Turner syndrome and clinical treatment

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Background: Turner syndrome (TS) is a genetic disorder associated with abnormalities of the X chromosome, occurring in about 50 per 100,000 liveborn girls. TS is usually associated with reduced adult height, gonadal dysgenesis and thus insufficient circulating levels of female sex steroids leading to premature ovarian failure and infertility. The average intellectual performance is within the normal range. New insight into genetics, epidemiology, cardiology, endocrinology and metabolism from a number of recent studies will be included in this review.

Sources of data: For this review we concentrated on all papers published on TS with special emphasis on the most recent literature. Also papers relating to cardiology, especially aortic dissection, paediatrics and the effects of estradiol in other conditions were considered. The main source was PubMed and the major endocrinology and cardiology journals.

Areas of agreement: Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy (HRT) is given during adult years. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular (CV) diseases, as well as the risk of type 2 diabetes, osteoporosis and thyroid disease.

Areas of controversy: 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. In most countries it seems that the transition period from paediatric to adult care is especially vulnerable and the proper framework for transition has not been established. Today, most treatment recommendations are based on expert opinion and are unfortunately not evidence based, although more areas, such as GH treatment for increasing height, are well founded.

Growing points: The description of adult life with TS has been broadened and medical, social and psychological aspects are being added at a compelling pace.

Areas timely for developing research: Proper care during adulthood should be studied, since most morbidity potentially is amenable to proper care. Especially, interventional strategy and follow-up with respect to congenital CV
malformations, as well as secondary CV disease, have to be developed and new treatment algorithms have to be studied.

In summary, TS is a condition associated with a number of diseases and conditions, which need the attention of a multi-disciplinary team.

**Keywords:** Turner syndrome/ adult height/ genes/ growth/ growth hormone/ insulin-like growth factor I/ androgens/ estrogens/ glucose metabolism/ cardiovascular diseases/ ischemic heart disease/ hypertension/ insulin resistance/ morbidity/ mortality/ puberty/ thyroid function/ liver function/ epidemiology

### Introduction

Since the description of Turner syndrome (TS) by Henry H. Turner in 1938, a wealth of information has been added and our current understanding of the syndrome is continuously being broadened. The syndrome affects only females and care must include the close collaboration of several specialties such as genetics, embryology, paediatrics, gynaecology and obstetrics, endocrinology, cardiology, gastroenterology, oto-rhinonology, ophthalmology and others.

In this review, the focus is on the diverse clinical aspects, including epidemiology, endocrinology, cardiology, gastroenterology and gynaecology of the syndrome with reference to recent genetic discoveries.

### Diagnosis, epidemiology and genetics

The genetic background of the TS phenotype is highly variable, but includes complete or partial absence of the sex chromosomes (the X and/or Y chromosomes). In addition, mosaicism with two or more cell lines may be present. The first described cases were with the ‘classical’ karyotype 45,X. In more recent series the classical karyotype only accounts for 50% of cases; the remaining cases comprise mosaic karyotypes (i.e. has cells with 45,X and cells with 46,XX), karyotypes with an isochromosome of X—for example i(Xq) or i(Xp)—or karyotypes with an entire or part of an Y chromosome. The genetic basis for the findings in TS is being further unravelled as the functions of the SHOX gene become clearer. Haploinsufficiency of SHOX explains the reduction in final height, changes in bone morphology, sensorineural deafness and other features, see Box 1. However, additional genes are thought to be involved in the pathogenesis of TS, but await new discoveries.
Box 1 Haploinsufficiency of SHOX probably explains

- A greater proportion of the recorded deficit in height, i.e. short stature
- Short 4th metacarpal
- Cubitus valgus
- Madelung deformity
- Mesomelic growth
- High arched palate
- Micrognathia
- Sensorineural deafness
- Dysproportionality of skeletal size

Haploinsufficiency of SHOX probably not explains

- The entire deficit in final height
- Congenital cardiovascular malformations
- Endocrine disturbances
  - SHOX is expressed in pancreas! Does this explain β-cell dysfunction?
- Estrogen deficiency and infertility
- Increased mortality?
- Other stigmata known to appear in Turner syndrome?

