcium and vitamin D, regular monitoring for vitamin D deficiency, and continuing HRT to the natural age of menopause[8]. Current guidelines recommend screening for low bone density with DXA once adult doses of HRT have been instituted, and to monitor with a DXA scan at least every 5 years[8]. When considering discontinuation of HRT, such as at the natural age of menopause, a DXA scan is recommended to aid the decision-making. At our institution, once low bone density has been identified, a repeat DXA scan in 2 years is done to monitor for declines in bone density (Table 1).

Psychosocial issues

TS is associated with impairment in specific cognitive, social and behavioral domains (Figure 1) which, together with medical co-morbidities, can be associated with psychological distress and a negative impact on educational attainment, work, relationships and quality of life. Important considerations to optimize psychosocial well-being are: (1) timely introduction and maintenance of HRT for feminization and sexual function[84]; (2) surveillance and management of co-morbidities (Table 1) especially hearing impairment; and (3) psychological assessment and support[8].

Conclusion

TS is a complex syndrome with multi-organ involvement. Women with TS are best managed in a dedicated multi-disciplinary clinic. Uncertainty persists regarding the optimal HRT, CVD monitoring and intervention and other aspects of TS management. However, widespread dissemination and use of internationally developed guidelines, together with ongoing research to fill knowledge gaps, will assist to improve health outcomes in women with TS.

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