HHS Public Access

Author manuscript

Genet Med. Author manuscript; available in PMC 2018 April 04.

Published in final edited form as:

Genet Med. 2018 June ; 20(6): 664–668. doi:10.1038/gim.2017.149.

Coronary Calcification in Adults with Turner Syndrome

Marissa Schoepp[1], **Fady Hannah-Shmouni, MD, FRCPC**[2], **Jatin Matta, PA**[1], **Ahmed M. Ghanem, PhD**[1], **John A. Hanover, PhD**[3], **Khaled Z. Abd-Elmoniem, PhD**[1,*], and **Ahmed M. Gharib, MD**[1]

[1]Biomedical and Metabolic Imaging Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), Bethesda, MD, USA

[2]Section on Genetics & Endocrinology (SEGEN), National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, MD, USA

[3]Laboratory of Cell and Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, USA

Abstract

Purpose—Adults with Turner syndrome (TS) have an increased predisposition to ischemic heart disease. The quantitative relationship between coronary atherosclerosis and TS has yet to be established.

Methods—128 females (62 with TS) participated in this prospective study. Coronary computed tomography angiography (CTA) was performed to measure coronary calcified plaque burden, and prevalent non-calcified plaque burden. Regression analysis was used to study the effects of TS and traditional cardiovascular disease risk factors on coronary plaque burden.

Results—Adults with TS were 63% more likely to have coronary calcifications than controls (odds ratio (OR) 1.63, 95% confidence interval (CI): 1.02, 2.61, P=0.04), with an age cutoff of 51.7 years for a probability of >50% for the presence of coronary calcifications when compared to 55.7 years in female controls. The average age of TS and calcified plaques was significantly lower than controls (51.5±8.9 years vs. 60.5 ±7.0 years, P<0.001). Age increased the likelihood of coronary calcifications by 13% per year (OR 1.13, CI 95%: 1.07–1.19, P<0.001).

Conclusion—This study demonstrates a higher prevalence and earlier onset of calcified coronary plaques in TS. These findings have important implications for cardiovascular risk assessment and the management of patients with TS.

*Correspondence: Khaled Z. Abd-Elmoniem, PhD, National Institutes of Health, Bldg.10, Rm.3-5340, MSC 1263, 10 Center Drive, Bethesda, MD 20892,USA., Tel.: +1 301 451 8982, Fax: +1 301 496 9933, abdelmoniemkz@mail.nih.gov.

DISCLOSURES

The authors report no relevant disclosures.

INTRODUCTION

Turner syndrome (TS) is one of the most common chromosomal disorders in females, characterized by partial or complete loss (monosomy) of one of the X chromosomes. This condition results in approximately 50 TS per 100,000 females births.[1, 2] Patients manifest a broad phenotypic spectrum, including short stature, premature ovarian failure, and a variety of congenital anomalies. The most common congenital heart disease include aortic coarctation and bicuspid aortic valves.[3, 4] In addition, patients with TS are at an increased predisposition for hypertension, dyslipidemia, obesity, diabetes mellitus, and vasculopathy [3–6].

Cardiovascular disease, including ischemic heart disease (IHD), is the leading cause of death in women. Females with premature ovarian insufficiency (estrogen deficiency) present an increased risk for cardiovascular disease, likely due to an earlier onset of vascular endothelial dysfunction. Additional causative mechanisms of IHD in TS may include multivessel atherosclerosis, embolism from intracardiac thrombus, vascular endothelial dysfunction, and coronary artery involvement in aortic dissection.[7] Vascular malformations, particularly aortic aneurysm (SMR 23.6, 95% confidence interval (CI); 13.8–37), account for the majority of cardiovascular related deaths (~ 41%) in TS.[2] However, the mortality from coronary artery disease (CAD) is also increased in TS (standardized mortality ratio (SMR) 3.47, confidence interval (CI) 2.06–5.48).[1] This highlights the need for early identification and quantification of CAD in this population.

