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ORIGINAL PAPER

Paraoxonase (PON1) activity in patients with subclinical thoracic aortic atherosclerosis

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Abstract High density lipoprotein (HDL), a powerful antioxidant, protects low density lipoprotein (LDL) particles against oxidative stress. By limiting LDL oxidation, HDL plays an important role in preventing atherosclerosis (AS). The antioxidant effect of HDL is mostly associated with the paraoxonase (PON1) activity. It has been known that increased aortic intima-media thickness (IMT) is an earlier marker AS than carotid IMT. We aimed to investigate the association between thoracic aortic IMT and serum PON1 activity. We studied 133 patients (mean age: 46.3 ± 8 years) who underwent transesophageal echocardiography (TEE) for various indications. The measurements of thoracic aortic IMT by TEE are classified into four grades (1, 2, 3 and 4). Serum PON1 activity was measured spectrophotometrically. Oxidative and anti-oxidative status was evaluated by measuring serum lipid hydroperoxide (LOOH), total anti-oxidant status (TAS). Serum PON1 activity was progressively decreasing from grade 1 IMT to grade 4 IMT ($p < 0.001$). However, serum LOOH was significantly lower and TAS was significantly higher in patients with grade 1 when compared with other grades. In multiple linear regression analysis, IMT was independently correlated with PON1 activity ($\beta = -0.495$, $p < 0.001$), TAS level ($\beta = -196$, $p < 0.009$), age ($\beta = 0.145$, $p = 0.029$) and LDL cholesterol level ($\beta = 0.169$, $p = 0.009$). Decreased PON1 activity was independently associated with the extent of thoracic AS. PON1 activity may play a role in pathogenesis of thoracic AS besides age, TAS and LDL cholesterol levels.

Keywords Aorta · Intima media · Atherosclerosis · Paraoxonase

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Introduction

High density lipoprotein (HDL) cholesterol, an independent negative risk factor for coronary heart disease (CHD), has a wide range of functions some of which are independent of its cholesterol content. These include anti-inflammatory, antioxidant, antiglycation, antithrombotic, nitric oxide—inducing and antimicrobial activities [1–5]. One of the most important functions of HDL is protection of low density lipoprotein (LDL) and cell membranes against oxidative damage, which has been known to be a pivotal event in preventing atherogenesis [3, 5, 6]. This protection is mostly associated with the paraoxonase (PON1) activity. PON1 is considered as the principal enzyme contained within HDL responsible for the anti-oxidant effect [6, 7]. It has been also showed that low activity of PON1 is associated with accelerated atherosclerosis (AS) [4, 8, 9].

Carotid artery study adds significant clinical incremental value in discriminating projected risk beyond metabolic scores and hs-CRP [10]. Also carotid intima media thickness (IMT) is an established marker of early AS [11]. On the other hand, it has been shown that increased aortic intima-media

