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ORIGINAL ARTICLE

Osteoprotegerin in Turner syndrome – relationship to aortic diameter

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Summary

Background Cardiovascular disease is a cardinal trait of Turner syndrome (TS), causing half of the threefold excess mortality. As osteoprotegerin (OPG) is a potential biomarker of cardiovascular disease, this cross-sectional and prospective study aimed at elucidating OPG levels in TS and its relationship to aortic diameter as well as validated cardiovascular risk markers.

Methods Adult women with TS ($n = 99$) were examined thrice (mean follow-up 4·7 ± 0·5 years), and 68 age-matched healthy female controls were examined once. Aortic diameter was assessed by cardiovascular magnetic resonance. Twenty-four-hours blood pressure monitoring and biochemical assessments were also performed.

Results Osteoprotegerin levels (median with range) were lower in TS (777 [326–10 569] ng/l) compared with controls (979 [398–1987] ng/l; $P < 0·05$) and did not change during follow-up. The OPG concentration was higher among women with TS older than 50 years of age (996 [542–4996] *vs* 756 [326–10 569] ng/l; $P < 0·05$) with a trend towards a higher OPG in TS who were on antihypertensive medication (938 [490–2638] *vs* 752 [326–10 569] ng/l; $P = 0·09$). Contrary to controls, OPG levels correlated with BSA-indexed aortic diameter ($r = 0·31$–$0·45$; $P < 0·05$), age ($r = 0·29$; $P < 0·05$) and high-sensitivity C-reactive protein ($r = 0·23$; $P = 0·02$) and inversely with BSA ($r = -0·20$; $P < 0·05$), weight ($r = -0·23$; $P < 0·05$) and plasma oestradiol levels ($r = -0·34$; $P < 0·05$).

Conclusion Levels of OPG are lower in TS and correlate with aortic diameter, age, BSA, weight and oestradiol in TS, but not controls. Future studies are needed to assess whether OPG may serve as a biomarker of aortic or cardiovascular disease in TS.

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Introduction

Cardiovascular disease causes half of the threefold excess mortality[1–3] in Turner syndrome (TS) secondary to a nearly 100-fold increased risk of aortic dissection and coronary artery disease being more than threefold increased.[3,4] Unfortunately, it is impossible to identify the subset of Turner females that develop cardiovascular events.

Osteoprotegerin (OPG) is a potential biomarker of cardiovascular disease, particularly aortic dilation and coronary artery calcification.[5–8] Emerging evidence has described the possible mechanisms by which OPG may contribute to the development of aortic aneurysms. OPG is expressed by macrophages and vascular smooth muscle cells (VSCMs) isolated from tissue within abdominal aortic aneurysms.[8] OPG also stimulates matrix metallo-protease (2 and 9) release from VSMCs and monocytes[6,8] and induces apoptosis in healthy aortic VSMCs, which are hallmarks of aortic aneurysm disease.[8] Moreover, OPG is up-regulated by angiotensin-II (ANG-II),[8] a possible key player in aortic aneurysm formation.[9] Further indications of a role played by OPG include its presence in atherosclerotic plaques,[10] its up-regulation in VSMCs by pro-inflammatory cytokines[11] and its role in early endothelial dysfunction, inducing expression of endothelial ICAM-1, VCAM-1 and E-selectin and promotion of leucocyte adhesion.[12] Intriguingly, these effects of OPG have been corroborated by outcome studies demonstrating that increased OPG in coronary artery disease associates with a threefold increased risk of mortality[13] and OPG predicts long-term prognosis in acute coronary syndrome[14] and angina pectoris.[15]

We hypothesized that OPG may serve as a biomarker for risk of aortic disease in TS. We therefore investigated OPG and its

relationship to aortic size as well as validated cardiovascular risk markers in a prospective observational study of TS and age-matched controls.[16,17]