Evaluating the amount of atherosclerotic disease in the coronary arteries (CAD) helps predict cardiovascular morbidity and mortality in the general population.[8–11] Atherosclerotic plaque burden can be reliably quantified in coronary computed tomography angiography (CTA) using several anatomic scores. These coronary plaque burden scores include; Agatston calcium score (CaS), segment involvement score (SIS), stenosis severity score (SSS), and segment volume score (SVS).[8–11] While CaS measures only the amount of coronary calcification, the other measures (SIS, SSS and SVS) include the non-calcified form of atherosclerotic plaques and account for their numbers, degree of stenosis and volumes, respectively. Hence, such comprehensive CTA based scores serve as noninvasive surrogates for overall coronary atherosclerotic burden, and are predictive for future adverse cardiac events.[8–11] Despite the implications of premature coronary atherosclerosis in TS,[1, 12] CTA use has been limited to the assessment of coronary anomalies for this population.[13, 14] No prior studies have investigated the magnitude of CTA coronary plaque burden scores in asymptomatic adults with TS. In this study, we demonstrate the extent of coronary atherosclerosis plaque burden and the average age of involvement in TS when compared to female controls.

MATERIALS AND METHODS

A total of 128 women participated in this study. TS (n=62) were non-mosaic 45X and all subjects were adults, asymptomatic and without known history of CAD. All TS subject were participants of a prospective observational study (ClinicalTrials.gov identifier: NCT00006334). Control volunteers were recruited under protocol NCT01399385. All

subjects gave written informed consent. Body mass index (BMI) and Framingham Risk Score (FrS) was calculated for each group. CTA images were acquired using multi-detector computed tomography (CT) as previously described.[14–16] Briefly, CaS was obtained without contrast,[10] then followed by CTA using intravascular contrast. Axial, multi-planar reformatted coronary images were obtained using a 3-dimentional-software tool (Virtual Place; AZE, Tokyo, Japan), which has been previously validated for assessment of the coronary arteries.[14, 15]

In each of the 16 coronary segments, three plaque characteristics were recorded: (A) presence of plaque (no=0, yes=1), (B) plaque luminal diameter stenosis severity (none: 0% luminal stenosis=0, mild: 1–49% luminal stenosis=1, moderate: 50–69% luminal stenosis=2, or severe: >70% luminal stenosis=3), and (C) plaque volume (none =0, small/trace =1, mild=2, moderate=3, large=4).[9, 11] To quantify the complete plaque burden for each subject, three scores were calculated based on CTA data (SIS, SSS, and SVS). SIS was calculated as the total number of coronary artery segments exhibiting plaque (minimum=0; maximum=16); SSS was the sum of all the stenosis scores of individual segments (minimum=0; maximum=48), a measure of the subject's overall plaque extent into coronary lumen;[11] and SVS was the sum of plaque volume scores of all the individual segments (minimum=0; maximum=64), a measure of the subject's total plaque volume along the coronary vasculature.[9, 11] In addition to the continuous quantification of calcium (CaS),[10] the presence or absence of calcified plaques was further quantified (CaP, no=0, yes=1). The presence of bicuspid aortic valve (BAV), aortic coarctation (ACo) and ascending aortic dilation (defined as body surface area (BSA) corrected aortic diameter; aortic size index (AI) >2cm/m^2)[17] were recorded for patients with TS.

We used a generalized linear model with binomial distribution and logit link function to evaluate the associations between atherosclerotic plaque scores (SIS, SSS, and SVS), CaS, CaP, and cardiovascular risk factors. Univariable and multivariable generalized linear regression analyses were used to determine the association of TS status, cardiovascular risk factors and each coronary plaque burden score. Final models of the continuous scores (SIS, SSS, and SVS) were represented by predictors' coefficient values and standard error (SE). Final models of the binary scores (CaS, CaP, SIS >5, and SSS>5) were represented by the predictors' coefficients (SE), odds ratio (OR) and CI. $P \leq 0.05$ were considered statistically significant. A subset of TS with BAV, ACo and dilated aorta (AI>2cm/m^2) was compared with TS without these conditions using Analysis of Covariance (ANCOVA) and Fisher tests.

RESULTS

Table 1 summarizes the baseline demographic, laboratory and imaging characteristics of the entire cohort. Age, BMI, hypertension and FrS were similar in the two groups. The control group had a higher percentage of African American subjects and participants with a history of smoking. For the entire cohort, age was the only common independent predictor for plaque burden and calcification in the final multivariable regression analysis. Moreover, African American ethnicity was associated with a significantly increased SSS ($P<0.05$) and SVS ($P=0.008$) for plaque burden scores.

