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# Cardiometabolic Health in Turner Syndrome

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## Abstract

Individuals with Turner syndrome (TS) have a higher morbidity and mortality compared to the general population. Diabetes and cardiovascular disease are the major contributors to this burden. Precursors to diabetes and cardiovascular disease make up what is known as metabolic syndrome, including abdominal obesity, hypertension, dyslipidemia, and elevated fasting glucose. These features of poor cardiometabolic health are also prevalent among women with TS. Youth with TS also exhibit many of these features, indicating that the pathogenesis of these cardiometabolic conditions may begin early in life. The etiology of the increased risk of cardiometabolic conditions in TS is likely multifactorial, involving genetics, epigenetics, hypogonadism, medical co-morbidities, medications, and lifestyle. Counseling for the increased risk of cardiometabolic diseases as well as efforts to prevent or lower this risk should be routinely provided in the care of all patients with TS. Clinical practice guidelines are now available to guide screening and treatment of cardiometabolic conditions in girls and women with TS.

### Keywords

Turner syndrome; sex chromosome aneuploidy; metabolic syndrome; diabetes; epigenetics

Turner syndrome (TS) describes 1 in ~2,000 females who have a full or partial deletion of the second X chromosome (Gravholt, Juul, Naeraa, & Hansen, 1996). TS is associated with short stature, ovarian failure, various congenital anomalies, and a higher risk of morbidity and mortality than occurs in the general female population. In a large epidemiologic study of 781 women with TS in Denmark, the standardized mortality ratio (SMR) compared to the general population was 3.5 for coronary heart disease and 2.2 for cerebrovascular disease (Stochholm, Juul, Juel, Naeraa, & Gravholt, 2006). Coronary artery calcifications are 63% more likely in women with TS and this appears to occur at a younger age than in the general population (Schoepp et al., 2018). The relative risk of type 2 diabetes mellitus is three to five times higher in women with TS and contributed to 22% of all deaths in the Danish cohort (Bakalov, Cheng, Zhou, & Bondy, 2009; Gravholt, Juul, Naeraa, & Hansen, 1998; Stochholm et al., 2006). These data support the need to closely examine the risk factors for diabetes, heart disease, and stroke in girls and women with TS.

Metabolic syndrome describes a constellation of conditions that confer a high risk for developing diabetes, heart disease, and cerebrovascular disease (stroke). These conditions

include central adiposity (increased waist circumference), elevated blood pressure, elevated fasting glucose, high triglycerides, and low high-density lipoprotein (HDL) cholesterol (O'Neill & O'Driscoll, 2015). The diagnosis requires at least three features and, although various definitions of metabolic syndrome have been proposed in part related to age and ethnic background (Alberti et al., 2009), there is insufficient evidence to support the use of one definition over another in TS. While metabolic syndrome is common in the general population, patients with certain genetic conditions, including TS, seem to be especially prone to develop the constellation of features observed in metabolic syndrome. This increased risk could theoretically be directly attributable to the genetic differences in TS, co-morbidities found in TS, and/or common treatments used in girls with TS. For this review, we assessed the literature for cross-sectional, longitudinal, and interventional studies that evaluated features of metabolic syndrome in girls or women with TS, as well as potential factors contributing to cardiometabolic risk.