Prenatal prevalence of the syndrome is much higher than the postnatal prevalence, for there is a well-described increased intrauterine mortality. Prenatal diagnosis of TS may not always be correct; therefore a more precise diagnosis rests on inclusion of high-resolution ultrasound scan or foetal echocardiography and other modern investigations. A European multi-centre study found an induced abortion rate of 66%, and thus most diagnosed foetuses with TS are legally aborted. The study confirms previous studies showing legal abortion rates of 60–80%. However, this is only a fraction of foetuses with TS since <10% of any pregnant population is subjected to invasive methods of prenatal diagnosis, and the use of prenatal ultrasound scan will only lead to diagnosis of the cases with the most pronounced phenotype, i.e. hydrops and increased nuchal fold.

Figures for the prevalence of TS are based on a number of cytogenetic studies with estimates ranging from 25 to 210 per 100 000 females, giving an estimated proportion of about 50 per 100 000 females in Caucasian populations.

Most postnatal diagnoses are made at birth (15%), during teenage years (26%), and in adulthood (38%), with the remainder being diagnosed during childhood, and therefore there is a considerable delay in diagnosing girls and adolescents (Fig. 1). Interestingly, the key to
diagnosis was lymphedema in 97% during infancy, and short stature in 82% during childhood and adolescence.

Morbidity is considerably increased in TS. In a study of all females diagnosed with TS compared with the general population of women, we compared the incidence rates of specific diseases we suspected might occur with increased frequency. The relative risk (RR) of an endocrine diagnosis in TS patients is significantly increased to 4.9 overall, with a significantly increased risk of hypothyroidism (RR 5.8), type 1 diabetes (RR 11.6) and type 2 diabetes (T2DM) (RR 4.4). The risk of ischaemic heart disease and arteriosclerosis (RR 2.1), hypertension (RR 2.9) and vascular disease of the brain (RR 2.7) were also significantly increased. The risk of other conditions such as cirrhosis of the liver (RR 5.7), osteoporosis (RR 10.1) and fractures (RR 2.16) was also significantly increased, as were the risks for congenital malformations of the heart, of the urinary system, of the face, ears and neck. The risk for all cancers was comparable to other women, with only the risk of colonic and rectal cancers being significantly elevated (RR 4.94). Congenital malformations are most frequent among women with the 45,X karyotype, whereas endocrine diseases, heart disease, hypertension and arteriosclerosis are more frequent in women with other TS karyotypes.

Mortality is also increased in TS. In a British cohort study the RR of premature death was increased to 4.2, with increases due to diseases in the nervous, digestive, cardiovascular (CV), respiratory and genitourinary systems. Death due to cancer was lower than expected, corroborating the morbidity studies. We found a comparable increase in
mortality among Danish patients (Fig. 2), with important differences between patients with 45,X or an isochromosome, who had a four-fold increase in mortality, while patients with other karyotypes only had a two-fold increase in mortality.\textsuperscript{5}

In summary, TS is a clinical description without firm guidelines for the diagnosis, but the cardinal stigmata include growth retardation with reduced adult height and, except in rare cases, gonadal insufficiency and infertility.

\section*{Ovarian insufficiency and hormone replacement therapy}

TS belongs to a number of conditions, which is collectively termed ‘premature ovarian failure’ (POF) and early ovarian demise presents in most patients with TS with estrogen insufficiency ensuing. The germ-cell count (45,X) is normal until week 18 of gestation, after which accelerated degeneration takes place. High levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are present in early childhood (2–5 years) and after the time of normal onset of puberty (11 years). In adulthood, the levels of FSH and LH increase to menopausal levels. Many untreated girls show signs of puberty and/or have regular periods for a varying length of time.\textsuperscript{6} This may be explained by new data showing that even in some 45,X patients follicles can still be found in 12–19 year olds.\textsuperscript{7} Understanding the processes in early
follicular apoptosis in TS may in the future lead to a treatment sparing
the follicles and maintaining fertility.