Participants with TS were more likely to have coronary calcifications than controls (OR 1.63, 95% CI: 1.02, 2.61, P=0.04; Figure 1A). After adjusting for age and FrS, the probability of >50% coronary calcification was at age 51.7 years for TS when compared with 55.7 years for female controls (Figure 1A and B). The average age of TS with calcified plaques was significantly lower than controls (51.5±9.0 years vs. 60.5±7.0 years, P<0.001; Figure 1C). Age was the strongest variable associated with severe plaque burden using SIS> 5 in TS (OR 1.07, 95% CI: 1.03–1.11, P<0.001). Aortic dilation was present in 39% (24/62) of patients with TS. Compared to TS without aortic dilation, after adjusting for age, this subset of patients demonstrated a higher prevalence of coronary calcifications (67% vs 21%) and calcium score (median 48.9 vs 0) (P<0.05). A sensitivity analysis, including FrS to the list of potential predictors, showed similar results (data not shown).

DISCUSSION

This study demonstrates a significant age-dependent difference in coronary atherosclerosis in TS using several CTA based plaque burden scores. These scores serve as validated surrogates for overall atherosclerotic burden in coronary arteries and are predictive for future adverse cardiac events.[8–11] This study shows that when matched for age, BMI, and FrS, adults with TS have a greater burden of coronary atherosclerosis and are younger when compared to controls (51.6 ±8.8 years vs. 60.4 ±7.0 years, P<0.001). African American subjects were underrepresented in the TS group, as is the case in many studies related to TS. However, race was included in the statistical models and was not an independent predictor for the presence of coronary calcium (CaP). The association between TS and CaP was also independent of the other known cardiac risk factors. This is in keeping with the notion that adults with TS are at an increased risk for cardiovascular disease, which is also likely exacerbated by their increased predisposition for hypertension, obesity, diabetes mellitus,[3] dyslipidemia,[6] and vasculopathy[5]. Thus, a careful cardiovascular risk assessment in these patients is required to prevent future adverse cardiovascular events.

Despite the increased awareness of increased mortality in TS from IHD and CAD,[1, 2, 4, 12] a quantitative and qualitative (calcified vs non-calcified) examination of the coronary atherosclerotic burden in TS have not been fully elucidated. Chromosomal abnormalities, including monosomy X, have been implicated in the development of cardiac calcifications[18] and altered immune activation,[19] and thereby, possibly affecting the natural progression of CAD. This might explain, in part, our observation of an earlier age of onset of coronary calcification in TS compared to controls in the absence of a significant difference in overall coronary plaque burden measures (i.e. SIS, SSS, SVS).

The development of coronary calcium in adults with TS might be linked to other vascular abnormalities, such as BAV, ACo or aortic dilation, seen in TS. Indeed, this was verified in the subset analysis of patients with TS and aortic dilation (AI>2cm/m^2), who demonstrated a significantly higher prevalence of coronary calcifications (CaP) and calcium score (CaS) when compared to patients with TS and normal AI after adjusting for age. Individuals with TS have estrogen deficiency, which contributes to intimal thickening, decreased production of nitrogen oxide in the vasculature, and increased levels of plasma lipoproteins, which are atherogenic.[5, 6] Estrogen and progestogen therapy has been shown to reduce intimal

thickening and increase high-density lipoproteins (HDL) cholesterol levels,[20] which brings to question as to whether elevations in HDL will help decrease cardiac events in TS, albeit conjecture. Thus, further studies are needed to assess the effects of hormone replacement therapy on the cardiovascular system in TS.

These results have beneficial implications and may guide clinical screening and counseling of adults with TS for cardiovascular disease. Our results indicate that patients with TS have a greater burden of coronary calcifications and are younger when compared to controls, which argue for heightened cardiovascular assessment using CTA in this population, especially since the typical symptoms of CAD may not be present. Moreover, CTA measurements may be considered as a valuable clinical parameter in addition to the recommended usual care for TS. Although CT is mentioned in these recommendations for aortic evaluation in TS, there tends to be a biased towards Magnetic Resonance and/or echocardiogram imaging as first line, primarily to avoid radiation exposure, with the drawback of not assessing the coronary vasculature.[4] In particular, patients with TS who exhibit aortic dilation (AI>2cm/m^2) on these modalities might benefit from CTA for coronary plaque burden measurements that may alter a patient's clinical course. Thus, these findings may modify cardiovascular risk assessment and management of patients with TS.

