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Review

Cardiometabolic and vascular risks in young and adolescent girls with Turner syndrome

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ABSTRACT

Background: Turner syndrome (TS) is the most common chromosomal abnormality in females and is associated with several co-morbidities. It commonly results from X monosomy which is diagnosed on a 30 cell karyotype. Congenital heart disease is a clinical feature in 30% of cases. It is becoming evident that TS patients have an increased risk of cardiovascular and cerebrovascular diseases.
Scope of review: This review provides a detailed overview of the literature surrounding cardiometabolic health in childhood and adolescent TS. In addition, the review also summarises the current data on the impact of growth hormone (GH) therapy on cardiometabolic risk in paediatric TS patients.
Major conclusions: Current epidemiological evidence suggests that young women and girls with TS have unfavourable cardiometabolic risk factors which predispose them to adverse cardiac and cerebrovascular outcomes in young adulthood. It remains unclear whether this risk is the result of unidentified factors which are intrinsic to TS, or whether modifiable risk factors (obesity, hypertension, hyperglycaemia) are contributing to this risk.
General significance: From a clinical perspective, this review highlights the importance of regular screening and pro-active management of cardiometabolic risk from childhood in TS cohorts and that future research should aim to address whether modification of these variables at a young age can alter the disease process and atherosclerotic outcomes in adulthood.

Contents

Abbreviations: ABPM, ambulatory blood pressure monitor; BMI, body-mass index; BP, blood pressure; BSA, body surface area; cIMT, carotid intima media thickness; DBP, diastolic blood pressure; DXA, dual energy X-ray scan; FM, fat mass; GH, growth hormone; HDLc, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; ISSI-2, insulin secretion-sensitivity index-2; IVGTT, intravenous glucose tolerance test; LBM, lean body mass; LDLc, low density lipoprotein cholesterol; MetS, metabolic syndrome; MRI, magnetic resonance scanning; OGTT, oral glucose tolerance test; PAT, peripheral arterial tonometry; TS, Turner syndrome; T2DM, type 2 diabetes.

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1. Introduction

Turner syndrome (TS) is the most common chromosomal abnormality in females, affecting 3% of all female foetuses [1] and occurring in 1:2500 live female births. It results from complete or partial X chromosome monosomy and is associated with a characteristic phenotype and comorbidities. Diagnosis requires the study of a minimum 30 cell karyotype [2]. Congenital cardiovascular disease affects 30% of patients with TS [3] however, it is becoming increasingly recognised that TS patients are at an increased risk of early acquired cardiovascular and cerebrovascular diseases and have a 2-fold risk of developing coronary artery disease [2,4].

An established precursor to cardiovascular disease is atherosclerosis, which results from a multifactorial process through a combination of several modifiable (hypertension, hyperglycaemia, hyperlipidaemia and obesity) and non-modifiable (including age, gender and family history) risk factors. The process of atherosclerosis begins in early childhood and metabolic risk factors at age 9 years in healthy children can be predictive of subclinical atherosclerosis in adulthood [5]. The early stages of atherosclerosis are reversible and thus, early detection offers a theoretical window of opportunity to modify disease progression. Similarly, in TS, the atherosclerotic process starts early [6] and the epidemiological data suggests that there is an associated 3-fold risk of mortality from cardiovascular and cerebrovascular diseases [7,8]. This review will discuss current data on cardiometabolic risk factors and acquired cardiovascular diseases in young girls with TS.

2. Cardiometabolic risk factors in Turner syndrome in childhood

2.1. Glucose metabolism

Approximately 35% of young girls with TS have abnormalities in carbohydrate metabolism and the frequency of impaired glucose metabolism varies with karyotype: mosaic TS patients have normal glucose tolerance compared to monosomy X patients [9]. Furthermore, type 2 diabetes mellitus (T2DM) is up to 4 times more common in TS patients [1] and the frequency of T2DM can vary according to karyotype: 43% in isochromosome Xq as compared with 9% in del Xq [9]. This suggests that haploinsufficiency of genes on Xp increases the impaired glucose metabolism and risk of T2DM and possibly impacts transcription factors involved in pancreatic islet and beta cell function [10].

