

# ASSOCIATIONS OF VASCULAR BIOMARKERS AND THE SOMATOTROPHIC AXIS WITH CAROTID ULTRASOUND AND ECHOCARDIOGRAPHY FINDINGS IN RELATION TO TURNER ARTERIOPATHY

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## Introduction

Turner Syndrome (TS) is associated with a range of comorbidities involving the cardiovascular system. The existence and degree of arteriopathy in the young TS population, along with factors associated with the ontogeny of arteriopathy remain unknown.

## Objectives

To assess arterial stiffness in uncomplicated, young normotensive TS patients who have no structural heart and major vessel disease. The secondary aim was to investigate associations of vascular biomarkers, growth hormone (GH) therapy status, and/or oestrogen exposure with arterial stiffness in TS.

## Subjects and Methods

Sixty-one patients with karyotype proven TS (mean age: 12.6 years, range: 6.6-27.3 years) and body surface area (BSA) matched 34 healthy peers were compared with respect to several arterial stiffness indexes (ASIs), and left heart size using carotid ultrasound and echocardiography. Several vascular biomarkers, GH therapy, and oestrogen exposure were investigated for potential associations with arterial stiffness after adjusting for potentially confounding covariates such as age, pubertal status, body mass index, ambulatory hypertension, percent nocturnal dipping, homeostasis model assessment-insulin resistance, and dyslipidemia. SPSS 17 package programme was used for statistical analyses. Statistical significance was set at  $p < 0.01$  in association analyses to account for multi-testing. Otherwise,  $p < 0.05$  was considered significant.

Table 1. Demographic and clinical characteristics in age- and body surface area- matched patients with Turner syndrome vs. controls

	TS (n=61)	Controls (n=34)	P
Age (years), mean (range)	12.6 (6.6-21.3)	12.0 (6.0-22.7)	0.22
Family history of diabetes (%)	16 (26.2 %)	7 (20.6 %)	0.62
Family history of coronary arterial disease (%)	13 (21.3 %)	5 (14.7 %)	0.59
Birth weight SDS	-1.1 (-1.4-(-0.7))	-0.2 (-0.7-0.2)	<b>&lt; 0.0001*</b>
<b>Anthropometric measurements (SDS)</b>			
Height	-2.7 (-3.1-(-2.2))	-0.2 (-0.6-0.1)	<b>&lt; 0.0001*</b>
Weight	-1.4 (-1.8-(-1.0))	0.1 (-0.2-0.4)	<b>&lt; 0.0001*</b>
Body mass index	0.5 (0.1-0.8)	0.0 (-0.3-0.2)	<b>0.015*</b>
Waist circumference	0.6 (0.4-0.9)	0.1 (-0.2-0.4)	<b>0.009*</b>
Body surface area (m <sup>2</sup> )	1.19 (1.11-1.27)	1.22 (1.13-1.30)	0.70
<b>Tanner stage for breast development n (%)</b>			
1	28 (45.9)	13 (38.2)	<b>0.005*</b>
2	25 (41.0)	5 (14.7)	
3-5	8 (13.1)	16 (47.1)	
<b>24-h ambulatory blood pressure</b>			
24-h Systolic Blood Pressure (SBP) SDS	0.1 (-0.1-0.2)	-0.1 (-0.3-0.1)	0.25
24-h Diastolic Blood Pressure (DBP) SDS	0.2 (0.0-0.3)	0.0 (-0.1-0.1)	0.11
<b>Nocturnal dipping</b>			
SBP (%)	11.2 [10.6-13.8]	12.0 [11.0-15.4]	0.16
DBP (%)	13.7 (13.2-14.2)	14.6 (13.8-15.5)	0.052

Table 2. Biochemical and hormonal characteristics in patients with TS vs. controls