## FEATURES OF METABOLIC SYNDROME IN TS

### Abdominal adiposity.

Adipose tissue is an important endocrine organ that regulates metabolism, and dysfunction of this organ is strongly associated with systemic inflammation, insulin resistance, and cardiovascular disease (Kershaw & Flier, 2004). Visceral (central) adiposity in particular is a source of inflammatory meditators and strongly correlates to cardiometabolic disease states in adults (Fried, Lee, & Karastergiou, 2015). Short stature that is nearly universal in women with TS who have not received growth hormone predisposes to altered body proportions compared to taller women without TS. Women with TS have a higher body mass index (BMI) and higher waist circumference even when matched for BMI than women without TS (Calcaterra et al., 2014). Adult women with TS have higher fat mass (FM) and lower fat-free mass (FFM) compared to women without TS when assessed by dual energy x-ray absorptiometry (Gravholt, Hjerrild, et al., 2006). Regional fat distribution assessed by MRI is unfavorable in TS, with increased visceral FM (Ostberg et al., 2005). In addition to its strong association with insulin resistance, visceral adiposity is associated with ectopic fat deposition, including fatty liver disease, which can lead to end-organ dysfunction. While the basis for liver disease in TS is diverse, non-alcoholic fatty liver disease is the most common pathology on biopsy, with a prevalence of ~15% (Roulot, 2013). One study found a 17% prevalence of fatty liver disease by ultrasonography in 85 females with TS with a mean age of 27 years (Calcaterra et al., 2014).

Data on adiposity in youth with TS are much more limited. Several studies report higher than normal BMI and/or waist circumference in girls with TS (Lebenthal et al., 2018; O'Gorman et al., 2013). In a study of 64 Chinese youth with TS, the girls were found to have both higher waist-to-hip and waist-to-height ratios than age- and BMI-matched controls (Zhang, Chen, Lin, Yuan, & Yang, 2018). This study also found altered circulating levels of adipokines in girls with TS; however, the direction of change was not entirely congruent with prior literature in high adipose and insulin-resistant conditions. Abdominal adiposity was evaluated by MRI in 102 girls with TS (mean age 13.8 years), and total body, subcutaneous, and intra-abdominal fat were all much greater than would be anticipated, but

they were not compared to a control group and normative data are limited (Wooten, Bakalov, Hill, & Bondy, 2008). Visceral adiposity in this study correlated with impaired glucose tolerance, further suggestive of abdominal adiposity as a risk factor for poor cardiometabolic health. Conversely, a cross-sectional study of 19 youth with TS and 17 age- and BMI-matched controls found higher waist circumference in youth with TS, but surprisingly there were no differences in total body adiposity, visceral adipose tissue, or the subcutaneous/visceral adipose tissue ratio (O'Gorman et al., 2013). In summary, abdominal obesity is prevalent among adult women with TS with strong associations to other features of metabolic syndrome, but the few studies in youth limit our understanding of when this particular risk factor develops.

### Hypertension.

Impaired vascular function and consequently high blood pressure are prominently associated with metabolic syndrome, type 2 diabetes, and cardiovascular disease. Women with TS have a 2.9-fold relative risk of hypertension compared to the general population in Denmark (Gravholt et al., 1998). Up to 40% of youth with TS and 60% of adults have elevated blood pressure, with potentially higher detection rates with ambulatory blood pressure monitoring (De Groote, Demulier, et al., 2015; Fudge, Constantacos, Fudge, & Davenport, 2014; Los, Quezada, Chen, Lapidus, & Silberbach, 2016). Hypertension is particularly important as it may predispose to the nearly seven times increased risk of acute aortic dissection seen in TS (Gravholt, Landin-Wilhelmsen, et al., 2006). Aortic coarctation and renal malformations may also contribute to the increased risk of elevated blood pressure in TS, but idiopathic hypertension is still the most common form (De Groote, Devos, et al., 2015; Gravholt et al., 2017). Although there are a lack of comparator studies, aggressive evaluation and treatment of systemic hypertension in TS is presumed to lead to a decreased risk of end-organ sequelae, such as left ventricular hypertrophy, stroke, and aortic dissection. Therefore, routine monitoring for, evaluation of, and aggressive treatment of high blood pressure in girls with TS is recommended regardless of the etiology (Gravholt et al., 2017).

