Aortopathies in Turner syndrome — new strategies for evaluation and treatment

Zaburzenia w budowie aorty u pacjentek z zespołem Turnera — nowe metody diagnostyki i leczenia

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Abstract

Turner syndrome is a rare genetic disorder which impairs women's growth, reproductive function, cardiovascular development and other functions. This syndrome has been proposed as an independent risk marker for cardiovascular disease. Despite this, life-threatening cardiovascular outcomes affecting young women are dismissed because of incomplete follow up. During assessment due to their smaller stature, it should be noted that, although the ascending aorta diameter is normal in absolute terms, after indexation for body size, patients with Turner syndrome may have a dilated aorta.

Based on recent guidelines and the latest studies, there is new evidence on the use of magnetic resonance imaging in diagnosing aortic lesions. New management possibilities of aortopathies have also been discussed. This approach should optimise medical care for women with Turner syndrome, but many areas of uncertainty still remain in the diagnosis and management of this syndrome, and new prospective studies are needed. **(Endokrynol Pol 2015; 66 (1): 58–65)**

Key words: *Turner syndrome; aortopathies; management*

Streszczenie

Zespół Turnera jest rzadko spotykanym schorzeniem o podłożu genetycznym u kobiet, u których występują między innymi zaburzenia wzrastania, płodności oraz zaburzenia w rozwoju układu sercowo-naczyniowego. Obecnie uważa się, że zespół Turnera jest niezależnym czynnikiem ryzyka rozwoju chorób układu sercowo-naczyniowego. Pomimo istotnego ryzyka rozwoju powikłań, które mogą nawet zagrażać życiu młodych pacjentek, wiele z nich odsyłanych jest do domu bez pogłębionej diagnostyki w kierunku zaburzeń w układzie sercowo-naczyniowym. Należy zauważyć, że chociaż wymiary aorty wstępującej są u wielu pacjentek obarczonych zespołem Turnera prawidłowe, to po uwzględnieniu rzeczywistych wymiarów ciała pacjentki można stwierdzić, że u części z nich aorta jest poszerzona.

Opublikowane ostatnio wyniki badań oraz zalecenia kliniczne wskazują na przydatność rezonansu magnetycznego (MRI, *magnetic resonance imaging*) w diagnostyce zmian organicznych aorty. W publikacji omówiono także nowe możliwości terapeutyczne w przypadku występowania zmian w aorcie, co mogłoby usprawnić leczenie pacjentek z zespołem Turnera. W dziedzinie diagnostyki i leczenia tego zaburzenia genetycznego istnieje jednak nadal wiele nierozwiązanych zagadnień, dlatego też konieczne jest prowadzenie dalszych badań, także o charakterze prospektywnym. **(Endokrynol Pol 2015; 66 (1): 58–65)**

Słowa kluczowe: *zespół Turnera; zaburzenia budowy aorty; leczenie*

Epidemiology, diagnosis and genetics of Turner syndrome

Turner syndrome (TS) is a rare congenital disorder caused by sex chromosome haploinsufficiency in a phenotypic female, associated with characteristic clinical features: short stature, primary amenorrhoea and cardiovascular pathology [1, 2].

The prevalence of TS is 50 per 100,000 live born females in Caucasian populations [2, 7]. Prenatal prevalence is much higher than the postnatal, because of the frequent intrauterine mortality [1, 37]. If TS is suspected in the intrauterine period, postnatal confirmation must be done [3]. Postnatal diagnosis requires a standard 30-cell karyotype which identifies at least 10% mosaicism with 95% confidence [5, 6]. Specific clinical findings are also required for the diagnosis. Individuals with a *45,X* without clinical features are not considered to have TS; phenotypic males are also excluded from the diagnosis of TS, regardless of the karyotype [3].

TS is related to various karyotypes [4]. A correlation between karyotype and phenotype has been reported [4, 18]. The most severe phenotypes are 45,X and *46,XXp* [4, 37].