	TS (n= 61)	Controls (n=34)	p
Oestradiol, pmol/l	45.5 [19.5-98.7]	61.7 [23.9-303.6]	0.057
<b>Insulin Resistance (IR)</b>			
Glucose, mmol/l	4.8 (4.7-4.9)	4.7 (4.6-4.9)	0.20
Insulin, pmol/l	47.4 [25.2-69.0]	36.0 [29.4-56.4]	0.30
HOMA-IR	1.6 [0.9-2.2]	1.2 [1.0-1.8]	0.18
<b>Plasma lipids</b>			
Total cholesterol, mmol/l	4.4 [3.9-4.9]	4.0 [4.0-4.7]	0.38
HDL-C, mmol/l	1.5 [1.3-1.8]	1.3 [1.2-1.6]	<b>0.033*</b>
LDL-C, mmol/l	2.6 [2.2-2.8]	2.4 [2.0-2.6]	0.12
Triglycerides, mmol/l	0.9 [0.7-1.4]	0.9 [0.8-1.0]	0.20
<b>GH-IGF-1 axis</b>			
IGF-1 SDS	0.9 [-0.8-1.8]	0.0 [-0.8-0.9]	0.06
IGFBP-3 SDS	0.84 [-0.34-1.33]	0.87 [-0.13-1.30]	0.81
<b>Biomarker panel</b>			
hs-CRP, mg/l	0.50 [0.30-1.80]	0.25 [0.12-0.93]	<b>0.039*</b>
BNP, ng/l	367 [85-632]	22 [11-57]	<b>&lt;0.0001*</b>
ANP, pmol/l	8.1 [1.6-62.0]	3.2 [1.6-8.4]	<b>0.035*</b>
Aldosterone, pmol/l	611 [317-964]	481 [278-603]	0.16
PRA, ng/ml/h	3.8 [2.3-6.1]	3.2 [2.4-4.7]	0.15
Aldosterone/PRA	5.61 [2.68-10.10]	5.67 [4.21-6.70]	0.76

The results are presented as mean (95 % confidence interval) or median [25%-75% interquartile range]. HOMA-IR= homeostasis model assessment-insulin resistance; HDL-C= high density lipoprotein-cholesterol; LDL-C= low density lipoprotein-cholesterol; IGF-1= insulin like growth factor-1; IGFBP-3= IGF binding protein-3; hsCRP= high sensitivity C-reactive protein; BNP= B-type natriuretic peptide; ANP= Atrial natriuretic peptide; PRA= plasma renin activity. \* $p < 0.05$  is statistically significant.

Table 3. Associations of individual biomarkers and of insulin-like growth factor-1 with measures of arterial stiffness and left ventricular mass in patients with Turner syndrome

Characteristics and Biomarkers†	Model R <sup>2</sup>	Global P*	β‡	p
<b>Carotid ultrasound</b>				
Carotid intima media thickness SDS	0.668	<0.0001	....	....
B-type natriuretic peptide (BNP)	....	....	1.68 ± 0.65	<b>0.005</b>
Atrial NP (ANP)	....	....	1.23 ± 0.51	0.022
IGF-1 SDS	....	....	0.81 ± 0.20	<b>0.001</b>
<b>β-index SDS</b>				
BNP	0.557	<0.0001	0.62 ± 0.21	<b>0.008</b>
High sensitivity-C reactive protein (hs-CRP)	....	....	0.09 ± 0.04	0.03
<b>Incremental modulus of elasticity SDS</b>				
BNP	0.274	0.001	0.39 ± 0.17	<b>0.01</b>
hs-CRP	....	....	0.10 ± 0.04	0.027
<b>Distensibility coefficient SDS</b>				
BNP	0.200	0.01	-0.53 ± 0.31	<b>0.009</b>
hs-CRP	....	....	-0.16 ± 0.05	<b>0.004</b>
<b>Echocardiography</b>				
<b>Left ventricle mass (ml/m<sup>2</sup>)</b>				
BNP	....	....	8.61 ± 3.63	0.023
IGF-1 SDS	....	....	3.61 ± 1.49	0.020

\*A test of whether any of the biomarkers and IGF-1 SDS differed with respect to arterial stiffness associated measures and echocardiography findings. Covariates in the multivariable models included age, obesity, pubertal status, dyslipidemia, insulin resistance.

†For carotid ultrasound and echocardiography measures with a global  $p < 0.01$ , individual biomarkers and IGF-1 SDS related ( $p < 0.05$ ) to vascular function and left ventricular volume measures after backward elimination are displayed.

‡β, the regression coefficient shows a change in carotid ultrasound or echocardiography related measure per 1 SD increment in log marker.

