

Clinical Care of Adult Turner Syndrome – New Aspects

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Abstract

Turner syndrome (TS) is characterized by numerous medical challenges during adolescence and adulthood. Puberty has to be induced in most cases, and female sex hormone replacement therapy (HRT) should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular diseases, as well as the risk of type 2 diabetes, hypertension, osteoporosis, thyroid disease and other diseases. The proper dose of HRT with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. The transition period from paediatric to adult care seems to be especially vulnerable and the proper framework for transition has not yet been established. Likewise, no framework is in place for continuous follow-up during adult years in many countries. Today, most treatment recommendations are based on expert opinion and are unfortunately not evidence based, although more areas, such as growth hormone and oxandrolone treatment for increasing height, are becoming well founded. Osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrine diseases and conditions are seen more frequently in TS. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease. The description of adult life with TS has been broadened and medical, social and psychological aspects are being added at a compelling

pace. Proper care during adulthood should be studied and a framework for care should be in place, since most morbidity potentially is amenable to intervention. In summary, TS is a condition associated with a number of diseases and conditions which need the attention of a multi-disciplinary team during adulthood.

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Introduction

Knowledge of Turner syndrome (TS) is expanding rapidly and especially adult aspects of the syndrome are increasingly recognized. The syndrome only affects females and clinical care must include the close collaboration of several specialties including genetics, embryology, pediatrics, gynecology and obstetrics, endocrinology, cardiology, gastroenterology, otorhinology and ophthalmology.

This review focuses on the diverse and complex clinical aspects encountered throughout adulthood in TS, including epidemiology, endocrinology, cardiology, gastroenterology, and gynecology.

Epidemiology

Figures for the prevalence of TS are based on a number of cytogenetic studies with estimates ranging from 25-210 per 100,000 females (1), giving an estimated prevalence of 50 per 100,000 females in Caucasian populations. Diagnosis is