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Cardiovascular phenotype in Turner syndrome

The most serious, life-threatening issues of *X-chromosome* haploinsufficiency are caused by lesions of the cardiovascular system [3, 10]. Due to a very high rate of spontaneous abortions (99% in *45,X* karyotypes), congenital heart disease occurs in about 25–45% of live-born girls with TS versus 75% of foetuses [5, 10].

Epidemiological studies have revealed a three-fold higher mortality in the TS population than the general population, because of the cardiovascular events affecting young women [9, 14]. Cardiovascular findings occurring in TS might be congenital or acquired [18]. Congenital cardiovascular defects in TS are associated mainly with left-sided malformations (Table I). Elongated transverse arch of the aorta (ETA) is seen in 50% of women with TS, and bicuspid aortic valves (BAV) in 13–43%, *versus* 1–2% in the general population [13, 25] and coarctation of the aorta (CoA) in 4–18% in those with TS [7, 11, 13].

The value of the partial fusion of the aortic valve has been discussed recently. Traditionally, it was thought that this is an acquired valve problem, but a recent study [58] has shown equal distribution across all age groups. It has also been found that partial fusion of the aortic valve has an influence on increasing ascending aortic diameter in subjects with TS.

Acquired cardiovascular problems in women with TS may be caused by a number of risk factors, including central obesity, impaired glucose tolerance, insulin resistance, and hyperlipidaemia [8, 12, 15, 16, 18]. More than 30% of young girls and adolescents, as well as 50% of adults with TS, are mildly hypertensive on 24-hour ambulatory blood pressure measurements, and an additional 50% display abnormal circadian blood pressure profile in the same age group [7, 11].

The mechanism has not been clearly identified: an increase in plasma rennin activity has been found in 50% of cases by some authors [11]. Conversely, normal rennin and aldosterone has been reported in another study [10].

Women with TS should undergo annual screening for cardiovascular risk factors [12].

Monitoring is based on expert consensus and includes clinical and laboratory evaluation, blood pressure measurement, echocardiography, and cardiovascular magnetic resonance imaging [3, 14, 27] but the follow-up remains quite poor.

This paper is focused on the aortic events which are characteristic for TS.

Thoracic aortic disease

In general, the term 'thoracic aortic disease' encompasses a broad range of degenerative, structural, acquired,

Table I. *The prevalence of congenital cardiovascular defects in Turner syndrome*

Tabela I. *Częstość występowania wad wrodzonych układu sercowo-naczyniowego u pacjentek obarczonych zespołem Turnera*

	BAV (%)	Coarc (%)	ETA (%)
Mortensen [10]	15–30	17	50
Gotzsche [13]	14	10	NR
Sybert [13]	14	14	NR
Mazzanti [13]	12	7	NR
Volkl [13]	18	18	NR
NIH	30	12	49
Donadille [14]	21	6.9	1
Lopez [34]	26	17	NR
Mortensen [43]	27.3	13.3	47.4
Kim [45]	39.2	15.7	31.4

BAV — bicuspid aortic valve; Coarc — aortic coarctation; ETA — elongated transverse arch of aorta; NR — not reported; NIH — National Institutes of Health

genetic-based, and traumatic diseases [19, 20, 24, 27, 29]. Aneurysms and dissections are major diseases of the aorta that lead to lethal outcomes [19]. There are two major types of thoracic aortic aneurysms (TAA) — degenerative/atherosclerotic and genetically triggered [22, 24, 27]. The most dangerous thoracic aortic aneurysms that lead to dissection of ascending aorta are usually associated with genetic mutations [26, 30].

The genetic background causing the lesion of ascending aorta in TS remains poorly understood [17, 47]. Aortic root dilatation does not appear to be related to atherosclerosis and is more likely to be due to a mesenchymal defect caused by genetic disorder [32, 35]. The most common histological finding of the dilated aorta is elastic fibber fragmentation and cystic medial degeneration [10, 21, 30, 31, 38]. These findings are associated with various connective tissue diseases such as Marfan or Turner syndromes, etc. There has been some research about the influence of disruption of the transforming growth factor *b* pathway [14], which causes lesion of ascending aorta [23]. Further research into the genetic aetiology of the cardiovascular phenotype of TS is needed [37].

