Cardiovascular and metabolic problems in Turner’s syndrome patients

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Abstract
The Turner syndrome (TS) is a chromosomal trait caused by X chromosome monosomy. Beside gonadal dysgenesis and short stature, which are classical features of the syndrome, the patients are at increased risk of cardiovascular disease. There is growing evidence, that the circulatory system diseases are the leading cause of morbidity and mortality in TS individuals. TS is known to be related with specific congenital heart defects especially of the left heart, with bicuspid aortic valve and coarctation of aorta being the most prevalent. Moreover, patients are at risk of aortic dissection and have increased risk of atherosclerosis and hypertension. The aortic dissection and rupture must be especially anticipated in patients with TS undergoing artificial fertilization programs. The cardiovascular morbidity is increased additionally by metabolic traits, especially dyslipidemia and glucose metabolism abnormalities. Concerning the increased risk of cardiovascular disease, the special attention should be paid by clinicians on those aspects in children and adults with TS. The cardiac system must be closely monitored throughout whole life.

Key words: Turner syndrome, cardiovascular diseases, heart defects, diabetes

Introduction
Turner syndrome is a clinical manifestation of X chromosome monosomy, described for the first time by Turner in 1938 [1]. According to The Turner Syndrome Consensus Study Group statement, diagnosis of TS “requires the presence of characteristic physical features in phenotypic females coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism” [2]. Complete 45,X monosomy accounts for 40-60% of the karyotypes, whereas 5-10% of patients have a duplication of the long arm of one X (isochromosome Xq) and most of the remaining karyotypes show a mosaicism [2-4]. A correlation between karyotype and phenotype has been reported, as, for example, the presence of an isochromosome Xq coupled with an increased risk for diabetes mellitus, hypothyroidism and inflammatory bowel disease [3].

The clinical characteristics of TS patients are predominantly hypogonadism and short stature, more than 90% of patients exhibit those signs. Women with TS present also a typical phenotype, including shield chest, signs of lymphedema (webbed neck, low posterior hairline) and skeletal deformities (cubits valgus, shortened fourth metacarpal and others) [4]. Many other comorbidities are known to be more prevalent in those patients. Among them there are a group of cardiovascular defects and metabolic traits interfering with this system. It has been known for long that left-sided congenital cardiac abnormalities are more common in women with TS, and recent studies have demonstrated that these women have a threefold increase in mortality, primarily as a result of cardiovascular complications and several risk factors for ischemic heart disease including hypertension, prediabetes and diabetes, and hyperlipidemia [3-5].

In this review we wanted to summarize the main findings concerning the status of circulatory system in TS patients and metabolic conditions affecting them and to analyze the available data about influence of hormonal replacement therapy on modifiable risk factors.

Congenital heart defects
Out of internal organ abnormalities and associated diseases, cardiovascular problems are most important causes of higher mortality among women with TS in comparison with the general population [5]. This fact is noticeable even during fetal development, when significant defects in development of the heart and aorta result in a very high abortion rate for fetuses with a 45,X karyotype. Fetuses with cardiovascular failure almost always demonstrate obstructed jugular lymphatics with nuchal cystic hygromas. These hygromas resolve as the lymphatics fenestrate later in gestation, but residual postnatal webbing of the neck predicts defects for example bicuspid aortic valve and aortic coarctation in survi-
Glucose metabolism abnormalities are known risk factors of hypertension and atherosclerosis in general populations [15]. Also hypoestrogenism may augment pathological processes leading to deposition of atherosclerotic plaque in arterial wall [16]. Women with TS are suffering from all those risk factors and growing body of evidence shows that those are leading to very rapid development of hypertension.

Hypertension affects as many as 50% of young adult patients and is accompanied by increased arterial wall stiffness and increased activity of sympathetic nerve system. Elevated blood pressure may be even observed in children with TS, since the hypertension was observed in 7-17% of girls. Half of TS individuals has altered 24-hour blood pressure profile, with smaller night pressure drop than in healthy persons [5]. Also the hypertrophy of left ventricle has been revealed in those patients, which might predict future cardiovascular events, including higher mortality [17].

The exact mechanism of hypertension in TS has not been clearly identified: an increase in plasma renin activity has been found in 50% of cases by some authors and abnormal vagosympathetic tone, explaining relative tachycardia [18]. In the series reported by Elsheikh et al. [5], hypertension was secondary to renal disease or coarctation in only 20% of patients with TS. Small vessel renovascular disease has been proposed as a possible explanation, given the elevated renin activity that may be found before estrogen therapy is instituted.