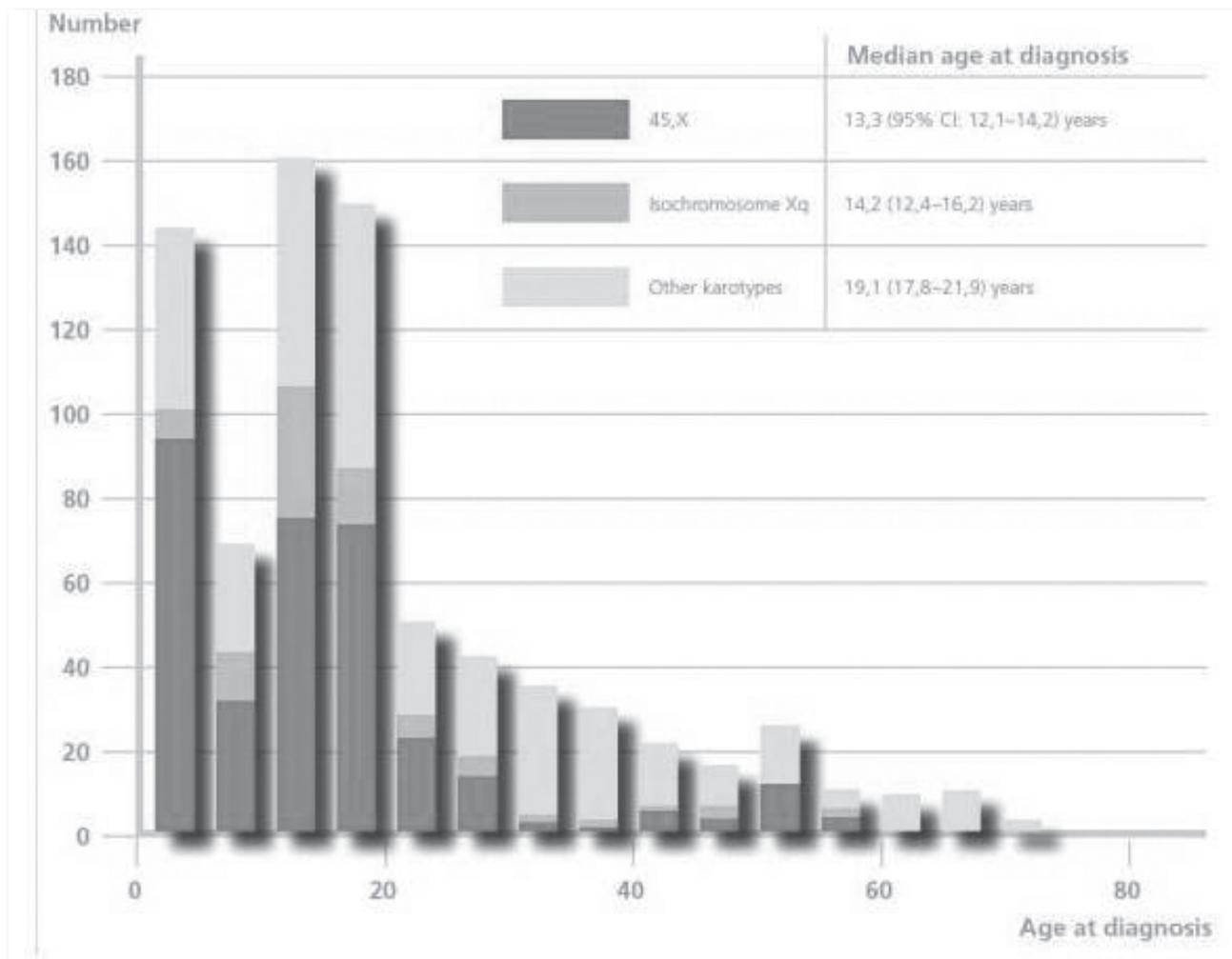


Figure 1: The number of people with Turner syndrome and their age at the time of diagnosis divided into three subgroups with differing karyotypes. CI: Confidence interval.

often delayed with potential prognostic ramifications for patients (Figure 1), and there is a need for new diagnostic strategies in order to promote early and timely diagnosis (2). Morbidity is increased in TS. In a national cohort study that included all females diagnosed with TS in Denmark, we compared incidence rates of diseases suspected to occur at increased frequency in TS to incidences in a control group comprised of randomly recruited women from the general population.

The relative risk (RR) of an endocrine diagnosis in TS patients was seen to be increased to 4.9 overall, with hypothyroidism (RR 5.8), type 1 diabetes (RR 11.6) and type 2 diabetes (T2DM) (RR 4.4) all being frequent encounters. The risk of ischemic heart disease and arteriosclerosis (RR 2.1), hypertension (RR 2.9) and vascular diseases of the brain (RR 2.7) was also increased (3). Furthermore, the risk of cirrhosis of the liver (RR 5.7), osteoporosis (RR 10.1) and fractures (RR 2.16) was increased, which also applied to the incidences of congenital malformations

of the heart (RR 13.4), the urinary system (RR (8.8) and the face, ears and neck (RR 3.3). The risk for all cancers was comparable to other women (3) as was also seen in a large British study (standardized incidence rate - SIR 0.9) (4). In this latter study, the risk of meningioma (SIR 12.0) and childhood brain tumour (SIR 10.3) was however increased whereas the risk of breast cancer was significantly decreased (SIR 0.3). In addition to this, the British study showed a cumulative risk of gonadoblastoma in Y chromosome-positive TS of only about 8% in the first 25 years of life, which is considerably lower than what small clinical studies suggest (5, 6, 7, 8). Not only morbidity but also mortality is increased in TS. In a British cohort study the RR of premature death was increased to 4.2 (9) due to diseases of the nervous, digestive, cardiovascular, respiratory and genitourinary systems. Death due to cancer was lower than expected, corroborating morbidity studies in TS. We found a comparable increase in mortality in the national Danish cohort, where karyotype predicted the mortality rates with patients