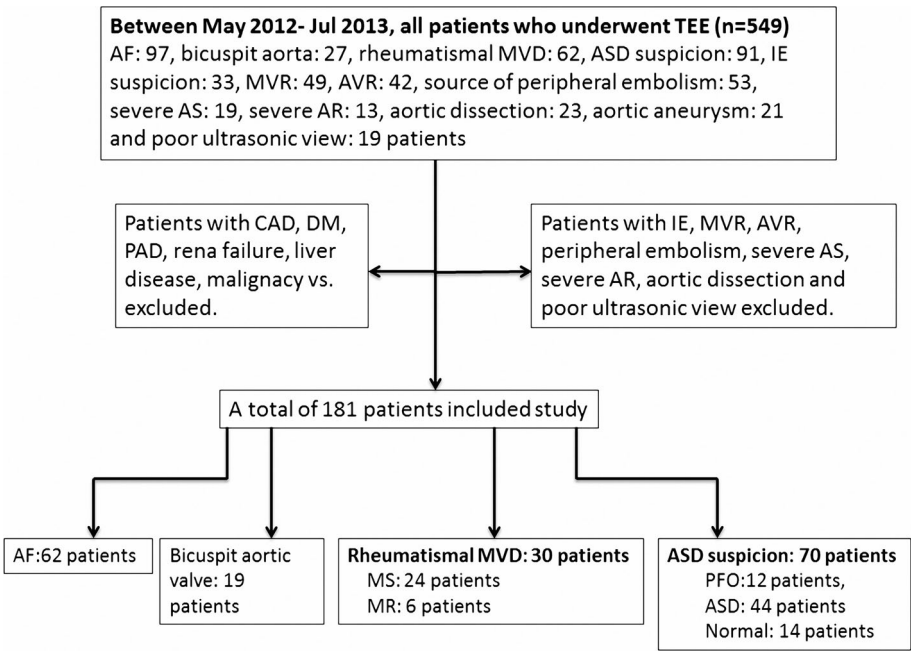

Fig. 1 Flow diagram of the study (*TEE* transesophageal echocardiography, *AF* atrial fibrilation, *MVD* mitral valve disease, *IE* infective endocarditis, *MVR* mitral valve replacement, *AVR* aorta valve replacement, *AS* aortic stenosis, *AR* aortic regurgitation, *CAD* coronary artery disease, *PAD* periferic artery disease, *DM* diabetes mellitus, *MS* mitral stenosis, *MR* mitral regurgitation, *PFO* patent foramen ovale)

thickness (IMT) is an earlier marker AS than carotid IMT. Transesophageal echocardiography (TEE) is a reliable tool for measurement of thoracic aortic IMT [12, 13].

The possible relationship between thoracic aortic AS and PON1 activity was not investigated in humans. We aimed to assess the relationship between thoracic aortic IMT and serum PON activity and oxidative stress markers in patients who underwent TEE examination.

Materials and methods

Subjects

Of the 401 TEE procedures performed between May 2012 and July 2013 in our clinic, we evaluated 133 patients (71 male, 62 female and mean age; 46.3 ± 8 years) who had non-atherosclerotic heart disease and underwent TEE examination for various indications, such as lone atrial fibrillation (51 patients), valvular heart disease (35 patients) or suspicion of atrial septal defect (47 patients) (Fig. 1). There was no patient presenting with TIA or stroke in this study.

Patients with hypertension, diabetes mellitus, history of smoking, familial hypercholesterolemia, known coronary artery disease, positive exercise treadmill test, peripheral vascular disease, carotid artery surgery, stroke, chronic kidney disease, chronic liver diseases, moderate or severe aortic stenosis, moderate or severe aortic regurgitation, aortic dissection or aortic aneurysm and poor ultrasonographic recording quality were excluded from the study. In addition, patients taking anti-oxidant drugs such as carvedilol and zofenopril and statins, diuretics, vitamins and alcohol were also excluded. Institutional ethics committee approved the study and written informed consent for participation in the study was obtained from all individuals.

Age and gender were recorded. Left ventricle ejection fraction (EF) was measured by the Teichholz method [14].

Transesophageal echocardiography

Transthoracic echocardiography and TEE were performed in all study subjects by using a commercially available system (Vivid 7®, GE Medical System, Horten, Norway). An experienced cardiologist (NYK) blinded to other laboratory results performed TEE. The subsequent analysis was performed by different experienced cardiologist (MC). A well-standardized protocol, which has been previously described, was applied to cardiac examinations in all patients [12].

After the cardiac examination the transducer was rotated posteriorly to obtain aortic images. The transducer was advanced to the distal esophagus (approximately 40 cm) and slowly withdrawn to obtain images from descending thoracic aorta (Fig. 2). The maximal IMT of the entire length of the descending thoracic aorta was measured in the horizontal plane and graded using a previously described classification [12]. The thoracic aorta was considered normal (grade 1) when the intimal surface was smooth and continuous without lumen irregularities or increased echodensity, with an intimal thickness less than 1.0 mm. Grade 2 was defined as a simple atherosclerotic plaque with increased echodensity of the intima extending <3.0 mm into the aortic lumen. Grade 3 was defined as an atherosclerotic plaque extending ≥3.0 and <5.0 mm into