Aortopathy in Turner syndrome

Cardiovascular phenotype of TS includes generalised vasculopathy characterised by arterial dilation, vessel wall thickening, and abnormal pulse wave propagation [34, 37]. Aortic diameter is the principal risk stratification tool for aortic dissection [20, 32, 34].

Important findings relating to cardiovascular pathology in TS patients have been demonstrated in a French

Table II. *Aetiology of thoracic aortic disease [30]*

Tabela II. *Etiologia rozwoju zmian w odcinku piersiowym aorty [30]*

Aetiology	Details
Degenerative aneurysms	Most common
	Associated with hypertension, age, smoking
Atherosclerotic	More commonly involves the descending aorta and arch
Genetically triggered aneurysm syndromes	
Marfan syndrome	Most common inherited connective tissue disease
	Mutation in FBN-1 gene leads to decreased tensile strength of the aorta
	Estimated that 75% of patients will have a dilated aortic root
Loeys-Dietz Syndrome	Aggressive vasculopathy linked to TGFBR1 or 2 mutation
	Early detection and intervention is important
Bicuspid aortic valve	> 50% have tubular/ascending aneurysm
	20% sinus of Valsalva involvement
	Faster rate of growth than aneurysms associated with a three leaflet valve
Turner syndrome	1/3 with bicuspid valve and coarctation of the aorta
	Ascending aortic aneurysm
Familial non-syndrome thoracic aortic aneurysm syndrome	Dilated aorta
	Absence of other connective tissue disease
	Family history dissection/aneurysm
Aortitis	
Infectious	Syphilis (historical)
	Salmonella
	Staphylococcal species
	Mycobacterium
Non infections/ inflammatory	More common:
	Giant cell and Takayasu's arteritis
	Less common:
	Behcet's syndrome, Cogan's syndrome, relapsing polychondritis
	Rare:
	Rheumatoid arthritis, spondyloarthropathies
Trauma	Typical location is at the aortic isthmus
	— Complications include rupture, pseudoaneurysm, chronic dissection with secondary aneurysm
	formation
Chronic aortic dissection	— Aneurysm due to growth and pressure differential of false lumen

cohort study [14]. The whole population with TS in France was evaluated. This study detected a rather poor cardiovascular monitoring in this population.

Cardiovascular data of 233 patients (children and adults) with TS was analysed, and only 38.6% of the cohort had undergone both echocardiography and MRI evaluation. BAVs were detected in 49 patients (21%) with a median age of detection being 20 years. Aortic coarctation was detected in 16 cases (6.9%). At least one aortic diameter exceeded 32 mm in 28 cases (12%), but after indexation to body size 91 (39%) patients from the cohort had at least one aortic diameter over 20 mm/m². There is more data showing that the prevalence of ascending aortic dilation is about 15–30% in TS patients, and usually it is asymptomatic [6, 12, 33]. Despite a normal ascending aortic diameter in absolute terms, after indexation for body size, patients with Turner syndrome may have a dilated aorta [10, 20, 37, 39, 44].

Two major strategies have been proposed to circumvent the size problem: the first is to use body surface area (BSA), the second is to use ascending/descending aortic diameter (AD/DD) ratios [35]. Significant aortic dilatation is defined by a ratio > 1.5 [13]. All measurements of the aorta should be done at the end of systole [3].

In patients with Turner syndrome, aortic dilatation is present when the maximum aortic diameter is greater than 2.0 cm/m², and at ≥ 2.5 cm/m² there is a high risk of aortic dissection [12, 20] Paediatricians usually adjust aortic diameters to body surface area using Roman nomograms or more recent normative data [37]. The DuBois and DuBois formula is used to estimate the approximate body surface area for adults [14].

Statistically significant relationships between 45,X karyotype and BAV, as well as between 45,X and aortic dilatation, were confirmed in the French cohort study and a more frequent cardiovascular follow-up for patients with X monosomy was strongly recommended [14]. Mortesen et al. did not find a direct influence of karyotype on the diameter of aorta, but it is probably associated with the indirect influence via bicuspid aortic valve and aortic coarctation [48]. High prevalence of BAV and aortic coarctation in a case of missing only the short arm (p) of X chromosome has also been reported [56]. This indicates that haploinsufficiency for Xp genes contributes to abnormal aortic valve and aortic arch development in TS [56].