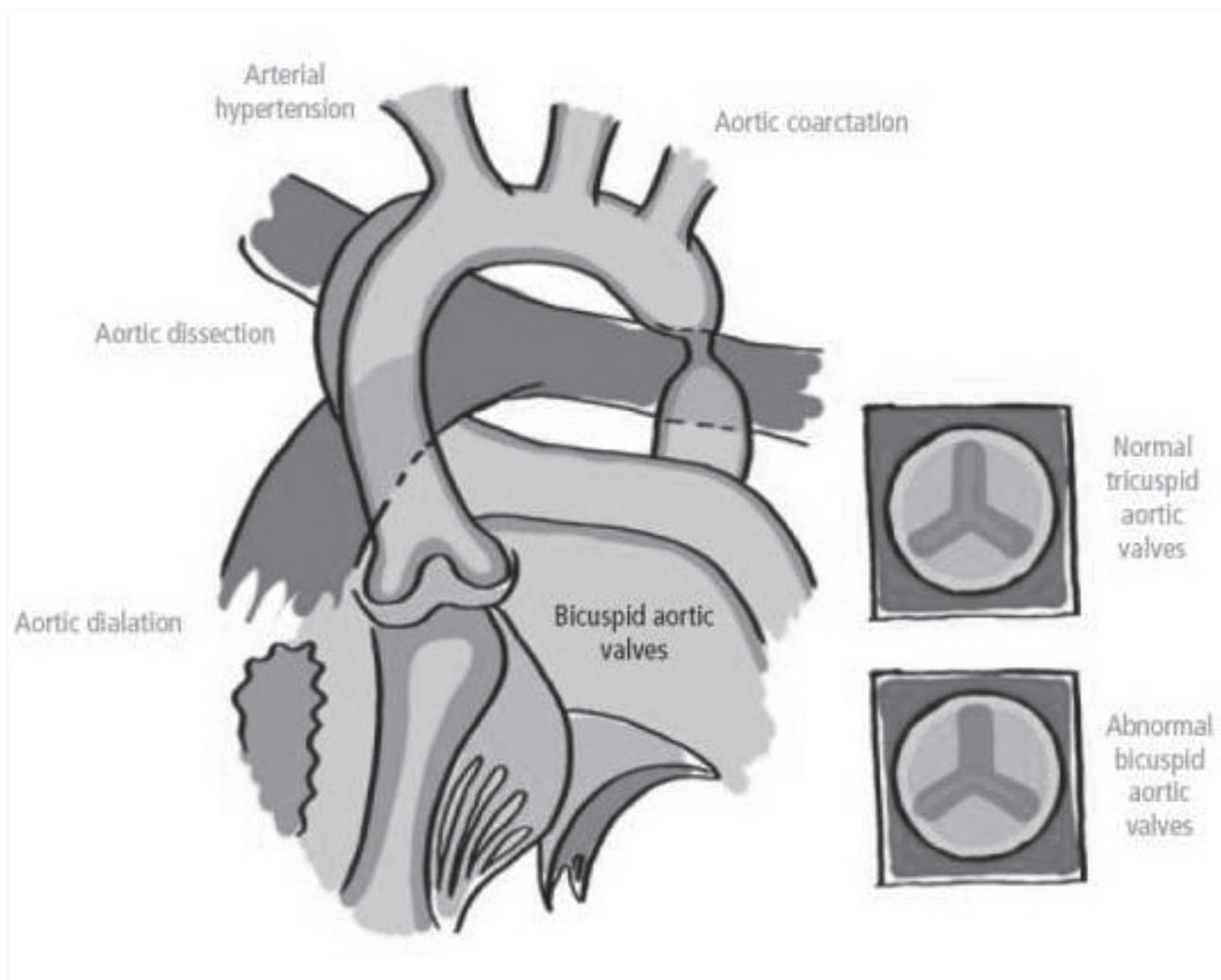


Figure 2: The figure illustrates the occurrence of bicuspid aortic valves, aortic coarctation and the place in the ascending aorta where dissection often occurs. Furthermore, the figure illustrates the frequent occurrence of hypertension.

with 45,X or an isochromosome having a approximately fourfold increased mortality whereas other karyotypes (predominantly mosaic karyotypes) had a twofold increased mortality (both compared to the female background population) (10).

Cardiovascular Disorders

Diseases of the heart account for 50% of excess mortality in TS (11). A number of left-sided cardiovascular malformations are frequent encounters in TS, such as elongated transverse aortic arch seen in 50% (12, 13), bicuspid aortic valves in 13-43% versus 1-2% in the general population (14), and 4-14% has aortic coarctation (Figure 2) (3). Less commonly right-sided malformations are seen, which include persistent left vena cava superior and partial anomalous venous return (12). These congenital heart defects often co-segregate and in a proportion of patients they may take the form of severe heart disease such as hypoplastic left heart syndrome.

Some of the cardiac defects call for early and potentially life saving high-risk cardiovascular (CV) intervention, contributing to increased mortality in infancy as well as later on in life that result from complications due to the congenital abnormalities themselves or associated interventions (10). Other defects present less acutely with symptoms associated with later life morbidity and some stay subclinical throughout the entire lifetime of the patient with hitherto unresolved roles to the pattern of morbidity and mortality in TS.