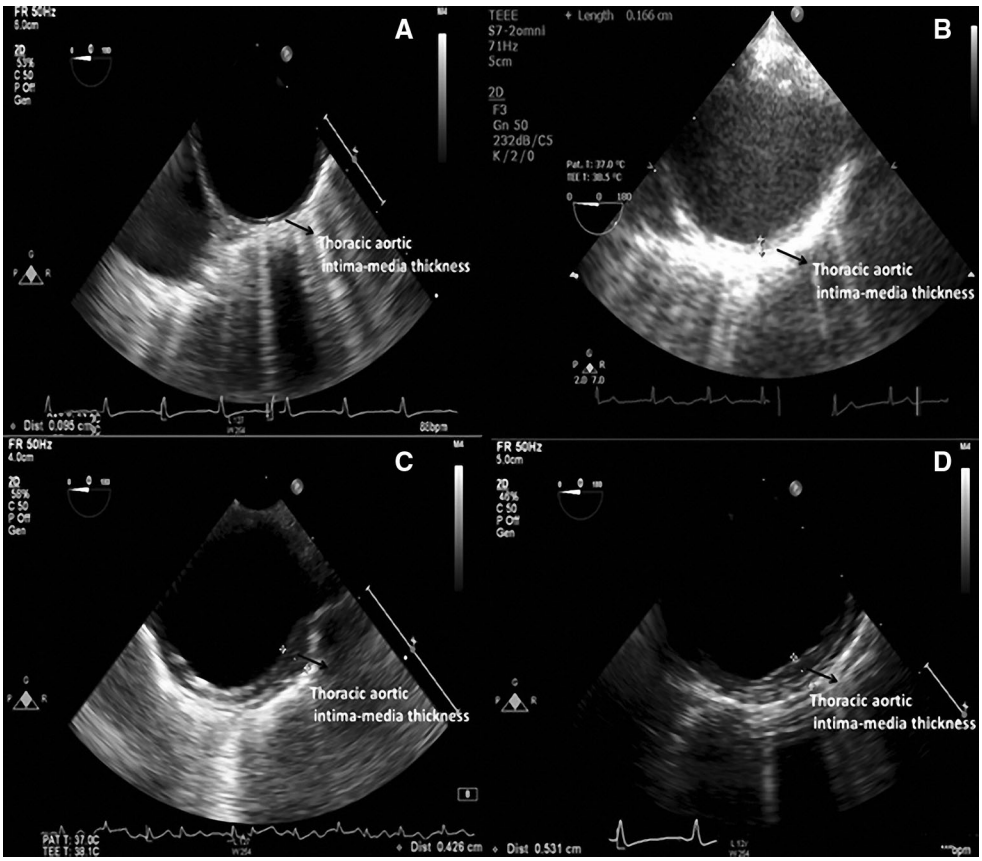

Fig. 2 **a** The thoracic aorta was considered normal (grade 1) when the intimal surface was smooth and continuous without lumen irregularities or increased echodensity, with an intimal thickness less than 1.0 mm (IMT: 0.095 mm). **b** Grade 2 was defined as a simple atherosclerotic plaque with increased echodensity of the intima extending <3.0 mm into the aortic lumen (IMT: 1.66 mm). **c** Grade 3 was defined as an atherosclerotic plaque extending ≥3.0 and <5.0 mm into the aortic lumen (IMT: 4.26 mm). **d** In grade 4, the atherosclerotic plaque was ≥5.0 mm in thickness (IMT: 5.31 mm)

the aortic lumen. In grade 4, the atherosclerotic plaque was ≥5.0 mm in thickness. Based on IMT grade, the patients were divided into four groups.

Blood sampling

Blood samples were obtained following an overnight fasting state just before TEE examination. Plasma samples were stored at −70 °C for the analysis of PON1 activity, total anti-oxidant status (TAS), serum lipid hydroperoxide (LOOH), hs-CRP, triglyceride, total cholesterol, LDL, HDL and fasting glucose.

Plasma triglyceride, total cholesterol, LDL, HDL concentrations and fasting glucose were measured with an automated chemistry analyzer (Abbott Aeroset, Holliston, Minnesota, USA) by using commercial kits (Abbott, IL, USA). Hs-CRP was measured with an autoanalyser (Abbott Aeroset, Holliston, Minnesota, USA) by using a spectrophotometric commercial kit (Scil Diagnostics GmbH, Viernheim, Germany). The intraassay coefficient of variation (CV) was 1.72 % and interassay CV was 4.70 %.

Measurement of serum PON1 activity

Measurement of serum PON1 activity was performed in the absence of NaCl (basal activity). The rate of paraoxon hydrolysis (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase of absorbency at 412 nm at 37 °C. The amount of generated *p*-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1} [15]. PON1 activity was expressed as U/L serum. CV for measurement of serum PON1 activity was 2 %.

Measurement of total antioxidant status (TAS), serum lipid hydroperoxide (LOOH)

Serum TAS of was determined by using an automated measurement method [16]. In this method, a standardized solution Fe^{2+}-*o*-dianisidine complex reacts with a standardized solution of hydrogen peroxide by a Fenton-type reaction, and produces hydroxyl radicals. These potent reactive oxygen species oxidize the reduced colorless *o*-dianisidine molecules to yellow–brown colored dianisidyl

radicals at low pH. The color formation is increased with further oxidation reactions. Antioxidants in the sample suppress the oxidation reactions and color formation. The assay has excellent precision values, which are lower than 3 %. The results are expressed as mmol Trolox equiv./l. Serum LOOH levels were determined by the ferrous ion oxidation-xylenol orange (FOX-2) method as previously described [17].