Ideally the timing of endocrine therapy should allow onset of puberty
at the same time as the peers of the patient to avoid social problems at
school, because of delayed physical and psychological development.
This would also allow optimal bone mineralization to take place (see
below). In most normal girls puberty starts around 12 years of age.
Since 30% of girls with TS undergo some spontaneous pubertal devel-
opment and 2–5% have spontaneous menses and may achieve preg-
nancy without medical intervention,6 signs of puberty should be
looked for before starting estrogen therapy. When FSH and LH are
clearly elevated, and with clinical signs of puberty lacking, pubertal
induction should be started although always considering individual cir-
cumstances. To induce pubertal development, the dosing and timing of
estrogen therapy should aim at mimicking normal pubertal develop-
ment. Doses should be individualized starting with very low doses of
estrogen as monotherapy, which may be monitored in terms of the
development of secondary sex characteristics (Tanner staging), serum
LH and FSH, bone maturation or uterine volume. A gestagen is added
when breakthrough bleeding occurs. Currently, it is not clear which
gestagen is the most advantageous. Estrogen therapy should be coordi-
nated with the use of growth hormone (GH). This should be individua-
lized for each patient, so as to optimize both growth and pubertal
development. When growth is a priority, delaying estrogen therapy is
an option to avoid compromising adult height; however, recent growth-
promoting trials have documented that the physiological timing of
estrogen therapy does not compromise adult height, when GH therapy
is started early and dose is increased stepwise.8 Proper estrogen replace-
ment during puberty has positive effects on motor speed, and on verbal
and non-verbal memory and processing. Females with TS present with
a particular neurocognitive profile, with impaired performance on
motor tasks, impaired visual–spatial ability, but normal verbal skills.9
The deficits in cognition are likely to be caused by haploinsufficiency
of X-linked genes that normally escape X-inactivation, but these puta-
tive genes await further elucidation.

Infertility is, during adulthood, rated as the most prominent problem
of the syndrome.10 Oocyte donation is an option in many countries.
The most recent studies show good results comparable with oocyte
donation in other groups of 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 17β-estradiol) may improve results. It is a high-risk endea-
avour for a TS woman to go through pregnancy, with a high risk of pro-
blems related to the CV system.
Androgen insufficiency is present,\(^{11}\) and one needs to evaluate the possible benefits of androgen substitution in TS.

During adulthood it is important to continue female sex hormone replacement therapy (HRT), although a number of issues, such as dose during the different ages, route of administration, type of estrogen, type of gestagen, etc., are still unresolved. Female hypogonadism is related to a number of other conditions (Fig. 3), and HRT may reduce or completely alleviate the risk of these. Currently, new studies indicate that the traditional dose of 2 mg of oestradiol used in TS and other conditions of POF may be too low for normalizing the CV system and for normal growth of the uterus.\(^{12,13}\) Available data on different routes of administration in TS has not demonstrated the advantages of any particular route,\(^{14-16}\) and additional studies will be needed to fully resolve this issue.

**Fig. 3** The serious effects of haploinsufficiency of genes on the X chromosome and/or premature ovarian failure (POF) and thus of female hypogonadism is illustrated in this figure. Hypogonadism has pervasive effects, affecting (1) different hormone levels, (2) CV features, (3) metabolic features and (4) features related to sex hormones, such as infertility. In addition, mounting evidence suggests that hypogonadism in TS leads either directly or indirectly to a reduced quality of life. Haploinsufficiency of genes on the X chromosome has been implicated in the presence of an increased risk of congenital malformations, although no specific genes have been identified so far. Arrows indicate possible consequences—not all interactions have been shown in scientific studies. Not illustrated in the present figure are effects on the central nervous system. \(\text{VO}_{2}\text{max}\), the maximum capacity to transport and utilize oxygen during incremental exercise; \(\text{IL-6, IL-8, TNF-}\alpha, \text{C-reactive protein}\); \(\text{PTH}\), parathyroid hormone.
Decreased stature in TS