Our study has several limitations. First, phenotypic analysis of TS due to other genetic defects, such as mosaicism, deletions, or X chromosome parental origin was not available for analysis. Second, this pilot study was designed to characterize the burden of coronary atherosclerosis in TS in comparison to controls and in relation to traditional coronary artery atherosclerosis risk factors (such as age, Framingham risk score, dyslipidemia, etc). The current data set is not sufficient to perform a specific analysis unique to TS, such as duration of hypertension and dosage or duration of oral hormone replacement therapy, without compromising the statistical integrity. Thus, further studies with a larger cohort of patients with TS are necessary to achieve a statistical power that will establish causality. Third, African Americans with TS were underrepresented and larger studies are required to address this ethnic gap. Our findings support the use of CT as a modality for cardiovascular risk evaluation of patients with TS, as endorsed for the general population by the 2013 ACC/AHA.[8]

In conclusion, this study demonstrates that adults with TS have a higher prevalence and earlier onset of calcified coronary atherosclerosis than controls. Additionally, TS with aortic dilation have a higher prevalence of coronary calcifications and calcium score than TS with normal AI. The increased coronary calcifications might have predictive value in studying the cardiovascular risk assessment, managing, implementing early lifestyle changes and counseling for TS. Further studies with larger TS numbers are needed to better understand the effects of specific factors related to this population (e.g. genotype and hormone replacement therapy) on CAD.

Acknowledgments

This work was supported by the Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human

Development (NICHD). In memory of Dr. Carolyn Bondy who supported this research effort and dedicated her professional career for caring after patients with TS.

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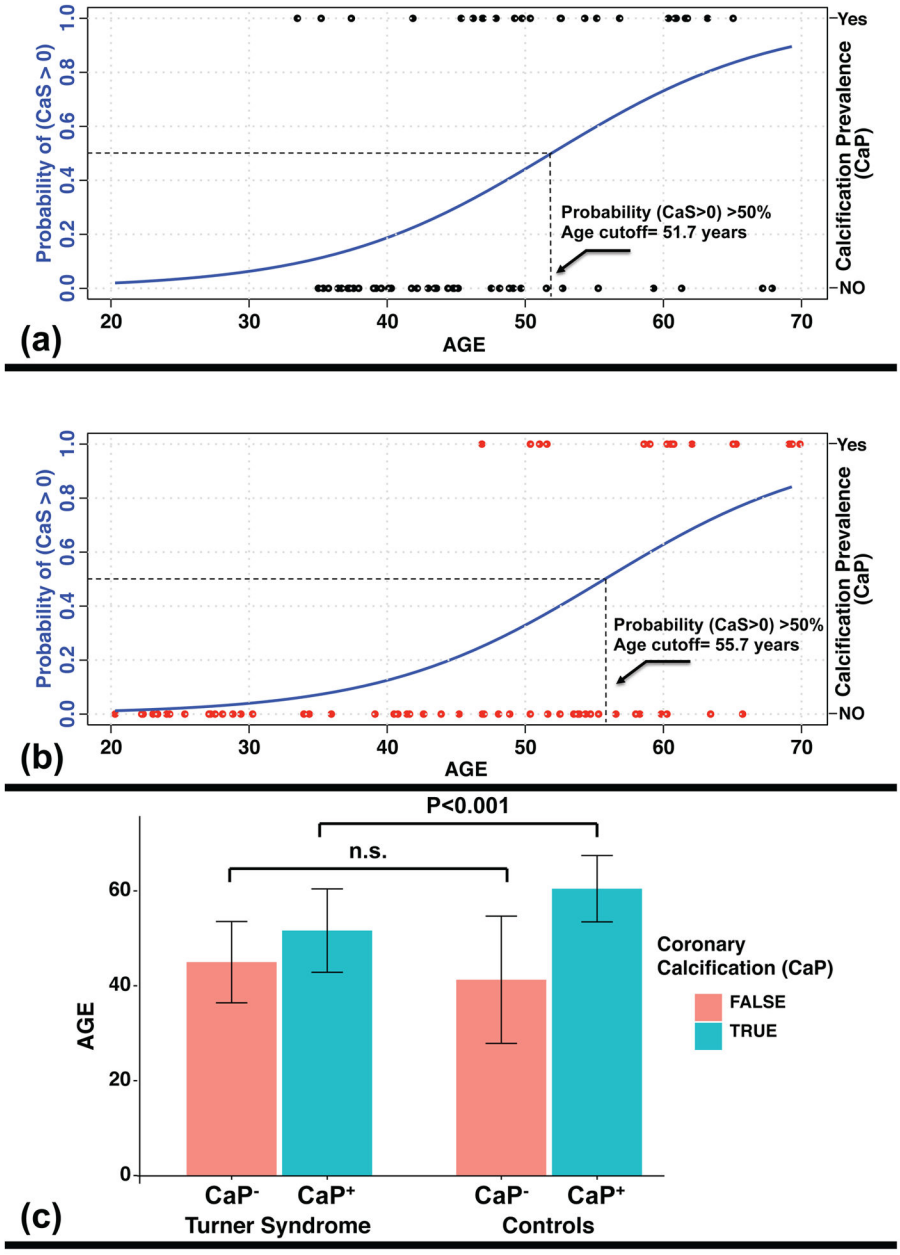