Statistical analysis

All analyses were performed using SPSS 11.5 (SPSS for Windows 11.5, Chicago, IL). Continuous variables were expressed as mean ± SD and categorical variables were expressed as percentages. Comparison of categorical variables between the groups was performed using the Chi square (χ^2) test. Analysis of normality was performed with the Kolmogorov–Smirnov test. Hs-CRP and triglyceride values were normalized by logarithmic transformation and the logarithmic transformation of hs-CRP and triglyceride values were used for statistical analysis. Analysis of variance (ANOVA) was used in the analysis of continuous variables. A stratified post hoc analysis of echocardiographic, clinical and laboratory variables was performed according to the grade of thoracic aortic IMT. Scheffe and Tamhane's T2 tests were used according to homogeneity test results. The correlation between aortic IMT and clinical, laboratory parameters was assessed by the Pearson correlation test. A stepwise multiple linear regression analysis was performed to identify the independent predictors of aortic IMT. All significant parameters on univariate analysis, such as age, LDL cholesterol, HDL cholesterol, hs-CRP, total antioxidant status, LOOH and PON1 were selected in the multivariate model. The inter-observer reproducibility (MG, ZE) of aortic IMT was evaluated by Bland–Altman analysis, the intra-observer reproducibility (ZE, baseline and after 2 weeks) of aortic IMT was evaluated by intraclass correlation coefficient. A two-tailed $p < 0.05$ was considered statistically significant.

Results

According to TEE examination, 38 (28.6 %) patients had grade 1, 35 (26.3 %) patients had grade 2, 31 (23.3 %) patients had grade 3 and 29 (21.8 %) patients had grade 4 thoracic aortic IMT. The inter-observer and intra-observer reproducibility of aortic IMT were substantial. A Bland–Altman plot is shown in Fig. 3. The intraclass correlation coefficient value was 0.96 (95 % CI 0.95–0.97).

Serum PON1 activity, TAS, LOOH, hs-CRP and lipid parameters were compared in the patient groups according to their grade of IMT (Table 1). The major decrease in PON1 activity was observed in patients with grade 4 IMT group when compared with grade 1, 2 and 3 groups ($p < 0.001$, $p < 0.001$ and $p = 0.028$, respectively). PON1 activity of patients with grade 3 IMT group was also lower than patients with grade 2 IMT and grade 1 IMT groups ($p < 0.001$, for all). Serum TAS levels of grade 2, 3 and 4 IMT groups were lower than grade 1 group ($p < 0.001$ for all). LOOH level of grade 1 IMT group was lower than grade 2, 3 and 4 groups ($p < 0.001$, for all). LDL levels of grade 2, 3 and 4 IMT groups were higher than grade 1 group ($p = 0.025$, $p = 0.001$ and $p = 0.001$, respectively).

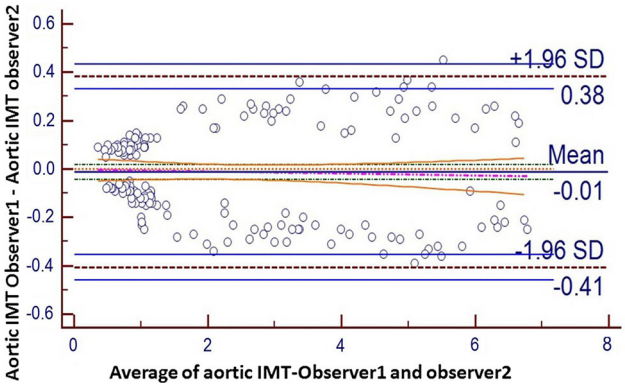

Fig. 3 Bland–Altman plots (interobserver reproducibility) for agreement of aortic IMT measurements between two independant observers (MG, ZE). The *solid lines* in the Bland–Altman plots represent the mean difference between the observers, and the *dashed lines* indicate the 95 % confidence intervals of the difference and ±1.96 SD. There was no variation of agreement across the range of values