Subjects and methods

Subjects

Women with karyotypically proven TS ($N = 102$) were recruited through the Danish National Society of Turner Syndrome Contact Group and an endocrine outpatient clinic. The patients were examined at baseline (visit 1), follow-up (visit 2, follow-up 2·4 ± 0·4 years) and end-of-study (visit 3 follow-up 4·7 ± 0·5 years). Healthy, age-matched women ($N = 68$) recruited by advertisement to serve as baseline controls were examined once. Exclusion criteria were technically unsuccessful blood sampling for OPG measurement, malignancy, liver disease or contraindications to cardiovascular magnetic resonance imaging, as this study is a component of a comprehensive study of cardiovascular phenotype.[16,17] Of 102 recruited patients, the eligible participants were the following: (i) baseline: $N = 99$ [missing values: heart surgery ($n = 1$) and insufficient sample material ($n = 2$)]; (ii) follow-up: $N = 88$ [heart surgery ($n = 2$), deaths ($n = 2$), loss to follow-up ($n = 9$) and insufficient sample material ($n = 1$)]; (iii) end-of-study: $N = 80$ (heart surgery ($n = 3$), deaths ($n = 4$), loss to follow-up ($n = 13$) and insufficient sample material ($n = 2$). All healthy controls were eligible.

Laboratory tests

EDTA-plasma samples were collected after an overnight fast. The plasma concentration of OPG was measured with a commercially available kit (R&D Systems, Minneapolis, MN, USA).[18] Plasma samples were diluted 1/3 and measured in duplicate. The intra- and interassay coefficients of variation were below 5% and 9%, respectively. Oestradiol was measured by newly developed liquid chromatography–tandem mass spectrometry (Supporting information). Hormone replacement therapy (predominantly 17β-oestradiol and in a subgroup oestradiol valerate taken orally) was not discontinued prior to sampling. High-sensitivity C-reactive protein (hsCRP) was quantified by commercially available monoclonal antibodies (MAB17071 and BAM17072; R&D Systems): recombinant human CRP (NIBSC 85/506) in the range 0·095–12·5 μg/l was used as standard, and samples were diluted 1000-fold in Phosphate-buffered saline with Tween containing 0·1% bovine serum albumin. The limit of detection was 5 ng/l. The intra- and interassay coefficients of variation (%CV) were below 5 and 6%, respectively. Plasma lipids and triglycerides were measured using an automated commercially available system (Aeroset, Abbott Diagnostics, North Chicago, IL, USA). Haemoglobin A1c was measured by high-performance liquid chromatography.

Cardiovascular magnetic resonance imaging

Magnetic resonance imaging was performed[17] with a 1·5 Tesla whole-body magnetic resonance scanner (ACS-NT, Philips Medical Systems, Best, NL) and a 5-element cardiac coil. A contrast-free, nearly isotropic, fat-saturated, 3D steady-state free precession and ECG-triggered gradient echo sequence (250 ms diastolic acquisition window) with a respiratory navigator was used to cover the entire thoracic aorta. Aortic diameter was measured at predefined levels through the thoracic aorta,[17] and all measurements were indexed for body surface area (BSA).

Blood pressure

Ambulatory blood pressures (BP) were recorded over 24 h with oscillometric measurements every 20 min (SpaceLabs 91207, Snoqualmie, WA, USA). Hypertension was defined as follows: A 24-h average >130/80, daytime average >135/85 and night-time average >120/70 mmHg.[19] Nondipper was defined as a decrease of night-time systolic BP of less than 10% of daytime systolic BP.

Statistical analysis

Statistical computations were performed using Stata Statistical Software: Release 12.1 (College Station, TX: StataCorp LP). Normality was assessed by QQ-plots of absolute, log-transformed or squared values, and box-plots were scrutinized for outliers. Baseline comparisons of continuous variables were performed using Student's independent *t*-test (given as mean ± SD or, if for transformed values, as median with range) or Mann–Whitney *U*-test (median with range) as appropriate. Bivariate associations of continuous variables were tested using Pearson's coefficient of correlation or Spearman's rank correlation coefficient. Five extreme outliers (values exceeding six times the interquartile range) resulted in a non-normal distribution of OPG even after transformation. No explanation for these extreme results could be given; hence, medians better described the central tendency of the data. Therefore, we chose to use nonparametric tests including the outliers; however, calculations were repeated with parametric tests excluding the outliers with similar results (data not shown). The Spearman's rank correlation coefficient was calculated correlating change in aortic diameter from baseline to end-of-study with OPG at baseline.

Explanatory models were constructed for OPG using median regression (quantile).[20] Independent variables were chosen from baseline correlation analysis and omitted from the model if collinearity existed. Results from median regression are given as unstandardized coefficients with *P*-value. Allowing for the use of $P < 0·1$ within these models, $P < 0·05$ was considered statistically significant.