More than 30% of young girls and adolescents and 50% of adults with TS are mildly hypertensive on 24-hour ambulatory measurements. Additionally, 50% have abnormal circadian blood pressure profiles (15, 16, 17). The presence of these risk factors add to the other adverse indices of cardiovascular risk in TS that include increased carotid intima thickness (18), propensity towards glucose intolerance and type 2 diabetes (16, 19), non-alcoholic steatohepatitis (NASH) (20, 21, 22) discordant lipid

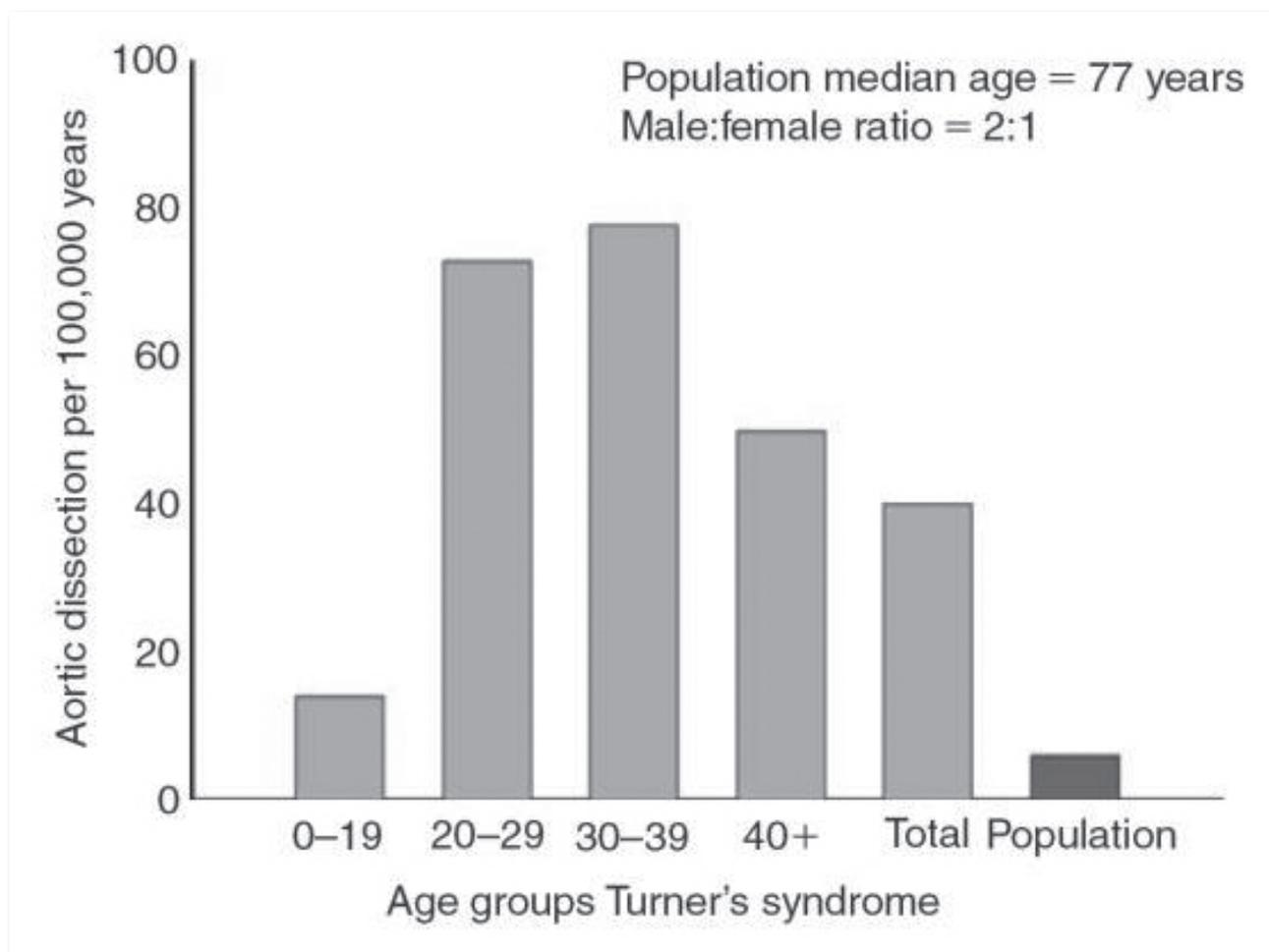


Figure 3: The incidence of aortic dissection per 100,000 years in women with Turner's syndrome and in the general population. Gray bars illustrate females with Turner's syndrome in different age groups, and the dark gray bar indicates the total incidence rate for the entire background population (28).

profile (23, 24), altered coagulant and fibrinolytic balance (25), oestrogen deficiency and unfavourable body composition (26).