Bivariate and multivariate relationships of the thoracic aortic IMT are summarized in Table 2. Thoracic aortic IMT was correlated with age ($r = 0.352$, $p < 0.001$), HDL ($r = -0.199$, $p = 0.022$), LDL ($r = 0.324$, $p < 0.001$), hs-CRP ($r = 0.171$, $p = 0.049$), PON1 activity ($r = -0.655$, $p < 0.001$), TAS ($r = -0.466$, $p < 0.001$) and LOOH levels ($r = 0.307$, $p < 0.001$) on bivariate analysis. In multiple linear regression analysis, IMT was independently correlated with PON1 activity ($\beta = -0.495$, $p < 0.001$), TAS level ($\beta = -196$, $p < 0.009$), age ($\beta = 0.145$, $p = 0.029$) and LDL cholesterol level ($\beta = 0.169$, $p = 0.009$). Relationship between thoracic aortic IMT and PON1 activity was demonstrated in Fig. 4.

PON1 activity was negatively associated with LOOH level ($r = -0.275$, $p = 0.001$) and was positively associated with TAS level ($r = 0.304$, $p < 0.001$).

Discussion

To the best of our knowledge the present study is the first in the literature, which evaluates the relation between PON1 activity and thoracic aortic IMT in patients without clinical

Table 1 Comparison of characteristics of the groups according to the grade of aortic IMT

Variable	Grade-1 (n = 38)	Grade-2 (n = 35)	Grade-3 (n = 31)	Grade-4 (n = 29)	Anova *p*
Age (years)	43.2 ± 7.6[¶]	45.2 ± 8.4[¶¶]	47.4 ± 7	50.6 ± 7.2	**0.001**
Female/Male(n)	22/16 (%57.9)	15/20 (%42.9)	13/18 (%41.9)	12/17 (%41.4)	0.435
SBP (mmHg)	118.7 ± 12.8	117.3 ± 13.4	119.5 ± 13.8	117.2 ± 12.4	0.882
DBP (mmHg)	75.3 ± 8	73.1 ± 10	74.5 ± 9.9	75.2 ± 8.5	0.754
EF (%)	66.3 ± 4.1	65.4 ± 4	60.4 ± 3.2	65.7 ± 2.4	0.699
TC (mg/dl)	190.9 ± 35.2*	214.1 ± 29.2	201.7 ± 30.3	210.2 ± 32.2	**0.013**
Triglyceride (mgl/dl)					
Median (25th–75th)	154 (129–179)	164 (125–228)[∞]	140 (100–181)	121 (89–164)	**0.040**
LDL (mg/dl)	120.9 ± 31.3[a]	136.3 ± 30.1	144.2 ± 27	146 ± 25.8	**0.001**
HDL (mg/dl)	41.4 ± 6.9[b]	37.7 ± 3.7	36.8 ± 7.7	37.8 ± 6.5	**0.014**
Glucose (mg/dl)	86.8 ± 9.6	86.6 ± 9.6	87.4 ± 9.9	87.1 ± 6.8	0.988
Hs-CRP (mg/dl)					
Median (25th–75th)	0.38 (0.17–0.77)[c]	0.78 (0.24–1.17)	1.1 (0.4–1.62)	0.53 (0.24–0.73)	**0.026**
TAS (mmol Trolox equiv./l)	1.90 ± 0.47[d]	1.28 ± 0.51	1.31 ± 0.30	1.18 ± 0.52	**<0.001**
Lipid hydroperoxide (μmol tBLOOH l^{-1})	5.7 ± 2.1[e]	9.4 ± 6.1	9.4 ± 3.5	9.5 ± 3.8	**<0.001**
Paraoxonase (U l^{-1})	121.5 ± 27[f]	111.1 ± 16.8[ff]	88.9 ± 19.3[fff]	75.9 ± 25.0	**<0.001**

DBP diastolic blood pressure, *EF* ejection fraction, *HDL* high density lipoprotein, *Hs-CRP* high sensitive C-reactive protein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *TAS* total antioxidant status, *TC* total cholesterol

Significance *p* values ($p < 0.05$) were indicated in boldface

[¶] $p = 0.025$ versus grade-3 group, $p < 0.001$ versus grade-4 group; [¶¶] $p = 0.006$ versus grade-4 group; [*] $p = 0.02$ versus grade-2 group, $p = 0.016$ versus grade-4 group; [∞] $p = 0.005$ versus grade-4; [a] $p = 0.025$ versus grade-2 group, $p = 0.001$ versus grade-3 and grade-4; [b] $p = 0.015$ versus grade-2 group, $p = 0.003$ versus grade-3 group, $p = 0.022$ versus grade-4; [c] $p = 0.002$ versus grade-3; [d] $p < 0.001$ versus grade-2, 3 and 4; [e] $p < 0.001$ versus grade-2, 3 and 4; [f] $p < 0.001$ versus grade-3 and 4; [ff] $p < 0.001$ versus grade-3, 4; [fff] $p = 0.028$ versus grade-4