Short stature is the cardinal finding in girls with TS affecting 95–99% of them. Growth retardation is already present in utero (birth weight about −1 SD), increases during infancy and childhood (height −2 SD) and, due to the lack of a pubertal growth spurt height at age 14, is approximately −4 SD if GH treatment is not initiated. The growth phase is prolonged (if puberty is not induced) achieving a spontaneous final height of −2.6 SD or about 20 cm below normal height.

Part of the explanation of the reduced final height relates to the action of the SHOX gene located to the PAR1 region of the X and Y chromosome, since haploinsufficiency of the SHOX gene, as seen in Leri–Weill dyschondrosteosis, leads to reduced final height. However, the height difference is only about 50–75% of what is seen in TS, leading to the conclusion that SHOX can only explain part of the height deficit in TS. Brain natriuretic peptide (BNP) is a transcriptional target of SHOX and is present alongside at the growth plate in proliferative chondrocytes. Whether the lack of SHOX-induced BNP is involved in CV malformations and diseases in TS remains to be clarified.

GH concentrations in TS are found to be normal in some, reduced in others, and it is generally concluded that girls with TS have a growth deficiency with reduced sensitivity to GH rather than a GH deficiency. GH treatment can increase growth velocity and final height. The effect is dose-dependent and normalization of final height has been shown to be attainable with high doses. In the only randomized, controlled study so far, using GH treatment (0.3 mg/kg/week) or placebo, a significant increase in final height of 7.2 cm (CI: 6.0–8.0) was seen, with estrogen replacement therapy started at age 13.

In cases where the TS diagnosis is made early (before 1–2 years of age), very early treatment with GH should be instituted. In a randomized, controlled, open label study including 9 month–4 year old girls with TS for GH treatment, it was possible to correct growth failure and promote catch up growth, bringing 93% of the toddlers back in the normal height range of the background population within 2 years. The control group had progressive growth failure.

Besides effects on growth and final height, GH treatment also has beneficial effects on body composition with reduced fat mass and an increase in lean body mass. Concerns about the effect of GH on the heart have arisen from evidence that left ventricular hypertrophy is found in acromegalic patients with high levels of GH. A Dutch study showed no signs of left ventricular hypertrophy and no increase in blood pressure in TS girls undergoing 7 years of GH treatment. GH treatment has also been shown to reduce blood pressure, improve cardiac function with increased ejection fraction and reduce intimal
thickness, when treating GH-deficient patients. In aggregate, these effects would seem beneficial to girls with TS.

**TS and the heart**

TS associates with mainly left-sided CV malformations such as elongated transverse arch of the aorta seen in 50% of the women, bicuspid aortic valves in 13–43% versus 1–2% in the general population and coarctation of the aorta (4–14% in TS). Less commonly right-sided malformations such as persistent left vena cava superior and partial anomalous venous return are seen. Rarely atrial and ventricular septal defects, persistent ductus arteriosus, aortic and mitral stenosis and insufficiencies as well as hypoplastic left heart syndrome appear. Interestingly, congenital malformations of the CV system are predominantly associated with the 45,X karyotype rather than with the isochromosomal karyotype. No syndrome-specific pathophysiological mechanism is known, though causative relationships of X-linked gene-defects such as SHOX gene deficiency, lymphogenic locus deletion on Xq or other genetic anomalies are proposed—while others theorize an underlying disruption of the normal embryonic development of the lymphatic system as the reason for the multiple congenital defects.

Some of these congenital abnormalities call for early and potentially life-saving, high-risk CV interventions, thereby partly accounting for the increased mortality from congenital anomalies. Other defects present less acutely, with symptoms correlating to the increased late life morbidity, whereas some remain subclinical throughout the entire lifetime.