In addition to congenital structural cardiac malformations such as bicuspid aortic valve and coarctation of the aorta, hypertension is thought to be a major contributing factor (27) to a strikingly high incidence of aortic dissection of 40 per 100,000 TS syndrome years as compared to 6 per 100,000 general population years. Strikingly, aortic dissection affects patients with TS at a median age of 35 years as opposed to 71 years in the general population (Figure 3) (28).

Aortic dilation normally precedes dissection and rupture, and abnormal aortic calibre is seen in 3-42 % of randomly selected TS women (29, 30), increasing with age (31) and following growth rates of other states of increased risk of aortic dissection (32). Aortic calibre correlates with systolic blood pressure but not with vascular atherosclerotic indices such as aortic stiffness or plasma

lipids in TS (27) and an intrinsic arterial defect is likely to play a part in the generalised vasculopathy in TS (18, 33).

An intrinsic cardiac abnormality is supported by our finding of an abnormal cardiac function in patients with TS and no obvious cause for the dysfunction (34). Further support of intrinsic myocardial abnormalities is indicated by prolongation of the QTc interval as seen in 30% of girls, adolescents and adults with TS (35). Prolonged QTc interval is an independent predictor of arrhythmia related sudden cardiovascular death, and sudden death without any obvious cause is often seen in TS (10).

Premature ovarian failure is the most prevalent cardiovascular risk factor in TS. It is however unclear from what age oestrogen deficiency might impact cardiovascular prognosis in TS - though young age at menopause in other populations confers a more adverse cardiovascular risk profile (36). Evidence confirming earlier observational findings of oestrogen-derived cardioprotection is supported by animal and human studies showing anti-inflammatory, antioxidant and lipid lowering

effects with modification of disruptive vascular processes. On the other hand, opposing such protective effects is the potential for the induction of myocardial hypertrophy, venous thromboembolic events and potential proarrhythmic territories (37). In postmenopausal women interventional studies with oral hormone replacement therapy (HRT) did not reduce total risk of cardiovascular disease in primary and secondary prophylaxis of atherosclerosis. There have been no prospective studies in populations of females with premature ovarian failure. However, evidence for alleviation of cardiovascular risk with early introduction of HRT in states of deficiency of female sex steroids is mounting - the so-called "timing hypothesis" (37).

The congenital and acquired cardiovascular morbidities occur at a backdrop of endocrine problems, creating highly variable cardiac phenotypes, where neither risk prediction nor modification is straightforward. We therefore recommend that all girls and women with TS are to be regarded to be at high risk of cardiovascular events (38), and all should be offered a baseline characterisation of their cardiac phenotype and regular clinical and imaging follow-up by cardiologists trained in congenital heart disease (39). Depending on the presentations, examination should include an electrocardiogram, 24-hour ambulatory blood pressure, echocardiography and cardiac magnetic resonance (39).

Ovarian Failure

Ovarian dysgenesis with resultant estrogen deficiency is a key feature of TS. Early ovarian demise presents in most patients with TS, resulting in premature ovarian failure with estrogen insufficiency or outright deficiency. Ovarian germ-cell count is normal until week 18 of gestation where after accelerated primordial follicle degeneration takes place. Inappropriately high levels of follicle-stimulating hormone and luteinizing hormone are present in early childhood (2-5 years), after normal puberty onset (11 years) and in adulthood levels increase to menopausal levels. Many girls may show signs of puberty and/or have regular menstrual periods for varying lengths of time even without estrogen substitution (40). This may be explained by new data showing that even in patients with 45,X follicles can still be found at age 12-19 years (41). Anti Mullerian hormone and inhibin B are emerging as possible markers of ovarian function (42, 43). Improved understanding of the processes in early follicular apoptosis in TS may in the future lead to a treatment sparing the follicles and maintaining fertility.