Results

Osteoprotegerin was lower in TS compared with controls (777 [326–10 569] *vs* 979 [398–1987] ng/l; $P = 0·001$) (Table 1 and Fig. 1a) and did not change (Fig. 1b) during follow-up (follow-up 4·7 ± 0·5 years).

Table 1. Anthropometrics and baseline descriptives

	Turner $n = 99$	Controls $n = 68$	*P*-value
Osteoprotegerin (ng/l)	777 (326–10 569)	979 (398–1987)	0·001
Age (years)	37·8 ± 10·8	38·9 ± 12·4	0·5*
BMI (kg/m^2)	25·5 (18·4–43·6)	22·7 (19·1–38·1)	<0·001*
BSA (m^2)	1·49 ± 0·15	1·76 ± 0·16	<0·001*
Oestradiol (pmol/l)	110 (0–4061)	136 (0–2989)	0·7
24 h systolic BP (mmHg)	121·9 ± 14·2	112·7 ± 10·5	<0·001*
24 h diastolic BP (mmHg)	77·0 ± 11·2	71·2 ± 7·95	<0·001*
Total cholesterol (mmol/l)	5·19 ± 0·96	5·01 ± 0·84	0·2*
hsCRP (mg/l)	1·67 (0·07–12·6)	1·03 (0·09–12·60)	0·003

Median (range) or mean ± SD. *P*-values are obtained by Mann–Whitney *U*-test unless otherwise stated.
BMI, body mass index; BSA, body surface area; hsCRP, high-sensitive C-reactive protein; 24 h, 24 hour; BP, blood pressure.
*Student's *t*-test.

Aortic diameter

In TS, contrary to controls, baseline OPG correlated with BSA-indexed aortic diameter from the distal ascending aorta to aortic isthmus. The association remained significant at the distal ascending aorta and proximal transverse aortic arch at follow-up but only the distal ascending aorta at end-of-study (Table 2). This association was unchanged when excluding mosaic karyotypes ($r = 0{\cdot}35$–$0{\cdot}38$; $P < 0{\cdot}03$). At baseline, OPG was increased in individuals with TS with an aortic diameter in the upper compared with the lower tertile for the proximal transverse aortic arch (985 *vs* 681 ng/l; $P = 0{\cdot}001$), the distal transverse aortic arch (854 *vs* 673 ng/l; $P = 0{\cdot}002$) and the aortic isthmus (889 *vs* 689 ng/l; $P = 0{\cdot}047$). The difference only remained significant at the proximal transverse aortic arch at follow-up (849 *vs* 724 ng/l; $P = 0{\cdot}03$), while by end-of-study, no difference could be found. OPG at baseline correlated inversely with change in aortic diameter at the proximal transverse aortic arch ($r = -0{\cdot}30$; $P = 0{\cdot}04$) and the aortic isthmus ($r = -0{\cdot}28$; $P = 0{\cdot}02$).

Cardiovascular risk factors

Baseline OPG trended towards being higher among women with TS receiving antihypertensive treatment (938 [490–2638] *vs* 752 [326–10 569] ng/l; $P = 0{\cdot}06$) or those who had increased diastolic BP (873 [580–2638] *vs* 770 [326–10 569] ng/l; $P = 0{\cdot}09$). Excluding individuals treated with ACE-inhibitors/angiotension-II receptor blockers did not change the finding of a lower OPG in TS compared with controls (763 [326–10 569] *vs* 979 [398–1987] ng/l; $P = 0{\cdot}002$). OPG correlated with hsCRP ($r = 0{\cdot}23$; $P = 0{\cdot}02$) and total cholesterol ($r = 0{\cdot}25$; $P = 0{\cdot}01$) (Table 3; Fig. 2).

Karyotype, anthropometrics, age and plasma oestradiol

The lower level of OPG was more pronounced for the 45,X karyotype ($n = 57$) compared with mosaic karyotypes ($n = 42$) (752 [326–7625] *vs* 829 [373–10 569] ng/l; $P = 0{\cdot}2$) although this did not reach statistical significance. OPG correlated inversely with body mass index, BSA and weight in women with TS but not controls (Table 2). Age correlated to OPG in TS but again not in controls (Table 2). In TS, oestradiol levels were comparable to controls. OPG correlated inversely with oestradiol in TS contrary to controls.