More than 30% of young girls and adolescents, and 50% of adults with TS are mildly hypertensive on 24-hour ambulatory measurements, and an additional 50% display abnormal circadian blood pressure profiles in the same age group. Though the pathological nature underlying the hypertensive disorder in TS remains unknown, it is uniformly accepted that hypertension and the sympathovagal dysfunction of nocturnal ‘non-dipping’ confer a high risk of future major CV events, as documented epidemiologically in TS. Diabetes and obesity place TS patients at an additional risk of premature CV disease, whereas findings on the effect of lipid profiles are divergent with some studies indicating an atherogenous state, whereas others show normal lipids. Indications of such an adverse CV prognosis are an increased resting heart rate secondary to probable sympathovagal dysfunction and increased carotid intima-media thickness.

In addition to the congenital structural cardiac malformations such as bicuspid aortic valve and coarctation of the aorta, hypertension is also thought to be a major factor shown by the relatively high incidence of
aortic dissection and rupture of 40 per 100 000 TS syndrome years versus 6 per 100 000 general population years. It also, strikingly, affects TS patients at a median age of 35 years as opposed to 71 years in the general population.\textsuperscript{32} Aortic dilation is normally preceding dissection and rupture is seen in 3–42\% of randomly selected TS women, where aortic diameter correlates significantly to systolic blood pressure, but surprisingly, is not associated with vascular atherosclerotic indices such as aortic stiffness or plasma lipids.\textsuperscript{31} An intrinsic arterial defect therefore is likely, as part of the generalized vasculopathy in TS.\textsuperscript{30,33}

Since hypertension and diabetes are generally associated with impaired left ventricular function, some degree of systolic and diastolic left ventricular dysfunction is to be expected in TS women. Surprisingly, subclinical systolic and severely impaired diastolic function associated with increased left atrial dimensions are present in normotensive and strictly metabolically controlled TS individuals.\textsuperscript{34} Such findings could indicate intrinsic myocardial dysfunction; however, no investigative studies have been performed. In addition, TS women display elevated N-terminal pro-BNP in the absence of symptoms of cardiac failure or former indices of systolic dysfunction,\textsuperscript{29} which is interesting in the light of the predictive capacity of this cardiac neurohormone in diagnosis and prognosis in heart failure. Intrinsic cardiac dysfunction is also supported by prolongation of the QTc interval seen in 30\% of girls, adolescents and adults with TS,\textsuperscript{35} a condition accepted as an independent predictor of sudden CV death.

In spite of presenting with a diverse spectrum of acknowledged CV risk factors, the most prevalent one in TS is POF. It is currently unclear, precisely how early oestrogen deficiency has an impact on CV prognosis—though young age at menopause seemingly confers greater risk. Evidence confirming earlier observational findings of oestrogen-derived cardioprotection is supported by animal and human studies showing anti-inflammatory, antioxidant and lipid-lowering effects, in addition to modification of disruptive vascular processes. Opposing such protective effects is the potential for the induction of myocardial hypertrophy, inducing venous thromboembolic events plus negative proarrhythmic territories.\textsuperscript{36} In interventional studies, oral HRT did not reduce total risk of CVD in primary and secondary prophylaxis of atherosclerosis in postmenopausal women, whereas potential alleviation of adverse risk in POF has not been investigated. However, in developing this approach, evidence of the alleviation of CVD risk with the early introduction of HRT in those with deficiency of female sex steroids is mounting—the so-called ‘timing hypothesis’.\textsuperscript{36}

It is recommended that TS girls and women should be submitted to regular CV examinations including initial screening for possible morbidity at diagnosis and subsequent regular monitoring at intervals
defined by individual comorbidity. Depending on the CV presentations, examination should include electrocardiogram, 24-hour ambulatory blood pressure, echocardiography and magnetic resonance imaging.37

**Gastroenterology and hepatology**

Increased concentrations of liver enzymes, especially alkaline phosphatase, alanine/aspartase aminotransferase and γ-glutamyl transferase (markers of hepatic cell lesion or turnover) are frequent in TS, whereas bilirubin (excretion) and coagulation parameters (production) are, in most cases, within the normal range.