The main risk factors for increased aortic size in TS are: hypertension, presence of BAV, aortic coarctation, and 45,X karyotype [17, 34, 37, 43, 44, 46, 48]. Hypertension leads to increased risk and progression of aortic dilation [23, 26]: the growth rate of the aorta is about 0.07 to 0.2 cm/y but it can be accelerated by hypertension [28]. Mortesen et al. found even more aggressive aortic growth rates in TS, ranging from 0.20 to 0.38 mm/year [48].

The age-related increase in the aortic root diameter is greater than that seen in normal women, and the optimal time for repeating aortic measurements is not clearly defined yet [11]. However, aortic root dilatation may occur in the absence of risk factors in approximately 5% of females with TS, indicating that all females with TS should be monitored for aortic root dilatation [32, 34, 35, 40].

Thoracic disease guidelines emphasise that all patients with Turner syndrome should undergo imaging of the heart and aorta for evidence of pathological cardiovascular findings. If initial imaging is normal, and there are no risk factors for aortic dissection, repeat imaging should be performed every 5–10 years; if abnormalities exist, an annual follow up is necessary [27]. Despite these guidelines and Turner syndrome clinical practice guidelines that were published in 2007, clinical monitoring for cardiovascular lesions is insufficient, as shown in the French cohort study [14, 57]. This revealed that only 3.5% of patients with TS are being followed in accordance with National Institute of Health recommendations [14].

Aortic dissection in Turner syndrome

According to the 2010 thoracic aortic disease recommendations, TS is considered one of the high risk conditions that cause aortic dissection [27].

The only available epidemiological information on aortic dissections in TS comes from the Danish Registry. The study reported a rate of 78 cases/100,000 years of patient observation for TS versus 1 case/100,000 for the 30- to 40-year-old female population in Denmark [35]. The risk is higher with age and during pregnancy [55].

The average age for dissection within the Danish cohort was 35 years, and 25% had no apparent risk factors for aortic dissection [35]. In contrast, the International Registry of Acute Aortic Dissection found that the mean age of dissection in non-TS women is 68 years [36, 38].

Risk for acute aortic dissection is increased by more than 100-fold in young and middle-aged women with TS [10, 12, 37]. Aortic dissection at a younger age is seen only in patients with connective tissue disorders (Table II) caused by genetic mutations [38].

In TS, aortic dissections predominantly include the ascending aorta (63%), with isolated descending aortic involvement occurring less frequently (37%) [10, 37].

The risk factors for dissection include: hypertension, karyotype 45,X, left-sided obstructive lesions including a bicuspid aortic valve, coarctation and dilated aortic root [10, 17, 38, 48]. The aortic growth rate is considered an additional risk factor for aortic dissection. The longest aortic follow-up study (4.8 years) in TS patients confirms the findings of previous studies about the aggressive nature of aortic disease in TS, with growth rates ranging from 0.20 to 0.38 mm/year [48].

Aortic dissection is the most serious complication in Turner syndrome, but it is has not been granted sufficient consideration. Patients with Turner syndrome should be offered a protocol for clinical follow-up similar to that offered to patients with Marfan syndrome, and each clinic should establish a suitable programme for follow-up [38].

Radiological evaluation of cardiovascular abnormalities in Turner syndrome

Because of the potentially lethal cardiovascular abnormalities, complete cardiac evaluation has been recommended for all patients when TS is diagnosed [3, 45]. Patients with TS should undergo imaging of the heart and aorta looking for possible changes e.g. bicuspid aortic valve, coarctation or dilatation of the aorta [3, 27, 46].