Our understanding of the physiological effects of 17 β -estradiol is incomplete and insight into states of deficiency of endogenous 17 β -estradiol is even more sketchy (44). There are no long-term studies in females lacking 17 β -estradiol. A few studies have addressed this issue by looking at different endpoints and with quite varying results concerning the multitude of effects 17 β -estradiol has in the female (45, 21, 46, 20, 47, 48, 24, 49, 50, 51, 52). The concept of route of administration has also been studied without reaching a firm conclusion on whether the oral

or transdermal route is more advantageous (53, 47, 49). As for the type of estrogen, it is currently recommended that human 17 β -estradiol is used, abandoning the use of conjugated estrogens or synthetic ethinylestradiol (54). However, this recommendation is not backed by much hard evidence but primarily rests on physiological reasoning. Currently it is recommended to institute endocrine therapy to allow onset of puberty at the same time as in healthy girls in order to avoid social problems secondary to delayed physical and psychological development. This facilitates optimal bone mineralization (55). In most normal girls puberty starts around 12 years of age. Since 30% of girls with TS undergo some spontaneous pubertal development and 2-5% have spontaneous menstruation with a small potential to achieve pregnancy without medical intervention (40), signs of puberty should be looked for before starting estrogen therapy. When FSH and LH are clearly elevated and AMH and inhibin B are low, and with clinical signs of puberty lacking, pubertal induction should be started although always considering individual circumstances. To induce pubertal development, the dosing and timing of estrogen therapy should aim at mimicking normal pubertal development. Doses should be individualized starting with very low doses of estrogen as monotherapy - oral or transdermal (53, 56). Treatment can be monitored using development of secondary sex characteristics (Tanner staging), serum ~~luteinising and follicle stimulating hormones~~, bone maturation or uterine volume as surrogate markers. A gestagen is added when breakthrough bleeding occurs. It is not clear which gestagen is better.

Estrogen therapy should be coordinated with the use of growth hormone (GH). This should be individualized, optimizing bone growth and pubertal development. When growth is a priority, delayed estrogen therapy may avoid compromising adult height. However, recent growth-promoting trials indicate that physiological timing of estrogen therapy does not compromise adult height, when GH therapy is started early and dose is increased stepwise (57). Females with Turner syndrome present with a particular neurocognitive profile of impaired performance on motor tasks and impaired visual-spatial ability but normal verbal skills (58). Proper estrogen replacement is thought important for neurocognitive function in TS since it has a positive effect on motor speed and verbal and non-verbal memory and processing when administered in puberty (59, 60).

Infertility is rated the most prominent problem in adult women with TS (61). Oocyte donation is an option in many countries and fertility preservation is an emerging option. Recent studies on oocyte donation are promising with outcomes comparable to oocyte donation in other infertile patients, although better preparation of the uterus for implantation (uterine size and endometrial thickness) with prolonged treatment with high daily doses of estradiol (4-6 mg or up to 8 mg of 17 β -estradiol) may improve pregnancy rates in TS. With regards to maternal outcome, undertaking pregnancy is a high-risk endeavor for the patient with TS. The adverse risks appear to relate especially to the cardiovascular system but endocrine disorders are also

important. A recent retrospective study showed that without proper metabolic and cardiovascular work-up before oocyte donation fetal and maternal outcome is poor (62), but with adherence to current recommendations (63), the outcome may be improved (64).

Androgen insufficiency is a further feature of both adolescent and adult patients with TS (65, 48) Androgen substitution could [take](#) a place in future clinical practice in TS seeing that a recent small scale study of methyl testosterone delivery to adolescents and young adults with TS showed increased lean body mass without visceral fat changes and improved quality of life though effects on neurological parameters were absent (51).

During adulthood it is important to continuously deliver exogenous estrogen though important clinical questions such as optimal dose at the different ages, administration route, type of estrogen and type of gestagen remain to be answered. Female hypogonadism is related to a number of other conditions, and HRT may reduce or completely alleviate the risk of these. Recent studies indicate that the conventionally used dose of 2 mg of 17 β -estradiol in TS and other conditions involving premature ovarian failure may be too low for normalization of the cardiovascular system and uterine growth to occur (66, 52). Available data on different routes of administration in TS has not demonstrated the advantages of any particular route (20, 16, 67); newer studies point towards transdermal or subcutaneous application being superior to oral delivery (50, 68, 69), but additional studies are needed to clarify the effect of delivery routes. In a comparison of the contraceptive pill with physiological 17 β -estradiol and a gestagen it was indicated that contraceptive pills should not be used as substitution therapy in long-term oestrogen treatment of TS (70, 71).