Figure 1.

Predictive probability curves after adjusting for age and Framingham Risk Score. The probability of >50% coronary calcifications were at age 51.7 years for patients with Turner syndrome when compared with 55.7 years for female controls (Figure 1A and B). The average age of patients with Turner syndrome and calcified plaques was significantly lower than controls (Figure 1C).

Table 1

Descriptive data in the Turner syndrome and control groups.

Parameters	All Subjects N=128	Turner syndrome N=62 (48.4%)	Controls N=66 (51.6%)	*P*-Value
Physical examination and demographic data				
Age (years)	46.90±12.34	47.33±9.23	46.50±14.73	0.873
Body mass index, BMI (kg/m^2)	27.82±7.34	28.67±8.69	27.01±5.75	0.734
Systolic blood pressure (mm Hg)	121.80±15.93	120.77±17.68	122.76±14.16	0.238
Triglycerides (mg/dL)	112.97±66.76	116.23±73.69	109.91±59.94	0.610
LDL cholesterol (mg/dL)	103.44±32.00	95.56±31.24	110.83±31.15	0.522
HDL cholesterol (mg/dL)	59.63±17.46	60.92±20.36	58.41±14.26	0.865
Total cholesterol (mg/dL)	186.96±34.74	183.61±34.87	190.11±34.60	0.905
Framingham Risk Score (FrS)	1.36±1.79	1.05±1.35	1.65±2.10	0.952
Race, N (%)				
Caucasian	88 (68.8%)	52 (83.9%)	36 (54.5%)	0.002
African American	26 (20.3%)	6 (9.7%)	20 (30.3%)	
Other	14 (10.9%)	4 (6.5%)	10 (15.2%)	
Medical history, N (%)				
Hypertension	52 (40.6%)	30 (48.4%)	22 (33.3%)	0.106
History of smoking	23 (18.0%)	6 (9.7%)	17 (25.8%)	0.022
Dyslipidemia[a]	56 (43.8%)	24 (38.7%)	32 (48.5%)	0.289
Bicuspid aortic valve	15 (11.7%)	15 (24.2%)	0 (0.0%)	<0.001
Coarctation of aorta	7 (5.5%)	7 (11.3%)	0 (0.0%)	<0.001
Coronary imaging measurements[b]				
Calcified plaque (CaP), N (%)	42 (32.8%)	24 (38.7%)	18 (27.3%)	0.191
Calcium score (CaC, Agatston units)*	0 (0–11.75)	0 (0–32.75)	0 (0–0.875)	0.502
Segment Involvement Score (SIS)*	4.5 (2.2–7)	4 (1.8–7)	5 (3–8)	0.960
SIS>5, N (%)	44 (34.4%)	19 (30.6%)	25 (37.9%)	0.458
Segment Stenosis Score (SSS)*	7 (2–12)	7.5 (2–14)	6 (2–12)	0.539
SSS>5, N (%)	71 (55.5%)	37 (59.7%)	34 (51.5%)	0.378
Segment Volume Score (SVS)*	5 (3–8)	5 (1.8–7.2)	5 (3–9)	0.912

[a]Serum lipids were measured in a morning fasting blood sample. Dyslipidemia was defined as any of the following abnormalities: total cholesterol >200mg/dL, low-density lipoprotein (LDL) >160mg/dL, high-density lipoprotein (HDL) <40 mg/dL, or triglyceride >150mg/dL.

[b]Data are represented as means ± standard deviations, except for * which are represented as medians, with interquartile ranges in parentheses.