The pathophysiology of impaired glucose tolerance in TS still remains unclear but there are several studies which attempt to elucidate the nature of the impairment. Adult women with TS have higher 2 h glucose levels and reduced measures of insulin secretion (HOMA-b and first phase insulin release) when compared to age matched controls, suggesting impaired insulin secretion [11]. However, studies demonstrating discrete reduction in insulin secretion following a glucose load in an IVGTT suggest a dysfunction in insulin secretion [12]. There is a study demonstrating higher fasting glucose and insulin levels (HOMA-S) using hyperinsulinemic–euglycemic clamps in 16 TS subjects, when compared to age- and body composition-matched controls, suggestive of decreased insulin sensitivity and lower whole body insulin sensitivity [13].

In paediatric TS cohorts, 34% of TS patients have impaired glucose tolerance on oral glucose tolerance testing (OGTT) as compared to 8% of controls but insulin sensitivity improves as the girls progress to 12–16 years of age [9]. Similar findings have been demonstrated in adolescents by using the IVGTT [14]. However, the reverse has also been demonstrated using the euglycaemic insulin clamp technique, where TS girls and adolescents have a significant reduction in insulin sensitivity and in non-oxidative glucose disposal compared to age-matched controls [15]. In a recent paediatric cross-sectional study evaluating cardiometabolic, 5/19 girls with TS and 0/17 controls had significantly impaired fasting glucose or impaired glucose tolerance on OGTT, and ISSI-2 (insulin secretion sensitivity index-2) was significantly lower in TS, suggesting a pancreatic beta cell dysfunction [16].

What is evident from these studies is that girls and women with TS are at increased risk of impaired glucose metabolism and T2DM and that the aetiology, though inconclusive, is multifactorial. Further, in TS, it appears that the processes of insulin secretion and sensitivity are dynamic at different ages of childhood, adolescence and adulthood. This maybe the result of small study numbers and varying age range as well as varied insulin methodologies used. Larger studies are clearly required and especially studies examining glucose metabolism in paediatric TS cohorts and its impact on cardiovascular risk in adulthood.

2.2. Body composition

Patients with TS have an altered body composition when compared to age-matched controls. This may be due to the fact that TS cohorts are on average 20 cm shorter but often have similar weights compared to controls resulting in an unfavourable body composition, with increased body mass index (BMI) and waist circumference [17–21]. However, it is evident from research methodologies, such as dual energy X-ray scan (DXA) and magnetic resonance scanning (MRI) that it is not just the shorter average height which places TS cohorts in an unfavourable body composition. DXA and MRI have demonstrated that adult TS cohorts have higher fat mass (FM) and lower lean body mass (LBM) with alterations in regional fat distribution (increased visceral FM, decreased truncal LBM and decreased skeletal muscle mass) [22,23]. A concerning finding is that the paediatric data demonstrates similar trends. TS girls have higher waist circumference than age-matched and BMI-SDS-matched control [16] and given that visceral fat is metabolically active and contributes to the development of insulin resistance, T2DM and metabolic syndrome, this presents clinicians with an opportunity for early detection and intervention in TS girls.

2.3. Lipid abnormalities

There are data which suggest that lipid metabolism in TS cohorts is altered, with approximately 50% of TS patients over 21 years displaying hypercholesterolemia [24]. Total cholesterol and low density lipoprotein cholesterol (LDLc) are elevated in TS and a positive correlation exists between total cholesterol and LDLc levels and age [24,25,26]. Furthermore, low high density lipoprotein cholesterol (HDLc) levels occur in about 25% of adult TS women [1] and other studies show increased triglycerides in TS women [27]. These are all components of the metabolic syndrome.

In paediatric TS cohorts, higher total cholesterol, triglycerides and HDL cholesterol have been described [6,28,29]. Furthermore, there is a significant positive correlation between LDLc and carotid intima media (cIMT) thickness and a negative correlation between HDLc ($r = 0.518$, $p < 0.01$) and cIMT [6] suggesting that dyslipidaemia may be associated with atherosclerosis in children with TS. Ross et al. (1995) [52] has previously shown a positive correlation between