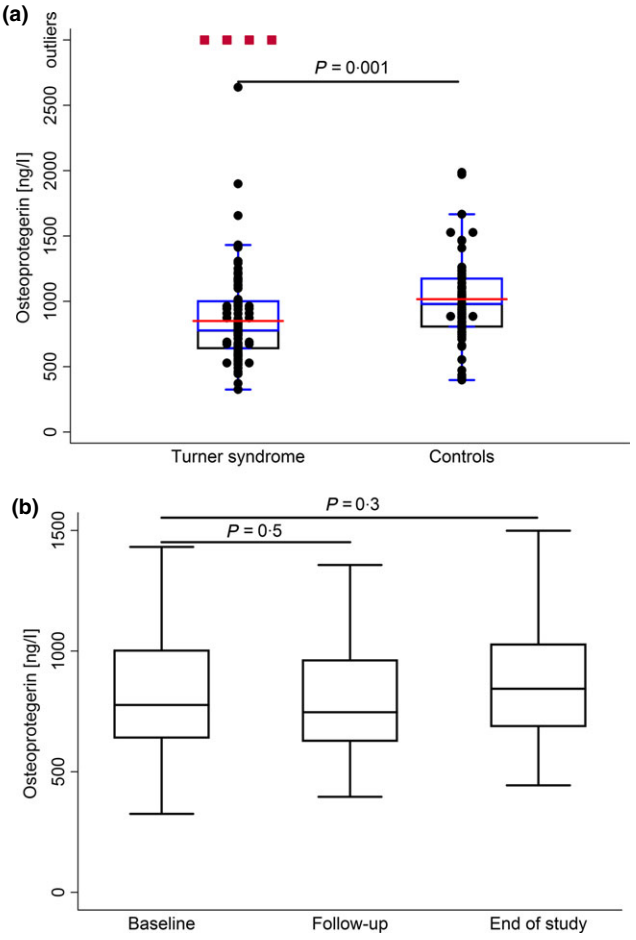

Fig. 1 (a) Osteoprotegerin levels (ng/l) in Turner syndrome and healthy age-matched female controls. The red line represents the mean based on the sample excluding the four most extreme outliers (above six times the interquartile range, indicated by red squares). The blue line in the box represents median, and the box indicates the 25th and 75th percentile, and whiskers the 1·5 lower and upper interquartile ranges. (b) Osteoprotegerin (ng/l) in Turner syndrome at each of the three visits. Baseline: 777 (326–10569), Follow-up: 747 (396–8184) and end-of-study: 844 (444–10045). Boxes represent 25th, 50th and 75th percentiles. Whiskers mark the 1·5 lower and upper interquartile ranges. For graphical reasons, outliers are excluded from plot but not from the calculations on which the plot is based.

Congenital malformations

Within the TS group, neither the presence of bicuspid aortic valve, coarctation of the aorta nor elongated transverse aortic arch resulted in significantly different OPG levels (Table 3).