Echocardiography has become the most common imaging test in the evaluation of cardiovascular disease and plays an important role in the diagnosis and follow-up of aortic diseases [39]. Transthoracic echocardiography visualisation can be adequate in many cases under expert cardiologist guidance, but it is not the technique of choice for overall assessment of the aorta; magnetic resonance imaging, which allows better visualisation of thoracic aorta, should be performed instead [6, 12, 39]. Recent guidelines suggest that girls who have only had echocardiography should undergo MRI when old enough to cooperate with personnel during the procedure and then every 5–10 years as adults [3]. Transoesophageal ECHO is too invasive for a screening examination [40], though transthoracic echocardiography visualisation is useful for the diagnosis and follow-up of some segments of the aorta [39, 44]. The value of echocardiography as a screening tool in the TS population may be suboptimal secondary to widespread abnormal chest dimensions, rendering achievement of appropriate echocardiography acoustic windows difficult [37, 44].

Several studies in Denmark, France, the UK and the USA have evaluated the benefits of MRI in aortic dilation diagnosis [40–46, 48]. Despite recent guidelines for monitoring patients with thoracic aorta lesions, the sites of measurements of aorta are not clearly defined [3, 27, 57]. There are eight main positions where aorta measurements are taken, and they have been described in previously mentioned studies [43, 44, 46, 48]: sinotubular junction (pos 1); ascending aorta at the level of the right pulmonary artery (pos 2); ascending aorta proximal to the innominate artery (pos 3); aortic arch midway between the innominate and the left common carotid arteries (pos 4); aortic arch just proximal to the

left subclavian artery (pos 5); the isthmus distally to the left subclavian artery (pos 6); descending aorta at the level between the left pulmonary artery and the top of the left atrium (pos 7); and descending aorta at the most caudal border of the left atrium (pos 8).

One of the largest studies evaluating aortic events in TS was performed by Mortesen et al. in 2013. This was a prospective, long-term (4.8 years) follow-up study. 102 adults with TS were evaluated. MRI was used to identify the changes of aortic diameter. This study showed that CoA, BAV, age, diastolic blood pressure, body surface area and use of antihypertensives were variables that significantly influenced aortic diameter in at least one position. From these findings, the authors generated mathematical models to be used in clinical practice which allow prediction of aortic dimensions and changes in dimensions, taking into account other risk factors. ETA was first described in 2004 in the first MRI study that evaluated the anatomy of thoracic vessels in TS: in women with TS, the most common arterial finding was elongation of the transverse arch (ETA; 42/85, 49%), which was typically described as increased distance between the origins of the left common carotid and the left subclavian arteries [42]. ETA is a clinically silent anomaly and only detectable by MRI. It is seen in almost 50% of women with TS [12]. Elongated transverse aortic arch and aortic coarctation were predominantly found in patients with *45,X* compared to other karyotypes [43].

In summary, ETA is also found to be associated with higher systolic and diastolic blood pressures, *45,X* karyotype, the presence of neck webbing, the presence of left superior vena cava, left subclavian artery dilatation, bicuspid aortic valve, and aortic dilatation [12, 43, 47]. Some data suggests that this pathological finding should be added to the growing list of risk factors for aortic dilation in Turner syndrome [43], but the real meaning of this pathology remains unclear.

The advantages of MRI include the ability not only to identify anatomic variants of aortopathies but also to assess branch artery involvement, and diagnose aortic valve pathology, as well as left ventricular dysfunction without exposing the patient to either radiation or iodinated contrast compared to computed tomographic imaging [27].

A recent study has shown that anatomic assessment of the aortic valve using transthoracic echocardiography might be inadequate: the 208 participants underwent transthoracic echocardiography and MRI evaluation. The frequency of inadequate and discrepant echocardiography studies among the paediatric subjects was 11% and 14% among adults [58].

Generally, MRI is more sensitive than echocardiography in detecting the aortic pathology. Ostberg et al. reported that 16% of women with TS had dilation of aorta in echocardiography. When measured using cardiac MRI, they determined that 33% of TS women had significant dilation [37]. In another study [44], only 35% of the women with TS who were diagnosed with dilation at more than one position by cardiac MRI were identified by echocardiography. In this study, echocardiography was sensitive to severe aortic dilatation (aneurysm) but less sensitive to less progressed dilatation as well as to dilatation at more positions [44]. Dilatation of the aorta, particularly in the descending portion, is not well imaged by echocardiography, and the prevalence of those patients considered to have aortic dilatation is increased using MRI [47].