Table 2 Bivariate and multivariate relationships of the thoracic aortic IMT

	Thoracic aortic intima-media thickness (mm)			
	Pearson correlation coefficient	*p* value	Standardized ß regression coefficients[a]	*p* value
Age	0.352	**<0.001**	**0.145**	**0.029**
Gender (male/female)	0.081	0.355		
Body mass index (kg/m^2)	0.016	0.851		
SBP (mmHg)	0.07	0.932		
DBP (mmHg)	0.020	0.920		
Triglyceride (mg/dl)	0.153	0.078		
Total cholesterol (mg/dl)	0.155	0.075		
HDL (mg/dl)	−0.199	**0.022**	−0.064	0.318
LDL (mg/dl)	**0.324**	**<0.001**	**0.169**	**0.009**
Fasting glucose	0.019	0.824		
Hs-CRP (mg/dl)	0.171	0.049	0.004	0.948
TAS (mmol Trolox equiv./l)	**−0.466**	**<0.001**	**−0.196**	**0.009**
LOOH (μmol tBLOOH l^{-1})	0.307	<0.001	0.061	0.390
PON1 (U l^{-1})	**−0.655**	**<0.001**	**−0.495**	**<0.001**
Lone AF	0.074	0.396		
Valvular heart disease	0.029	0.741		
ASD suspection	−0.079	0.367		

Significance *p* values ($p < 0.05$) were indicated in boldface

AF atrial fibrillation, *ASD* atrial septal defect, other abbreviations as in Table 1

[a] From multiple linear regression

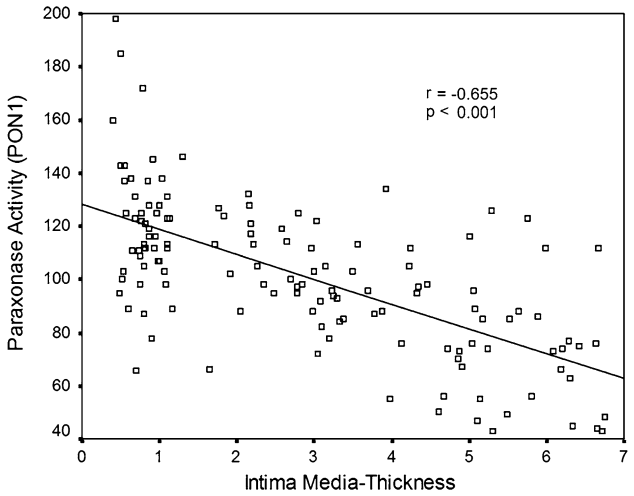

Fig. 4 Relationship between thoracic aortic IMT and PON1 activity

manifestation of atherosclerotic cardiovascular disease. The main finding of this study is that thoracic aortic IMT was independently correlated with PON1 activity in addition to TAS level, age and LDL cholesterol level. We also found that, patients with a higher grade thoracic aortic IMT had higher hs-CRP levels than those with lower grade thoracic aortic IMT.

PON1 is an antioxidant enzyme closely associated with high-density lipoproteins [18]. PON1 has been found to hydrolyze hydrogen peroxides, which are a major reactive oxygen species produced by the arterial wall during atherogenesis [19]. Human epidemiological studies have revealed an association between PON1 levels and CAD risk [4, 8, 9]. Several studies reported that decreased PON1 activity related with both presence of CAD and extend of CAD and carotid AS [4, 8, 9, 20]. Presence of relation between PON1 activity and thoracic IMT may be plausible, because it has been shown that decreased PON1 activity is significantly related with both coronary and carotid AS. In our study, patients with increased thoracic IMT had decreased PON1 activity. Thus, our results suggest that decreased PON1 activity may play a role in the pathogenesis of thoracic AS.