Table 2. Correlations with osteoprotegerin at baseline

	Turner $n = 99$	Controls $n = 68$
Age	0·29 (0·003)	0·03 (0·8)
BMI	**−0·22 (0·03)**	−0·15 (0·2)
BSA	**−0·20 (0·048)**	−0·22 (0·07)
Height	−0·02 (0·9)	−0·08 (0·5)
Weight	**−0·23 (0·03)**	−0·20 (0·1)
Oestradiol	**−0·34 (<0·001)**	−0·02 (0·9)
High-sensitivity C-reactive protein	**0·23 (0·02)**	0·09 (0·5)
Haemoglobin A1C	0·02 (0·8)	−0·17 (0·2)
Total cholesterol	**0·25 (0·01)**	0·23 (0·06)
BSA-indexed Aortic diameter at baseline		
Aortic sinus	0·09 (0·4)	$r < 0·1$ (NS)
Sinotubular junction	0·17 (0·11)	$r < 0·1$ (NS)
Mid-ascending aorta	0·11 (0·3)	$r < 0·1$ (NS)
Distal ascending aorta	**0·23 (0·03)**	$r < 0·1$ (NS)
Proximal transverse aortic arch	**0·41 (<0·001)**	$r < 0·1$ (NS)
Distal transverse aortic arch	**0·27 (0·009)**	$r < 0·1$ (NS)
Aortic isthmus	**0·32 (0·002)**	$r < 0·1$ (NS)
Proximal descending aorta	0·16 (0·11)	$r < 0·1$ (NS)
Distal descending aorta	0·21 (0·05)	0·16 (NS)
BSA-indexed aortic diameter at follow-up		
Aortic sinus	0·13 (0·2)	
Sinotubular junction	0·14 (0·2)	
Mid-ascending aorta	0·16 (0·1)	
Distal ascending aorta	**0·25 (0·02)**	
Proximal transverse aortic arch	**0·29 (0·02)**	
Distal transverse aortic arch	0·15 (0·2)	
Aortic isthmus	0·19 (0·09)	
Proximal descending aorta	0·23 (0·04)	
Distal descending aorta	0·28 (0·01)	
BSA-indexed aortic diameter at end-of-study		
Aortic sinus	0·03 (0·8)	
Sinotubular junction	0·06 (0·6)	
Mid-ascending aorta	0·10 (0·4)	
Distal ascending aorta	**0·15 (0·02)**	
Proximal transverse aortic arch	0·21 (0·1)	
Distal transverse aortic arch	0·17 (0·1)	
Aortic isthmus	0·08 (0·5)	
Proximal descending aorta	0·11 (0·3)	
Distal descending aorta	0·15 (0·2)	

Results are given as Spearman's rank correlation coefficient (*P*-value). *P*-values <0.05 are marked in bold.

Multiple regression analysis

Using median regression modelling with OPG as the dependent variable and weight, plasma oestradiol, hsCRP and prescription of antihypertensive drugs as independent variables, OPG remained significantly lower in TS (unstandardized coefficient: 314; $P \leq 0·001$) compared with controls after adjustment for weight (−5·07; $P = 0·06$), prescription of antihypertensive drugs (121; $P = 0·1$), total cholesterol (38·6; $P = 0·2$), level of plasma oestradiol (−0·13; $P = 0·02$) and hsCRP (8·97; $P = 0·3$), explaining 8·6% of the variation in TS. However, limiting the analysis to women with TS, the model explained 7·9% of the variation in OPG (weight (−5·09; $P = 0·1$), antihypertensive treatments [136·5; $P = 0·09$), total cholesterol (46·1; $P = 0·2$), oestradiol (−0·14; $P = 0·04$) and hsCRP (6·04; $P = 0·6$)].

Table 3. Baseline comparison of osteoprotegerin levels (ng/l) within the Turner syndrome group

	Yes	No	*P*-value
45,X karyotype ($n = 57$ *vs* 42)	752 (326–7625)	829 (373–10 569)	0·2
Bicuspid aortic valve ($n = 29$ *vs* 69)	749 (326–2638)	837 (373–10 569)	0·1
Coarctation of the aorta ($n = 12$ *vs* 84)	847 (326–7625)	767 (373–4996)	0·7
Elongated transverse aortic arch ($n = 46$ *vs* 50)	731 (326–7625)	811 (373–4996)	0·1
Oestrogen replacement therapy ($n = 83$ *vs* 14)	764 (326–10 569)	941 (529–1432)	0·1
Diabetes ($n = 7$ *vs* 92)	906 (516–1432)	771 (326–10 569)	0·9
Antihypertensive treatment ($n = 29$ *vs* 70)	938 (490–2638)	752 (326–10 569)	0·06
Nondipper ($n = 22$ *vs* 71)	821 (426–10 569)	772 (326–7625)	0·3
Treatment with statins ($n = 6$ *vs* 93)	877 (586–1308)	772 (326–987)	0·7
24 h ambulatory BP >130/80 mmHg ($n = 34$ *vs* 60)	854 (542–2638)	770 (326–10 569)	0·1
24 h systolic BP >130 mmHg ($n = 21$ *vs* 73)	868 (542–1294)	777 (326–10 569)	0·2
24 h diastolic BP >80 mmHg ($n = 30$ *vs* 64)	873 (580–2638)	770 (326–10 569)	0·09
Growth in aortic diameter >5 mm ($n = 22$ *vs* 77)	910 (462–10 569)	764 (326–7625)	0·3

Results are given as median (range). Samples are compared using the Mann–Whitney *U*-test.
24 h, 24 hour; BP, blood pressure.