Gastrointestinal Disorders

Increased concentrations of functional liver markers, especially alkaline phosphatase, alanine/aspartase aminotransferase and γ -glutamyl transferase (markers of hepatic cell lesion or turnover) are frequent in TS (72). Bilirubin (excretion) and coagulation parameters (production) tend to be normal (25). In a liver biopsy study of 27 patients with TS and persistently elevated liver tests (73) multiple abnormalities were present and included marked nodular regenerative hyperplasia, multiple focal nodular hyperplasia and cirrhosis which in some patients was related with obliterative portal venopathy. Moderate changes like portal fibrosis, inflammatory infiltrative change and non-alcoholic fatty liver disease was also seen. The authors concluded that the main causes of liver abnormalities in TS were both vascular disorders (hypothesized to be congenital in origin) and non-alcoholic fatty liver disease. Importantly, there were no signs of liver toxicity from concomitant estrogen therapy, which is in keeping with no adverse effects or even normalization of markers of liver function during estrogen replacement in TS (22, 50). Furthermore, prolonged estrogen deficiency seems to be correlated to a higher amount of intrahepatic fat accumulation (74).

Celiac disease is present in 8% of patients with TS with increasing prevalence with age (75, 76) and seeing that this disorder may cause additional growth stunting it should always be excluded in the presence of relevant symptoms as well as regularly assessed through antibody testing. Inflammatory bowel disease also seems to be more frequent in TS (2-3%) and the clinical suspicion should be suspected in girls that do not respond adequately to growth hormone therapy.

Diabetes

The risk of both type 1 and type 2 diabetes mellitus is increased (3). In the general cohort of patients with TS, fasting glucose levels tend not to be different from healthy peers but fasting hyperinsulinaemia is present and impaired glucose tolerance has been found in 25-78% of adult patients with TS (16, 19). In addition to higher glucose levels during oral glucose loading, the insulin response is altered and a delayed insulin peak is seen. The impaired glucose homeostasis seems to be partly explained by an attenuated 'first phase insulin response' which could be viewed as an inappropriately low β -cell response (16, 19). Body composition is altered in TS with increased BMI, decreased muscle mass and increased total fat mass and visceral fat mass (26, 77). A relatively sedentary lifestyle and decreased physical fitness has also been demonstrated (78). These factors may be causally linked with reduced insulin sensitivity, although this trait has only been shown in some (79, 80, 81), but not all studies (82, 19), and manifest diabetes (3, 83).

Appropriate estrogen replacement also seems to be important for glucose homeostasis even though the findings in TS diverge. Exogenous estrogen reduced fasting glucose and fasting insulin in TS (45), [and](#) while not improving insulin sensitivity; fat free mass and physical fitness increased, as also seen by others (47) - both latter factors secondarily tend to improve glucose homeostasis. In the latter study a decreased glucose tolerance was seen during HRT (47). On balance, HRT may slightly improve glycemic control though more studies are necessary to elucidate the relation between glucose metabolism and states of deficiency of and replacement with estrogens in TS

Insulin levels increase during GH treatment, decreasing after termination of treatment but remaining higher than pre-treatment levels (84). GH generally reduces insulin sensitivity in the first 6-12 months of treatment, where after it stabilizes. This stabilization could be due to changes in body composition with increasing lean body mass and decreasing fat mass. The proportion of patients with TS patients with overtly impaired glucose tolerance does not seem to increase and HbA1c remains unchanged or even decreases during GH therapy (84). While most of the effects on the glucose metabolism seem to reverse after cessation of GH treatment, the long-term effects of hyperinsulinism and insulin resistance induced during GH delivery are not known.

In the face of widespread abnormalities of glucose homeostasis and increased risk of type 1 and type 2 diabetes mellitus there is

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a need for persistent attention to these factors in clinical follow-up. Recommendations for diagnosis and treatment of diabetes adhere to general population guidelines and annual screening of fasting glucose and HbA1c should be performed.