Oxidative stress increases oxidized-LDL which promotes atherogenesis. Oxidative effects of free radicals are controlled by antioxidants. The measurement of TAS reflects the antioxidative status of plasma [21]. Oxidative stress, owing to increased lipid and protein oxidation products and decreased anti-oxidant enzymes and vitamins, is associated with cardiovascular diseases [22] and affects PON1 expression and activities [23]. Serum PON1 activity is inhibited by oxidative stress [24].The relation between thoracic oxidative stress and AS is not well established previously. Demirbag et al. [21] reported that serum TAS level was decreased in proportion to the severity of thoracic AS. But, PON1 activity and LOOP levels were not studied in that study. In our study, patients with increased thoracic IMT had an increased LOOH level, decreased TAS level and decreased PON1 activity, which implicate increased has a potential role in the pathogenesis of thoracic AS. Serum TAS level and PON1 activity were independently related to extend of thoracic aortic IMT. Thus, our findings suggest that increased oxidative stress indicated by higher LOOH and lower TAS levels may decrease PON1 activity in patients with higher IMT such as grade 4 IMT.

High density lipoprotein cholesterol has a variety of functional effects including both proinflammatory and antiinflammatory properties [25]. HDL particles are highly heterogeneous that contain various antioxidant or pro-oxidant enzymes. In the absence of cellular and/or systemic inflammation, antioxidant enzymes of HDL maintain an anti-inflammatory state. However, in the presence of systemic inflammation, antioxidant enzymes can be inactivated and HDL acquires prooxidant and proinflammatory properties [26–28]. Recently, Novak et al. [29] reported that PON1 activity is negatively correlated with CRP. In our study, patients with a higher grade thoracic aortic IMT had lower HDL and higher hs-CRP levels than those with lower grade. Thus, our results suggest that due to chronic inflammation, patients with higher grade thoracic aortic IMT might have more prooxidant and proinflammatuar HDL which may promote the atherosclerotic process.

Clinical implication

We demonstrated an association between thoracic aortic IMT and PON1 activity, TAS level and LOOH level. In patients with increased thoracic IMT, we found an increased LOOH level, decreased TAS level and decreased PON1 activity, which implicate increased oxidative stress. Increased oxidative stress may play a potential role in the pathogenesis of thoracic AS. Thus, our findings suggest that oxidative stress-lowering strategies may be a promising approach for the treatment of AS.

Study limitations

Our study group consisted of patients with different diseases. Additionally, coronary angiography was not performed to our patients. However, the diagnosis of coronary artery disease has been excluded according to treadmill exercise test, ECG and medical history. In this study, we used paraoxon as a substrate for determining activity levels of PON1. However, PON1 has two coding region amino acid polymorphisms, one at position 55 and another at position 192 [30]. The Q192R polymorphism has such a significant effect on PON1 activity. It is possible, but not

advisable, to use PON1 activity within a 192 genotype/phenotype (e.g. Q/Q; Q/R or R/R). In this study, the PON1 phenotype or genotype was not determined. It has also been suggested that serum PON1 activity was a better predictor of the risk of cardiovascular diseases than the PON1 genotype [31, 32]. However, in most studies, PON1 activity was measured with paraoxon as a substrate, while diazoxon was used in very few occasions [33, 34].

In conclusion, PON1 activity was decreased with the extent of thoracic AS. PON1 activity together with oxidative stress may play a role in thoracic aortic AS. Oxidative stress-lowering strategies may be a promising approach for the treatment of AS.

Conflict of interest There are no conflicts of interest.