Monitoring should be undertaken using MRI, the most appropriate modality allowing complete evaluation of the thoracic aorta [40]. MRI can identify aortic root anomalies missed on an echocardiogram [41]. However, transthoracic echocardiography seems to be more sensitive than MRI in detecting valvular pathologies, when assessing aortic valve function [40, 43, 46, 58].

On the other hand, there may be contraindications to MRI use in patients with indwelling metal-containing devices or implants, and it may not be tolerated well by all TS patients due to anxiety that is common in this population [47]. In contrast to MRI, echocardiography is universally accessible, quick, cheap, safe, and never contraindicated [44].

Turner syndrome and pregnancy

Spontaneous pregnancies have been reported in 2% to 5% in TS. Oocyte donation has made it possible for many women with TS to become pregnant [66]. Increasing numbers of women with TS are seeking pregnancy with modern reproductive technologies [57]. However, this population with a high prevalence of cardiac malformations is considered as very high-risk pregnancies [61–64]. The overall risk for major pregnancy complications in TS women is approximately 10% and the risk of maternal death is approximately 3.5% [64]. The risk of aortic dissection is significantly increased during pregnancy, particularly in the third trimester, with mortality from aortic dissection during pregnancy in excess of 100 times the general population risk [57, 65]. The rate of aortic dissections associated with TS pregnancies published in case reports is 4.8% [64]. Recent guidelines recommend a cardiovascular check-up before pregnancy [59]. Aortic diameters above 25 mm/m^2, aortic coarctation, and a history of aortic surgery are considered contraindications to pregnancy [59, 63, 64].

Only one embryo should be transferred in women with TS, to reduce the risk of morbidity and mortality due to twin gestations [62, 64].

PRACE POGLĄDOWE

The first study to clearly show that pregnancies obtained by oocyte donation in TS are very high-risk pregnancies was performed in France. This was a multicentre retrospective study of about 20 years including all French centres that performed oocyte donation. 93 pregnancies with TS were included in analysis and two cases of aortic dissection were reported [63]. Another retrospective cohort study which included 106 women with TS who delivered after oocyte donation was performed in three Nordic countries (Finland, Denmark and Sweden) between 1992 and 2011. Potentially life-threatening complications occurred in 3.3% of pregnancies. The main finding in this large Nordic collaborative study was that the pregnancies among women with TS carry a substantial risk, particularly for hypertensive disorders [60].

During pregnancy, women with TS should be closely followed by a multidisciplinary team of specialists in maternal-foetal medicine, cardiology, and endocrinology [65]. With appropriate screening and follow-up, the risk of cardiac complications is reduced during pregnancy and delivery [61].

Delayed diagnosis of Turner syndrome

Early diagnosis of TS improves outcomes of numerous health problems [55].

TS diagnosis can be established at birth or in early childhood, if lymphedema and webbed neck appears, but some postnatal diagnoses may be delayed for years, with 38% being diagnosed in adulthood [5, 7, 8]. The condition may be diagnosed fairly early if growth failure or delayed puberty occurs. Unfortunately a lot of patients are lost during the transition period [8].

Recent guidelines recommend that karyotype analysis should be performed in all girls with short stature, delayed puberty, webbed neck, lymphedema, and CoA. However, karyotype screening of all girls who have CoA for possible Turner syndrome has not been reported [55].

A study assessing the prevalence of Turner syndrome in girls presenting with coarctation of the aorta has been done. A large cohort (132 girls) has been evaluated. It found that 5.3% of girls presenting with CoA had Turner syndrome confirmed by karyotyping analysis [55].

Failure to diagnose TS is highly unfortunate because morbidity and mortality are higher than in the general population [2, 10]. In TS, cardiovascular morbidity and mortality are attributed to: congenital heart disease (SMR, 20.7), aortic dilation and dissection (SMR, 23.6), ischaemic heart disease (SMR, 2.8), and cerebrovascular disease (SMR, 3.9). All-cause mortality is raised in *45,X* compared to mosaic karyotypes [10].