Bone Disorders

Peak bone mass depends on a number of factors, such as genetic background, nutrition, physical activity, local growth factors and a spectrum of hormones. Estradiol secretion is deficient in childhood and adolescence. Children and younger and middle-aged adult patients with TS have low bone mineral density, and studies show that the risk of fracture (RR 2.2; Osteoporosis RR 10.1) is increased (3, 85, 86) pointing towards the major clinical consequences of the decreased bone mineral density. Estrogen replacement is crucial in order to induce maximal peak bone mass in adolescents and young adults and avoid a rapid decline in density (87). This is supported by longitudinal studies of estrogen deficient and estrogen replete adolescents with TS. Patients with spontaneous menstruation have normal BMD, whereas absent menarche associates with a reduced BMD (88). A 3-year longitudinal study of 21 women with TS (age 20-40) with iliac crest biopsies performed before and after 3 years of estrogen treatment showed marked improvements of estrogen on bone structure. Treatment consisted of estradiol implants (and an oral gestagen cyclically) (68) resulting in estradiol levels comparable to levels in premenopausal women, and considerably higher than levels achieved with regimens used to date (estradiol 2 mg orally or equivalent transdermal doses). The bone biopsies pointed towards an anabolic effect on the skeleton of estradiol in young adult patients with TS (68). Growth hormone treatment may also improve bone mineral density in TS. In a 7-year study with growth hormone treatment given at three different doses, bone mineral density increased in a dose-dependent manner. However, estrogen was added after 4 years of GH treatment and it is therefore difficult to ascertain the individual effects of GH and estrogen (89). No very long term studies (both follow-up and intervention studies) of the effect of estradiol have been published but 5 years of appropriate HRT maintains BMD unchanged (46). There is a definite need for such studies to determine the ideal treatment regimen (possibly consisting of a cocktail of growth hormone, oxandrolone and estradiol) during adolescence in order to achieve two goals: obtaining maximal peak bone mass and maintaining BMD without compromising adult height; and, with appropriate timing of pubertal induction. Furthermore, the optimal dosage of estrogen during adult life has yet to be determined.

Thyroid Disorders

Thyroid dysfunction is common in TS (90). Thyroid antibody formation is a frequent encounter and increases with age (76), and more than 30-50% of patients with TS eventually develop hypothyroidism (90). A recent study showed a considerable

increase in the prevalence of hypothyroidism during a 5-year follow-up period (Figure 4) (90). It remains an enigma why so many patients with TS are affected by disorders related to autoimmunity (91), and the basis for this grossly increased risk in TS of autoimmune disease (including thyroid disease, celiac disease and diabetes (see above)) is unaccounted for. A genetic basis seems likely although undocumented. Growth hormone treatment does not increase the frequency of autoantibodies. Attention to symptoms should be increased and regular screening is recommendable with treatment of hypothyroidism adhering to general population guidelines.

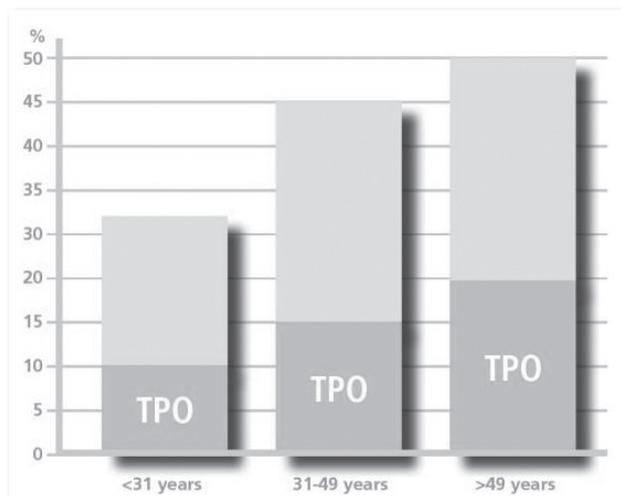


Figure 4: Prevalence of hypothyroidism in women with Turner syndrome <31 years, 31-49 years and >49 years (n=171). The percentage of Turner syndrome women with elevated thyroid peroxidase antibody titer (TPO) is given in each bar (90).

Conclusions

Patients with TS are in need comprehensive monitoring and care preferably delivered by a multidisciplinary team. This has recently been very clearly documented in a study where the authors followed the newest clinical guidelines in their clinical setup (63) and found a substantial and hitherto undiagnosed morbidity in a large cohort (92), and this can be most optimally handled with centralized care. Glucose metabolism, weight, thyroid function, bone metabolism, blood pressure, liver function and cardiovascular status should be regularly assessed (Box 4). Estrogen deficiency should be treated, preferably with natural estrogens and a gestagen, and growth hormone treatment should be commenced early in life.

Unfortunately, an array of important clinical questions is left to be answered with regard to optimal care in patients with TS. There is a substantial deficit in our understanding of the syndrome but a hope to improve patient outcome through not only a specialized multidisciplinary clinical approach but also via a continuous effort to span disciplines in future research.

Disclosure

All authors declare no conflict of interest.

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