It must be stated that, the role of the sex steroids deficiency in pathogenesis of hypertension is not clearly understood. Some authors showed beneficial effects of hormonal replacement therapy on blood pressure. Elsheikh et al. [19] demonstrated that suitable and systematic estrogen substitution significantly decreases diastolic blood pressure in 24 h monitoring, and decreases systolic blood pressure during the day. The authors speculate that, the effect may be due to the influence of estrogens on vascular reactivity as a result of interaction with vascular smooth muscle cells, stimulation of nitric oxide secretion by endothelial cells, inhibition of platelet aggregation, monocyte adhesion, and smooth muscle hypertrophy. Also Gravholt et al. [17] showed positive effects of natural estrogens on diastolic blood pressure. On the contrary Giordano et al. [20] did not found the relationship between hormonal therapy and decreased blood pressure levels during 24 h ambulatory monitoring.

The hypertension in TS is, at least partially, caused by increased atherogenesis which is additionally augmented by metabolic problems. Some authors studied
the link between arterial wall stiffness and TS. Measurement of arterial wall stiffness is an independent marker of cardiovascular risk and is associated with other cardiovascular risk factors such as blood pressure, insulin resistance, central obesity, and greater carotid intima-media thickness in the general population [21]. Mortensen et al. [22] failed to found significant correlation between TS and arterial stiffness index. Moreover, in the same study there was no influence of the hormonal treatment on those indices. This results were opposed in other studies by Elsheikh [19] and Osberg [23] in which arterial stiffness was significantly increased in TS patients and was lowered by the treatment with hormonal preparations.

Inconsistent data were also obtained regarding the intima-media thickness in TS women. As increased intima-media thickness is considered a precursor of clinically detectable atherosclerosis and is connected with higher cardiovascular risk [24]. Some authors were unable to detect increased thickness of this complex of arterial wall. However, Ostberg [23] found an increased intima-media thickness in TS patients in comparison to healthy eumenorrheic women. Interestingly, the results were indifferent comparing to patients with primary amenorrhea with normal karyotype. The similar increase in intima-media thickness seen in TS and 46,XX primary amenorrhea women implicates estrogen deficiency as the key determinant of neointimal hyperplasia in these subjects.

Aortic dilatation and dissection

Aortic dilatation and dissection are more prevalent among patients with TS than it has been estimated until recent data was published. The greatest excess risk is dissection or rupture of the aorta, which accounts for death in 2-8% of TS women [25]. In majority of patients (> 60%) the cardiovascular comorbidities were described, especially hypertension and congenital heart defects [26].

In the retrospective series reported by Price et al. [25], three out of 156 patients died from aortic dissection, and a fourth from aortic rupture with coarctation. In the literature review by Elsheikh et al. [5], almost 50% of those with aortic dilatation were under the age of 21 years. Recently, the National Institutes of Health (NIH) provided the first prospective measure of the incidence of aortic dissection in TS, which then served as a basis for proposing new guidelines to identify high-risk patients [27]. The study used cardiac magnetic resonance imaging to prospectively screen for cardiovascular defects in more than 300 unselected girls and women with TS, and about half of them (n = 158) were followed for an average of 3 years. From this group 3 had aortic dissection. In conclusion authors of the study, proposed a aortic diameter equal or bigger than 2.5 cm/m² after adjusting for body surface area (aortic size index) as an indicative for evaluation and possible prophylactic intervention.

In recent times American Practice Committee of the American Society for Reproductive Medicine [28] published paper concerning the maternal mortality associated with pregnancy in women with Turner syndrome. The Committee, on the basis of available data assessed the risk of death during the perinatal period from aortic dissection or rupture in women with Turner syndrome as high as 2%. For comparison the similar risk in general population is approximately 0.01% [28]. In light of this finding, authors suggest echocardiography and MRI in every TS patient. An aortic size index > 2.0 cm/m² is proposed as a cut off level for patients at a particularly increased risk for dissection.

Atherogenic lipid profile

Abnormalities of carbohydrate and lipid metabolism are important clinical aspects of TS as well as short stature and gonadal dysfunction.

There are several studies analyzing the lipid profile in patients with TS, most of them showing dyslipidemia in those individuals, however of different degree. Most authors found either isolated hypercholesterolemia or hypercholesterolemia accompanied by decreased levels of high density lipoprotein cholesterol (HDL-C) and hypertriglyceridemia. In untreated TS the presence of abnormal lipid profile was reported to be independent of body mass index and karyotype [20]. On the other hand, other investigators have not confirmed that in TS, cholesterol concentrations differ from values of healthy women [17]. Higher prevalence of hypertriglyceridemia in TS was reported in some studies [29, 30]. Interestingly, in the latter study, the levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol, and triglycerides were all significantly higher in women with Turner syndrome compared with women with 46,XX premature ovarian failure [30]. Such a result suggest that chromosomal aberration is an independent causative factor for dyslipidemia, aside from hypoestrogenism. The absence of correlation between lipid profile and estradiol levels suggests that the influence of estradiol in the development of hypercholesterolemia in TS is minor. This conclusion was confirmed by studies assessing the influence of hormonal
treatment on lipid metabolism in TS. In most of the studies there was lack of clear association between hormonal treatment and lipid concentrations. Mauras and colleagues [31], did not find the difference in plasma lipids, neither lipolysis nor lipid oxidation rates in TS patients treated with different (oral vs transdermal) estrogen preparation, even though the circulating concentrations of hormone was significantly higher in orally treated group.