### Dyslipidemia.

High triglycerides, high low-density lipoprotein (LDL) cholesterol, and low HDL cholesterol may contribute to atherosclerosis. Women usually have a healthier lipid profile than men contributing to their lower risk of coronary artery disease; however, whether this is due to genetic differences or a protective effect of estrogen is debated. From either a genetic or hormonal mechanism, women with TS would be at risk for and indeed have worse lipid profiles than women without TS. Half of adult women with TS have elevated total cholesterol levels and a quarter has low HDL (Mavinkurve & O'Gorman, 2015). Even when compared to women with premature ovarian failure, women with TS have higher LDL levels as well as reduced LDL particle size, conferring a more atherogenic lipid profile (Van, Bakalov, & Bondy, 2006). Youth with TS also have higher total cholesterol levels compared to controls, even after controlling for age and BMI (Ross et al., 1995). A recent retrospective cohort study reported that 27% of youth with TS had documented hypercholesterolemia in their medical records (Lebenthal et al., 2018). Carotid artery intima-medial thickness, a surrogate measurement of early atherosclerosis, has a positive correlation with LDL cholesterol and a negative correlation with HDL cholesterol levels in youth with TS (Pirgon,

Atabek, Oran, & Guclu, 2008). In summary, lipid profiles appear to be more atherogenic in patients with TS than individuals without TS, and this appears to begin in childhood and worsen with age.

### Insulin resistance.

Insulin resistance is undeniably involved in the pathogenesis of type 2 diabetes, fatty liver disease, and atherosclerosis. Glucose and insulin metabolism is altered in TS, and this appears to start early in life with a combined picture of insulin resistance and β-cell dysfunction. Impaired glucose tolerance to an oral glucose load has been reported to occur in as many as 30% of prepubertal girls with TS (Wooten et al., 2008). In a retrospective cohort study of 98 individuals with TS, impaired glucose tolerance was documented starting in childhood, with increasing prevalence during adolescence, young adulthood, and early adulthood (10%, 16.7%, 21.4%, and 41.2%, respectively) (Lebenthal et al., 2018). Insulin resistance, defined by a homeostatic model of assessment of insulin resistance (HOMA-IR) ≥3, was detected in 20% of patients with TS tested during childhood and adolescence, and in 33% of patients tested in young adulthood.

## DIABETES MELLITUS IN TURNER SYDNROME

Both type 1 (autoimmune-mediated) and type 2 diabetes mellitus are more common in patients with TS with relative risks of 11.56 and 4.38, respectively (Gravholt et al., 1998). Diabetes mellitus contributed to 22% of deaths in females with TS in Denmark (Stochholm et al., 2006). A prospective study of 113 Italian women with TS found the prevalence of diabetes was 12.4% with a mean age of onset of 38 years (range 21–60 years), which is four times higher than the prevalence of diabetes in similarly-aged women in Italy (Ibarra-Gasparini et al., 2018). Importantly, this diagnosis was made based on plasma glucose levels >200 mg/dL measured at the two-hour time point of an oral glucose tolerance test rather than as a result of elevated levels of HbA1c, which showed poor concordance for diagnosis of diabetes in this population. Another study of Japanese women with TS found similar results to the Italian study, with a diagnosis of diabetes mellitus in 9.5% of women in their 30's, compared to <1% of the general female population of the same age (Hanew et al., 2016). Although there are several studies reporting abnormal glucose tolerance in youth with TS, the actual diagnosis of type 2 diabetes in girls with TS under 18 years is rare (Lebenthal et al., 2018).

## ETIOLOGY OF METABOLIC SYNDROME RISK IN TS

### Genetics and epigenetics.

While all features of the TS phenotype are ultimately related to missing genetic information on the X chromosome, the short stature homeobox-containing (*SHOX*) gene located in the pseudoautosomal region of the short arm of the X-chromosome is the only single gene that has been shown to be directly associated with the clinical phenotype in patients with TS, *i.e.*, short stature. The exact causative pathways involved in the metabolic dysfunction of TS are more elusive. At one point, it was assumed that haploinsufficiency of single genes escaping X inactivation was responsible for the clinical phenotype of TS, including cardiometabolic