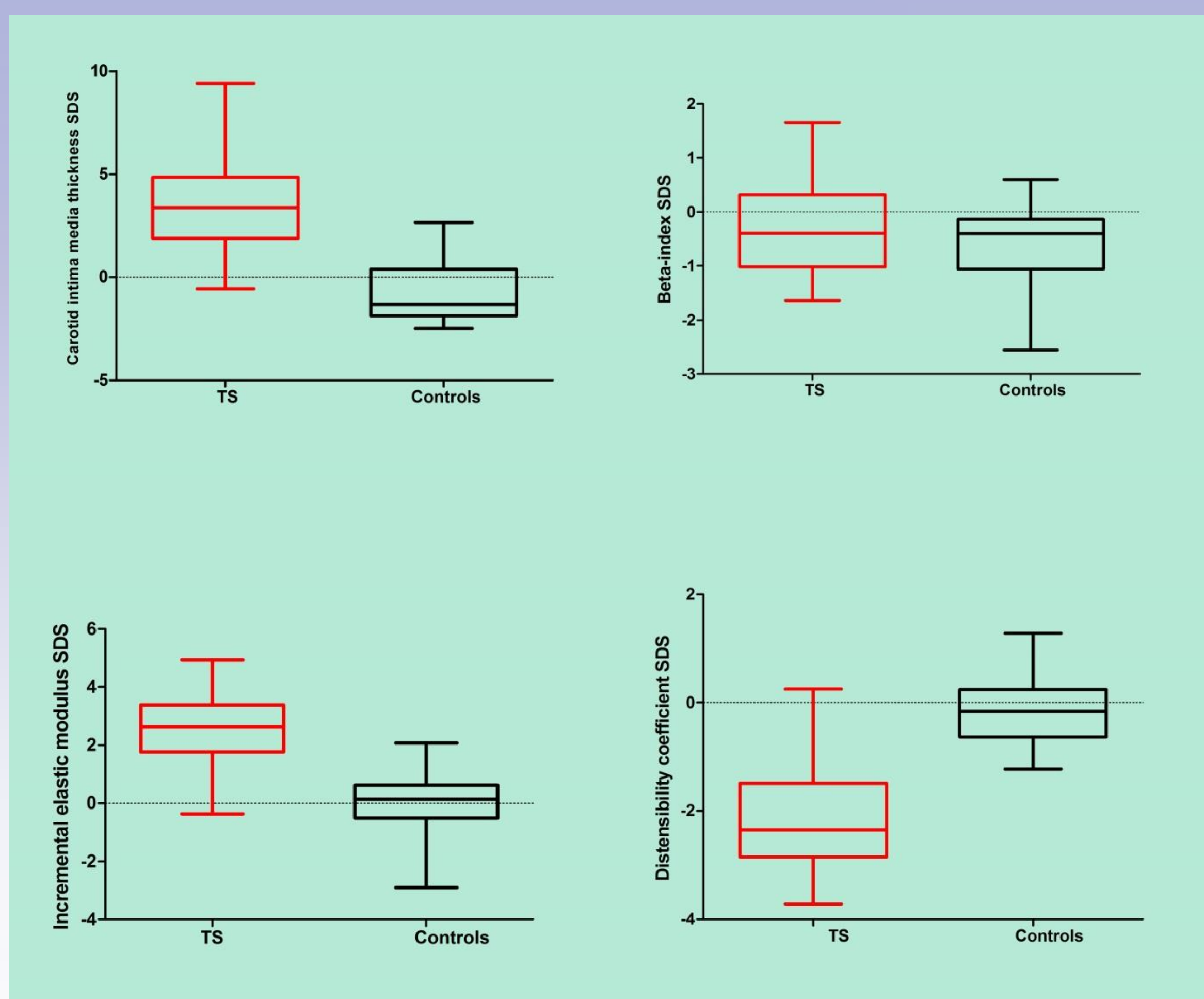


Figure 1. Comparison of carotid intima media thickness, Beta-index, incremental elastic modulus and distensibility coefficient SDSs in patients with Turner syndrome (TS) vs. controls. The whiskers indicate the maximum and minimum values.  $P < 0.01$  for all the between-group comparisons.

## Results

Carotid intima media thickness SDS, beta-index SDS, incremental modulus of elasticity SDS were higher, and distensibility coefficient SDS was lower in TS patients. BSA adjusted left ventricle mass and left atrial size were higher in TS (data not shown). ASIs were similar in TS patients who were receiving GH for  $< 2$  years ( $n=12$ ) vs. for  $> 2$  years ( $n=21$ ), and non-significant findings were retrieved when oestrogen naive ( $n=35$ ) and oestrogen exposed ( $n=26$ ) patients were compared.

## Conclusions

- ✓ Arterial stiffness is increased in young normotensive TS patients.
- ✓ B-type natriuretic peptide, and to a variable extent, hsCRP and IGF-1 are associated with arterial stiffness.