In contrast to results regarding influence of hormonal replacement therapy and lipid metabolism, it has been proved that recombinant human growth hormone (rGH) strongly influences lipid metabolic processes in TS. Van Pareren et al. [32], as well as Bannink et al. [33] evaluated the metabolic consequences of long-term rGH treatment in girls with TS and showed a decrease in total cholesterol and LD-C and an increase in HDL-C and triglycerides during the first 4 years of therapy and an increase of total cholesterol and LDL after discontinuation of rGH treatment.

The abnormalities of carbohydrate metabolism

There are several abnormalities in glucose metabolism in TS and they include an increased frequency of abnormal glucose tolerance, hyperinsulinemia and reduced insulin sensitivity. There are many reports concerning the high prevalence of abnormal carbohydrate metabolism in TS patients. Type 2 diabetes is common in TS. It has been reported to be 2-4 times more common in women with TS [5]. An oral glucose tolerance test uncovers impaired glucose tolerance or diabetes in more than 50% of cases, usually associated with an insulin secretory defect in TS [17]. It is estimated diabetes mellitus contributes to 25% of the causes of death in adulthood in TS [17, 25].

Despite the increased incidence of glucose intolerance in TS, the pathology of this phenomenon remains unclear. An impaired insulin secretion in response to exogenous stimuli (inter alia glucagon and tolbutamide) as well as a defect of insulin action, as assessed by the hyperinsulinaemic euglycaemic clamp, have been implicated [34, 35]. The development of diabetes in TS has been suggested to be due to deficient insulin responses to oral and intravenous glucose loads [36]. However, insulin levels in nondiabetic and diabetic women with TS have been reported to be high, normal, or low [17, 37, 38]. Earlier studies have provided evidence that a putative intrinsic defect underlying the insulin resistance in TS may reside at the level of the muscle. Gravholt et al. [39] found that women with TS have enlarged type IIa muscle fibres, suggesting a decreased oxygen and substrate supply for glucose metabolism. Moreover, women with TS tend to demonstrate increased adiposity compared with age-matched controls [40], and their hypogonadism and hormone replacement therapy may pose additional confounding effects in studies of glucose metabolism. The studies focusing on those issues are problematic because of relatively small groups of subjects included. In many studies there have been also problems in obtaining well matched groups controlling for age, body mass and composition [34, 36].

The effect of sex hormone replacement therapy on insulin sensitivity remains unclear [17, 19]. Gravholt et al. [17] showed that insulin sensitivity was similar before and during replacement in a TS cohort, however others found negative correlation with frequency of prediabetes and diabetes and estradiol administration [19]. At present, data concerning the effects of estrogens on glucose metabolism and insulin sensitivity in humans are conflicting. In particular, short-term supraphysiological estrogen administration possesses an adverse effect on glucose tolerance, resulting from the suppression of first-phase insulin secretion and increased insulin, whereas the main longterm effect of estrogens is preservation of the pancreatic insulin responses to glucose [41]. These data, explain, at least partially the diversity of results concerning carbohydrate metabolism in estrogen treated TS.

Summary

Turner’s syndrome is a rare congenital disease affecting about one in every 2500-3000 live-born females, is the result of chromosomal abnormalities in a phenotypic female [2].

Subjects with TS usually receive intensive medical care during childhood, but the majority are discharged from specialist clinics after the induction of puberty and attainment of final height. Since the description of TS by Henry H Turner in 1938 [1], a wealth of information has been added and our current understanding of the syndrome is continuously being enlarged. By contrast with the intensive medical follow-up in childhood, follow-up is often foully inadequate in adult patients with TS, although early medical intervention may reduce morbidity and improve life expectancy, as stressed by The Turner Syndrome Consensus Study Group in 2007 [2]. There are growing number of evidence, the TS patients are at increased cardiovascular and metabolic risk, and this risk correspond strictly to increased mortality and morbidity in those patients.
According to the available data and recommendations, it should be highlighted that every patient with TS should undergo cardiology assessment from the earliest possible time, including prenatal period [2, 5, 28]. The echocardiography should be performed in infants and children with TS diagnosed and the study should be repeated in following years of life. There is growing evidence of utility of MRI in older TS patients and the study seems to be mandatory in individuals desiring pregnancy. Blood pressure should be also comprehensively examined, at the beginning in all limbs and should be checked annually. If appropriate, the 24 hour blood pressure monitoring should be applied to uncover the cases with lack of night fall of pressure. The additional risk factors of ischemic heart disease must be regularly checked in TS patients. Fasting lipids and glucose should be checked on regular annual basis and oral glucose tolerance test should be performed, especially in overweight and obese patients [2, 5, 10, 28].

References


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