health (Alvarez-Nava & Lanes, 2018). In support of this, women with an isochromosome resulting in loss of Xp, and the presence of three copies of Xq, had the highest prevalence of diabetes mellitus (40%) compared to women with other TS genotypes, suggesting that excess gene dosage from Xq coupled with haploinsufficiency of Xp contributed to the increased diabetes risk (Bakalov et al., 2009). Gene expression profiles comparing 46,X,iso(X)q vs 45,X patients showed a significant increase in Xq transcripts in the iso(X)q group compared to the monosomic patients. The most pronounced difference (>16-fold) between groups was in the expression level of *XIST* (X inactivation-specific transcript; Xq13.2), a non-coding RNA involved in X-chromosome inactivation; 100 other Xq genes also demonstrated altered expression levels (Alvarez-Nava & Lanes, 2018; Bakalov et al., 2009). One gene on the long arm of the X chromosome encoding O-linked *N*-acetylglucosamine transferase (*OGT*), a regulator of many cellular processes, has been proposed as a candidate gene for the high risk of diabetes in women with TS with isochromosome Xq, as well as in males with Klinefelter syndrome (47,XXY) (Abramowitz, Olivier-Van Stichelen, & Hanover, 2014). This gene, located on the X-chromosome, close to the *XIST* locus, regulates the addition of O-linked *N*-acetylglucosamine onto serine and threonine residues of proteins. Variation of *OGT* expression and abundance of its substrate, uridine diphosphate *N*-acetylglucosamine, in response to glucose may play a role in metabolic and cardiovascular dysfunction.

Beyond the gene dosage effect, differential epigenetic regulation has emerged as an alternative hypothesis to explain how the 45,X genotype, as well as other TS genotypes, may lead to the TS phenotype and individual phenotypic variability (Alvarez-Nava & Lanes, 2018). Imprinting, the concept that gene expression depends on the parent-of-origin that the chromosome is from, is a well-recognized epigenetic phenomenon that has been hypothesized to contribute to clinical variation in patients with TS. While there is some evidence for differential BMI, cholesterol profiles, visceral adiposity, and aortic stiffness depending on the parental origin of the lost X chromosome, other studies have failed to confirm that parental imprinting influences cardiometabolic phenotype (Abd-Elmoniem et al., 2014; Alvarez-Nava et al., 2013; Ko, Kim, Kim, Lee, & Yoo, 2010; Sagi et al., 2007; Van, Bakalov, Zinn, & Bondy, 2006). Data have recently emerged suggesting that the presence of only one X chromosome may change gene expression on not only the sex chromosomes, but also the autosomes (Alvarez-Nava & Lanes, 2018). Genome-wide epigenetic alterations, such as methylation, have been shown to differ between women with and without TS (Trolle et al., 2016). These epigenetic differences resulted in differentially expressed genes on both the sex chromosomes and the autosomes, and many of these deregulated genes have known functions for growth, metabolism, inflammation, and atherosclerosis (Trolle et al., 2016). These observations underscore the complexities involved in genotype-phenotype correlations in TS and expand the mechanistic understanding beyond number of copies of specific DNA sequences on the X chromosome.

### Hypogonadism.

Estrogen is cardioprotective, with deficiency in women (*i.e.*, post-menopausal) associated with abdominal adiposity and dyslipidemia (Rosano, Spoletini, & Vitale, 2017). TS is associated with premature ovarian failure with over half of the girls showing biochemical

evidence of ovarian dysfunction already in infancy (elevated gonadotropin concentrations) and less than 6% with non-mosaic TS experiencing spontaneous puberty (Fechner et al., 2006; Hagen, Main, Kjaergaard, & Juul, 2010). Given the high prevalence of ovarian insufficiency, it is difficult to determine with certainty what features of the TS phenotype are due to chronic hypogonadism. Bakalov et al (2004) compared insulin sensitivity and secretion in non-obese young women with TS to women with a normal karyotype, but with premature ovarian failure for other reasons matched for age and BMI. They found that impaired glucose tolerance was present in 36% of women with TS, but in none of the women with premature ovarian failure from other causes, suggesting that altered glucose homeostasis was unique to TS and not due to hypogonadism (Bakalov et al., 2004). Furthermore, treatment with estradiol in a small cohort of young women with TS did not alter insulin sensitivity or body composition (Gravholt et al., 2005).