Discussion

As cardiovascular disease is a cardinal trait of Turner syndrome (TS), we expected, in this first study of adults with TS, to find increased OPG levels compared with age- and gender-matched controls, but found the opposite. Nevertheless, OPG levels correlated with aortic diameter, aortic dilatation and several other cardiovascular risk markers.

The potential explanations for low levels of OPG are manifold. Firstly, the sex hormone deficiency of TS may have an impact on OPG. Oestradiol has been reported to increase OPG,[21] while others have been unable to reproduce this association despite a documented increased OPG in premenopausal women.[22] In this study, we found a negative association with oestradiol and a trend towards lower OPG when receiving oestrogen replacement therapy. However, oestradiol levels were comparable between TS and healthy controls and failed to explain the difference in OPG in our regression analysis. Interestingly, one previous study found low OPG in girls with TS,

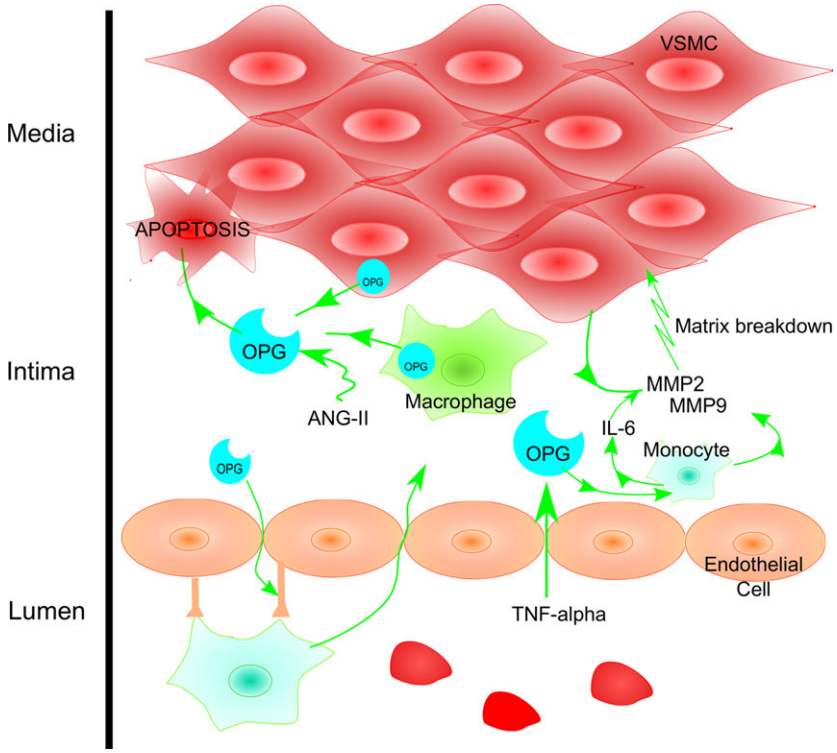

Fig. 2 Role of osteoprotegerin in aortic dilation. A possible mechanism by which osteoprotegerin (OPG) could contribute to aortic dilation and development of aortic aneurysm. ANG-II, Angiotensin-II; TNF-alpha, Tumour Necrosis Factor Alpha; MMP, Matrix Metallo-proteinase.

indicating that it is not a result of oestrogen replacement therapy.[23] Secondly, the lower bone mass in TS due to smaller size and sex hormone deficiency could result in both fewer osteoblasts and a lower production of bone-derived OPG. Thirdly, the X chromosome haploinsufficiency of TS may be an important factor due to epigenetic changes such as differential DNA methylation. Despite the fact that OPG is encoded by the TNFRSF11B gene located on chromosome 8, the bone morphogenetic protein 8b located on chromosome 1 has been found to be differentially methylated in TS compared with 46,XX individuals.[24] Interestingly, crosstalk exists between this protein and other bone morphogenetic and SMAD proteins, thereby potentially affecting OPG.[25]