In a study of liver biopsies in 27 women with TS, taken because of persistently elevated liver tests,38 multiple abnormalities was found, including marked nodular regenerative hyperplasia (n = 6), multiple focal nodular hyperplasia (n = 2) and cirrhosis (n = 2), associated, in some, withobliterative portal venopathy. Other patients showed more moderate changes, including portal fibrosis, inflammatory infiltrates and non-alcoholic fatty liver disease. The authors conclude that the main causes of liver abnormalities in TS are vascular disorders thought to be congenital in origin, and non-alcoholic fatty liver disease, without the signs of liver toxicity from concomitant estrogen therapy. The study is important for several reasons: it is the largest; it includes liver biopsies as well as thorough evaluation of other causes of liver disease; excluding viral, autoimmune and alcoholic causes; and it excludes estrogen therapy as a player in the liver abnormalities. Studies show that HRT normalizes measures of liver function, and dynamic liver tests are normal and not affected by HRT in TS.39

Inflammatory bowel disease (IBD) also seems to more frequent in TS (2–3%) and should especially be suspected in girls not responding to GH therapy. Celiac disease is present in 8% of patients according to an Italian study, and is also a potential cause for growth stunting, and should always be excluded. The usual guidelines should be followed for IBD and celiac disease.

**Glucose metabolism and type 2 diabetes**

In the clinical setting, attention has been paid to glucose homoeostasis in TS. T2DM and perhaps also type 1 diabetes occur more frequently in women with TS. Early reports of impaired glucose tolerance (IGT) in TS are found and IGT has been reported in both TS girls and women with TS. An epidemiological study including 594 TS women found an increased RR of both TIDM and T2DM.1
Generally, fasting glucose levels are not significantly different from controls, but fasting hyperinsulinemia has been found by some, and during an oral glucose tolerance test (OGTT) IGT has been found in 25–78%\textsuperscript{15,40} of adults with TS. In addition to higher glucose levels, the insulin response is increased and some have found a delayed insulin peak during an OGTT. The impaired glucose homoeostasis seems to be explained by a decreased insulin sensitivity as well as a reduced ‘first-phase insulin response’ which could be viewed as an inappropriately low \(\beta\)-cell response.\textsuperscript{15,40} Body composition is distinctly altered in TS with increased BMI, as well as decreased muscle mass, increased total fat mass and visceral fat mass. A more sedentary lifestyle and decreased VO\textsubscript{2max} is also found in this population. All factors contribute to the risk of developing reduced insulin sensitivity and diabetes.

Appropriate HRT in TS also seems to be important regarding the glucose homoeostasis. HRT has been found to significantly reduce fasting glucose and fasting insulin.\textsuperscript{41} Insulin sensitivity has not been found to be significantly improved; however, fat-free mass and physical fitness increase both factors that improve glucose homoeostasis. Contrary to this more subjects were found to have IGT during an OGTT while receiving HRT.\textsuperscript{15} HRT may slightly improve glycemic control.

Insulin levels, both fasting and as an OGTT response, increase during GH treatment. The insulin levels decrease after termination of GH, but do not return to levels as low as before treatment. GH therapy reduces insulin sensitivity, although this effect subsides with cessation of treatment. GH generally reduces insulin sensitivity in the first 6–12 months of treatment, whereafter it stabilizes. This stabilization could be due to changes in body composition with increase in lean body mass (LBM) and decrease in fat mass (FM). The number of TS with IGT does not seem to increase significantly during treatment, and HbA\textsubscript{1c} remains unchanged or even decreases during GH therapy. Despite the fact that most effects on the glucose metabolism seem to reverse after cessation of GH treatment, the long-term effects of the GH-induced hyperinsulinism and insulin resistance are not known.

Finally, it should be noted that there is a need for attention to the increased risk of impaired glucose homoeostasis and diabetes in TS. Recommendations for diagnosis and treatment of diabetes as with any patient should be followed. However, yearly screening of fasting glucose and on suspicion an OGTT should be performed.