### Other Co-Morbidities.

Females with TS have an appreciably higher prevalence of congenital anomalies, particularly congenital heart disease (~50%) and renal anomalies (~25%) (Gravholt et al., 2017). Some of these structural differences may directly contribute to metabolic syndrome features, particularly hypertension. Many girls with TS are born small for gestational age, which is itself a risk factor for later metabolic syndrome, possibly related to programming *in utero* or during the infancy if rapid catch-up growth occurs (Barker, 1995; Hong & Chung, 2018; Ibanez, Ong, Dunger, & de Zegher, 2006). Short stature, autoimmunity, recurrent illnesses, osteoporosis, and psychosocial deficits may also indirectly contribute to these conditions, through differences in lifestyle or other pathways.

### Growth Hormone Treatment.

Growth hormone is known to induce or increase insulin resistance. Therefore, there previously has been concern about the use of this treatment in an already at-risk population (Moller et al., 1995). Small longitudinal studies in girls with TS have shown an increase in insulin resistance after starting on growth hormone, but importantly also found favorable changes to body composition with decreased adiposity (Gravholt et al., 2002). After discontinuation of growth hormone treatment, insulin sensitivity returned to normal, suggesting that any negative impact on insulin resistance was reversable and likely not clinically meaningful (Van Pareren, De Muinck Keizer-Schrama, Stijnen, Sas, & Drop, 2002). Furthermore, a cross-sectional study of 102 girls with TS found significantly better cardiometabolic profiles in girls treated with growth hormone, including reduced visceral adiposity and a lower prevalence of impaired glucose tolerance (Wooten et al., 2008). These cardiometabolic benefits were seen both in girls currently on growth hormone and those who had previously been treated. In some studies, growth hormone has been reported to have no effect on blood pressure whereas in others it has been associated with a lowering of diastolic blood pressure (Mavinkurve & O'Gorman, 2015). In summary, growth hormone does not appear to worsen cardiometabolic risk in TS and may actually reduce the risk of some features.

### Behavior and Lifestyle.

Lifestyle factors, including reduced caloric intake and increased physical activity, are well-recognized to favorably impact obesity and risk of type 2 diabetes and cardiovascular disease in the general population. Very little work has been done to explore whether lifestyle factors contribute to the higher rates of cardiometabolic disease in TS. In a Scandinavian study of 80 adult women with TS and 214 controls, the women with TS reported that they liked physical activity in childhood and adolescence less than the control group. At the time of the survey, only a third of the women with TS were physically active, but this did not differ from controls (Naess, Bahr, & Gravholt, 2010). A group in Poland conducted two self-report questionnaire studies on physical activity in adolescents with TS (Sienkiewicz-Dianzenza, Milde, & Frac, 2006; Sienkiewicz-Dianzenza, Milde, Tomaszewski, & Frac, 2011). They found that a quarter of the girls with TS were disqualified by physicians from physical education classes, another 30% disliked physical education classes, and only 19% were meeting the recommended level of activity per week. There is no research on dietary habits in TS or whether any of these lifestyle factors correlate with cardiometabolic disease.

## SCREENING, PREVENTION, AND INTERVENTION

All parents and patients, if age-appropriate, should be counseled on these known risk factors in patients with TS. Preventive measures recommended in the general population should also be emphasized for youth with TS, including promoting moderate-to-vigorous intensity physical activity for at least an hour per day, healthy diet with high intake of vegetables and low intake of high-caloric density foods, and adequate sleep (Daniels, Hassink, & Committee on Nutrition, 2015). Although educating and supporting parents about these health behaviors is logical, whether or not these universal guidelines are enough to decrease the inherent increased risk in patients with TS is unknown.