References

1. Barter PJ, Nicholls S, Rye KA et al (2004) Antiinflammatory properties of HDL. Circ Res 95:764–772
2. Mineo C, Deguchi H, Griffin JH et al (2006) Endothelial and antithrombotic actions of HDL. Circ Res 98:1352–1364
3. Mackness MI, Durrington PN, Mackness B (2000) How high-density lipoprotein protects against the effects of lipid peroxidation. Curr Opin Lipidol 11:383–388
4. Soran H, Younis NN, Charlton-Menys V et al (2009) Variation in paraoxonase-1 activity and atherosclerosis. Curr Opin Lipidol 20:265–274
5. Soran H, Hama S, Yadav R, Durrington PN (2012) HDL functionality. Curr Opin Lipidol 23:353–366
6. Mackness MI, Arrol S, Abbott C et al (1993) Protection of low-density lipoprotein against oxidative modification by high density lipoprotein associated paraoxonase. Atherosclerosis 104:129–135
7. Mackness B, Durrington PN, Mackness MI (2002) The paraoxonase gene family and coronary heart disease. Curr Opin Lipidol 13:357–362
8. Gur M, Aslan M, Yildiz A et al (2006) Paraoxonase and arylesterase activities in coronary artery disease. Eur J Clin Invest 36:779–787
9. Sarkar PD, TMS, Madhusudhan B (2006) Association between paraoxonase activity and lipid levels in patients with premature coronary artery disease. Clin Chim Acta 373:77-81
10. Hung CL, Po HL, Liu CC, Yen CH, Wu YJ, Hou CJ, Kuo JY, Yeh HI, Su S (2013) The utilization of carotid artery imaging beyond metabolic scores and high-sensitivity CRP in screening intermediate-to-high Framingham risk of asymptomatic Taiwanese population. Int J Cardiovasc Imaging 29(4):765–775
11. Ko GT, Chow CC, Leung G, Au-Yeung TW, Chan WB, Lam CS, Lo M, Lee KK (2011) High rate of increased carotid intima-media thickness and atherosclerotic plaques in Chinese asymptomatic subjects with central obesity. Int J Cardiovasc Imaging 27(6):833–841
12. Tribouilloy C, Shen WF, Peltier M et al (1994) Noninvasive prediction of coronary artery disease by transesophageal echocardiographic detection of thoracic aortic plaque in valvular heart disease. Am J Cardiol 74:258–260
13. Harrington J, Peña AS, Gent R et al (2010) Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. J Pediatr 156:237–241
14. Teichholz LE, Kreulen T, Herman MV et al (1976) Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. Am J Cardiol 37:7–11
15. Eckerson HW, Wyte CM, La Du BN (1983) The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 35:1126–1138
16. Erel O (2004) A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 37:112–119
17. Arab K, Steghens JP (2004) Plasma lipid hydroperoxides measurement by an automated xylenol orange method. Anal Biochem 325:158–163
18. Sentí M, Tomás M, Fitó M et al (2003) Antioxidant paraoxonase 1 activity in the metabolic syndrome. J Clin Endocrinol Metab 88:5422–5426
19. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN (1998) Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 101:1581–1590
20. Tartan Z, Orhan G, Kasikçioglu H et al (2007) The role of paraoxonase (PON) enzyme in the extent and severity of the coronary artery disease in type-2 diabetic patients. Heart Vessels 22:158–164
21. Demirbag R, Yilmaz R, Kunt AS et al (2006) Relationship between plasma total antioxidant capacity and thoracic aortic intima-media thickness. Echocardiography 23:183–188
22. Serdar Z, Aslan K, Dirican M et al (2006) Lipid and protein oxidation and antioxidant status in patients with angiographically proven coronary artery disease. Clin Biochem 39:794–803
23. Navab M, Hama SY, Van Lenten BJ et al (1997) Mildly oxidized LDL induced an increased apolipoprotein J/paraoxonase ratio. J Clin Invest 99:2005–2020
24. Aviram M, Rosenblat M, Billecke S et al (1999) Human serum paraoxonase (PON 1) is inactivated by oxidized low density lipoprotein and preserved by antioxidants. Free Radic Biol Med 26:892–904
25. Van Lenten BJ, Navab M, Shih D et al (2001) The role of high-density lipoproteins in oxidation and inflammation. Trends Cardiovasc Med 11:155–161
26. Ansell BJ, Fonarow GC, Fogelman AM (2007) The paradox of dysfunctional high-density lipoprotein. Curr Opin Lipidol 18:427–434
27. Ansell BJ, Fonarow GC, Fogelman AM (2006) High-density lipoprotein: is it always atheroprotective? Curr Atheroscler Rep 8:405–411
28. Navab M, Anantharamaiah GM, Fogelman AM (2005) The role of high-density lipoprotein in inflammation. Trends Cardiovasc Med 15:158–161
29. Novak F, Vavrova L, Kodydkova J et al (2010) Decreased paraoxonase activity in critically ill patients with sepsis. Clin Exp Med 10:21–25
30. Mackness MI, Mackness B, Durrington PN (2002) Paraoxonase and coronary heart disease. Atheroscler Suppl 3:49–55
31. Mackness B, Davies GK, Turkie W et al (2001) Paraoxonase status in coronary heart disease. Are activity and concentration more important than genotype? Arterioscler Thromb Vasc Biol 21:1451–1457
32. Jarvik GP, Rozek LS, Brophy VH et al (2000) Paraoxonase (PON1) phenotype is a better predictor of vascular disease than is PON1(192) or PON1(55) genotype. Arterioscler Thromb Vasc Biol 20:2441–2447
33. Costa LG, Vitalone A, Cole TB, Furlong CE (2005) Modulation of paraoxonase (PON1) activity. Biochem Pharmacol 69:541–550
34. Gupta N, Binu KB, Singh S et al (2012) Low serum PON1 activity: an independent risk factor for coronary artery disease in North-West Indian type 2 diabetics. Gene 498:13–19