Early diagnosis of Turner syndrome would improve the outcomes of numerous health problems, including growth failure, autoimmune and inflammatory disease, possible gonadal malignancy, and psychological problems [55].

Treatment options for patients with TS

Basic medical treatment recommendations for patients with thoracic aortic disease were provided in guidelines issued in 2010: strict control of hypertension, optimisation of lipid profile, smoking cessation, and other atherosclerosis risk-reduction. Antihypertensive therapy should be administered to hypertensive patients with thoracic aortic diseases to achieve a goal of less than 140/90 mm Hg (patients without diabetes) or less than 130/80 mm Hg (patients with diabetes or chronic renal disease) [27, 35].

There are no evidence-based recommendations for the treatment of TS patients with aortic dilatation. In the absence of such evidence, it may be helpful to borrow from the successful experience in treating patients with Marfan syndrome [34, 37]. Beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers [35] are considered first line therapy for patients with Marfan syndrome because of the reduction in the rate of aortic dilatation [27, 35].

In a small cohort study, the use of ARB therapy in patients with Marfan syndrome significantly slowed the rate of progressive aortic-root dilation [52]. If strong evidence of treatment benefit for angiotensin receptor blockers in patients with Marfan syndrome can be obtained, the natural history of Marfan syndrome and aortic aneurysms due to another aetiology may change dramatically in future [53]. RAS blockers are promising new tools in treating other thoracic aortic diseases [54].

Careful handling of the obesity and metabolic disease that are common in TS may also improve aortic outcomes. Hypertension management is crucial in avoiding the progression of dilation, but drug trials are lacking in TS [48].

Numerous observational, retrospective and interventional studies in recent years, as well as those using animal models, have supported the hypothesis that sex hormone replacement therapy exerts important beneficial effects on heart disease, diabetes and obesity in TS patients [18]. Oestrogen replacement therapy appears to reduce central arterial stiffness, improve endothelial function, and decrease carotid intima media thickness in short-term studies in TS [10].

There are concerns that recombinant human growth hormone (GH) treatment therapy could induce unfavourable aortic wall changes and may increase the risk for aortal lesions, including aortic dissection and

rupture [10, 49]. Outcomes of studies to date have been controversial, as animal and human cell models have shown that GH may directly influence homeostasis within the media layer of the aortic wall [10], while reports on GH treatment in Turner syndrome show no effect on aortic or ventricular size when the data is adjusted for height or BSA [34].

One of the studies [50] compared aortic diameters in GH treated and untreated girls with TS. Both ascending and descending aortic diameters were increased in GH-treated individuals, but multivariate analysis indicated that this increase was explained by an increase in height without evidence for any additional impact of GH treatment of cardiovascular system. Another study [51] reported that GH treatment of girls with TS increases stature but does not disproportionately affect cardiac dimensions. Adjusting for their larger body size, there were no significant differences in cardiac dimensions in the two groups. There is some data about the positive affect of reductase inhibitors (statins).

They stop the progression of aortic aneurysms by reducing the inflammation in the arterial wall [29].

There is a lack of evidence-based guidelines on monitoring and interventions for dilated aorta in TS [48], just as there is no clear evidence that would help to define precise timings for medical or surgical intervention in TS patients [44].

Management and follow up are areas that remain poorly developed in TS, and require further research and more careful monitoring.

Conclusion

Despite the high prevalence of cardiovascular pathology affecting young women with TS, management of this disorder is still a challenge. The aetiology of aortic lesions remains poorly understood; the genetic background has been considered in recent studies, but evidence is inconsistent. Diagnosis of TS is quite often delayed and this can have serious medical consequences. Careful follow up using modern techniques such as MRI for cardiovascular screening is necessary, but usually this is still not considered in clinical practice. Pregnancy is much more common these days in women with TS. This condition requires extremely close monitoring, but experience for follow-up is insufficient. As of yet, no agreement on the best time for medical or surgical intervention in TS patients has been established.

In conclusion, there are numerous areas of uncertainty in the management of Turner syndrome, and more careful monitoring for cardiovascular pathology in young women with Turner syndrome must be done.

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