The Clinical Practice Guidelines for the Care of Girls and Women with Turner Syndrome published in 2017 provide a rigorous summary of evidence and expert consensus-based recommendations for comprehensive care in TS (Gravholt et al., 2017). The guidelines recommend screening for features of metabolic syndrome as outlined in Table I. In addition, and not discussed at length in this review, is the recommendation to obtain liver enzymes annually starting at age 10 years. Liver disease in TS is multifactorial, including, but not limited to, non-alcoholic fatty liver disease that is often associated with metabolic syndrome (Roulot, 2013). Finally, cardiac imaging with echocardiography is needed at diagnosis and at least every five years in childhood and every 10 years in adulthood, and more often if structural defects are identified. Recommendations for cardiac MRI and electrocardiography are also provided in the clinical practice guidelines.

Abnormal cardiometabolic screening results warrant follow-up, referrals, and interventions as would be appropriate for youth without TS (Gravholt et al., 2017). Reversible causes of hypertension that are more prevalent in TS, such as renal anomalies, coarctation of the aorta, and other left-sided cardiac defects need to be evaluated for and treated as appropriate. Additionally, the TS clinical practice guidelines call for more proactive treatment of hypertension if aortic dilatation is present. Clinical practice guidelines for the treatment of dyslipidemia in both children and adolescents have different thresholds for initiating

treatment with statins for elevated LDL cholesterol depending on what risk factors are present in the individual (Daniels, Greer, & Committee on Nutrition, 2008; Jellinger et al., 2017). Given the earlier onset cardiovascular disease and greater mortality related to this in women with TS, the genetic disorder itself may be considered a risk factor even in the absence of other more common risk factors such as family history and cigarette smoking when considering when to initiate pharmacological therapy for dyslipidemia and the corresponding treatment targets. However, additional research is needed to identify and validate TS-specific recommendations for management of central obesity, hypertension, dyslipidemia, and dysglycemia.

## CONCLUSION

In conclusion, all five of the features of metabolic syndrome have been found to be more prevalent in females with TS compared to females in the general population. The reasons for this increased risk are likely multifactorial, including genetics, epigenetics, physical differences, co-morbid health conditions, hormonal influences, prescribed treatments, and behavior. Girls and women with TS should be counseled about these risks and screened according to expert consensus guidelines (Gravholt et al., 2017). Like for all at-risk youth, counseling should include healthy dietary habits, routine physical activity, and encouragement to maintain a normal BMI. Unique to TS is the use of growth hormone (which can help normalize BMI) and timely estrogen replacement (for its cardio-protective properties) as indicated. More research is needed to better understand the etiology of the increased risk of cardiometabolic conditions in women with TS. Future work should especially focus on effective interventions to prevent the development or progression of features of metabolic syndrome in girls with TS, with the ultimate goal of reducing the increased morbidity and mortality from type 2 diabetes and cardiovascular disease seen in adults in this population.

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**Table I.**

Metabolic Syndrome Screening Recommendations for Patients with TS

| Metabolic Syndrome Feature | Screening method | Starting Age | Frequency |
|---|---|---|---|
| Adiposity | Body Mass Index | Infancy | Every visit |
| Hypertension | Blood Pressure | Infancy | Every visit |
| Dyslipidemia | Fasting Lipid Panel | 10* | * |
| Insulin Resistance | HbA1c ± fasting glucose | 10 | Annually |

*While the TS clinical practice guidelines do not recommend cholesterol measurement until age 18, the American Heart Association and the American Academy of Pediatrics recommend that at least a total cholesterol be measured between 9–11 years of age, again after puberty is complete, and before transition to adult care (Daniels et al., 2008; Daniels, Jacobson, McCrindle, Eckel, & Sanner, 2009).