**Diseases of the bone**

Peak bone mass depends on a number of factors, such as genetic background, nutrition, physical activity, local growth factors and a number
of hormones. During childhood and adolescence estradiol secretion is clearly deficient in TS. Children and younger and middle-aged adult patients with TS have low bone mineral density (BMD). Studies show that fracture risk is increased\textsuperscript{1,42,43} pointing towards a clinical consequence of the decreased BMD. HRT is considered crucial to avoid a rapid decrease in BMD and to induce maximal peak bone mass in adolescents and young adults.\textsuperscript{44} This is supported by longitudinal studies of estrogen-deficient and estrogen-replete adolescents with TS. Patients with spontaneous menstruation have normal BMD, whereas patients without menstruation have reduced BMD. A 3-year longitudinal study of 21 women with TS (age 20–40), with iliac crest biopsies before and 3 years after treatment with HRT, showed marked effects of estrogen on bone. Treatment consisted of estradiol implants (and an oral gestagen cyclically)\textsuperscript{45} resulting in estradiol levels comparable to levels in premenopausal women, and considerably higher than levels achieved with hitherto used regimens (estradiol 2 mg orally or equivalent transdermal doses). Bone biopsies pointed towards an anabolic effect on the skeleton of estradiol in young women with TS.\textsuperscript{45} Further, GH may improve BMD. In a recent 7-year study with GH treatment given at three different doses, BMD increased in a dose-dependent manner. However, estrogen was added after 4 years of GH treatment, and it is difficult to ascertain the individual effects of GH and estrogen in this study.\textsuperscript{46}

No very long-term studies (both follow-up and intervention studies) of the effect of estradiol have been published. There is a definite need for such studies to determine the ideal treatment regimen during adolescence to achieve two goals: attaining 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, hypothyroidism is frequent and thyroid antibody formation even more so and as many as 30% or more TS patients eventually develop hypothyroidism. A recent study showed a considerable increase in new cases with hypothyroidism during a 5-year follow-up period.\textsuperscript{47} It remains an enigma why so many TS patients suffer from diseases related to autoimmunity, and the basis for this grossly increased risk in TS [also including celiac disease, and diabetes (see above)] is unaccounted for. A genetic basis seems probable, although undocumented. GH treatment does not increase the frequency of autoantibodies. The treatment of hypothyroidism follows normal guidelines.
Conclusions

Patients with TS need comprehensive care preferably from a multidisciplinary team, which can best be practised from an out-patient clinic with special emphasis on TS. Knowledge concerning TS is still very limited—the syndrome is only seen infrequently by most clinicians, and patients typically have a range of questions related to the syndrome when we first see them.

Glucose metabolism, weight, thyroid function, bone metabolism, blood pressure, liver function and CV status should be assessed (Box 2). Estrogen deficiency should be treated, preferably with natural oestrogens and a gestagen. We recommend centralization of clinical care. A broad cooperative effort is ideal with the involvement of a large number of specialties; for example, we enjoy the participation of departments of cardiology, gynaecology (including a fertility clinic), otorhinology, ophthalmology and gastro-enterology.

Box 2 Suggested clinical out-patient program for patients with Turner syndrome.

Baseline
- Karyotype
- Renal and pelvic ultrasound
- Echocardiography and MRI of the aorta
- Thyroid status and antibodies
- Celiac screen
- Gonadotropins
- Renal and liver function
- Bone densitometry (DEXA scan)

Annual
- Physical examination, including blood pressure, heart auscultation
- Thyroid function
- Body composition status (BMI < 25), including physical exercise and diet instruction
- Fasting lipids
- Fasting blood glucose
- Renal and liver function

Every 3–5 years
- Echocardiography, MRI of the aorta
- Bone densitometry (DEXA scan)
- Audiogram
- Celiac screen
- Thyroid antibodies (thyroid peroxtdase)
References

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