Osteoprotegerin was positively correlated with aortic diameter in TS, corroborating prior studies in other cohorts.[5–8,26] This is an intriguing finding as biomarkers to identify high-risk individuals in TS are needed. Even though previous studies have linked OPG with atherosclerosis, increased OPG concentrations were also found in nonatherosclerotic human aortic aneurysm biopsies compared with atherosclerotic narrowed aortic biopsies,[8] indicating that the relationship between OPG and aortic diameter is not explained by atherosclerosis. Importantly, there is a lack of studies on OPG in thoracic aortic dilatation, which is currently considered to be of nonatherosclerotic aetiology.[27] There is little evidence regarding the precise aetiology of aortic dilatation in TS with only a few available reports on aortic wall composition, pointing towards a nonatherosclerotic disease process.[28] In TS, aortic dilation is prevalent at all aortic positions excluding the distal transverse aortic arch with aortic dissection predominantly, but not exclusively, occurring in the ascending aorta.[17] However, in our study, OPG did not correlate significantly with aortic diameter in the most proximal part of the ascending aorta. This lack of association may be due to the heterogeneity of the cohort with respect to cardiovascular malformations (e.g. bicuspid aortic valve) and comorbidity (e.g. hypertension) while medical treatment such as antihypertensives and statins may have influenced aortic diameter without affecting OPG. The prospective nature of our study permitted evaluation of the relationship between OPG and aortic enlargement, showing a negative, albeit borderline significant, correlation. This was demonstrated in areas that are not the predominant sites of aortic aneurysm formation in TS, and where there is often other morphological pathology such as kinking and elongation of the transverse aortic arch, dilatation of head and neck vessels or coarctation. This association might represent a chance finding but could also indicate that high-risk individuals for aortic dilation were treated more aggressively with ACE-inhibitor or angiotensin-II receptor blockers, with the potential to decrease OPG through decreased levels of angiotensin-II.[8] Furthermore, treatments of hypertension, diabetes and hypercholesterolaemia in this pragmatic observational study, where clinicians caring for the patients were intensifying treatment as results were made available to them, and initiation of hormone replacement therapy may have lowered OPG. Similar issues, as well as a declining study power, may well explain why the correlation between aortic diameter and OPG only remained significant at the aortic isthmus at end-of-study.

We evaluated OPG in subgroups with and without bicuspid aortic valve, aortic coarctation, and elongated transverse aortic arch due to their potential effect on aortic diameter. However, levels of OPG were not significantly different.

We went on to assess the correlation between OPG and cardiovascular risk factors of atherosclerosis. Osteoprotegerin was nonsignificantly ($P = 0{\cdot}06$) increased in TS with diastolic

hypertension; however, baseline OPG trended towards being higher among women with TS receiving antihypertensive treatment. Despite the fact that ACE-inhibitors/angiotension-II receptor blockers may lower OPG[29,30], excluding individuals treated with these drugs did not change the finding of a lower OPG in TS compared with controls. The Copenhagen City Heart Study recently reported that OPG was associated with hypercholesterolaemia and hsCRP.[14] High-sensitivity CRP levels were higher in TS and positively correlated with OPG. Apart from a correlation with total cholesterol in TS, no association with other cholesterol subtypes were present in our study. We observed higher OPG levels in individuals who were diabetic or blood pressure non-dippers, although without reaching significance. Interestingly since both are high risk groups with respect to cardiovascular complications.

The low stature of TS in relation to the lower level of OPG could indicate that the reduced bone mass in TS results in lower OPG production. It would be highly relevant to clarify levels of OPG in cohorts with short stature, for example., SHOX deficiency. It is possible that the association between OPG, cardiovascular disease and aortic dilation could be even stronger if corrected for bone mass. In future studies, a coronary artery calcium score and segment involvement score would be essential in evaluating the relationship between OPG and coronary artery atherosclerosis in TS.

Limitations

Abnormal height and body composition is inherent in TS and this could introduce bias, although we included BMI and BSA as confounders in our calculations. Different regimens of hormone replacement therapy were prescribed, and no attempt was made to correct for this due to the size of the cohort and complex medical histories.

Conclusion

Levels of osteoprotegerin are reduced in Turner syndrome but correlate with aortic diameter, age, body surface area, weight and oestradiol in Turner syndrome. Women with Turner syndrome appear to have lower level of osteoprotegerin with a preserved relationship to aortic diameter and certain cardiovascular risk factors. Future studies are needed to assess whether osteoprotegerin may serve as a biomarker of aortic or cardiovascular disease in Turner syndrome.

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