The role of oxidative stress-related biomarkers in ascending aortic dilatation: malondialdehyde and paraoxonase-1 activity

Asendan aort dilatasyonunda oksidatif stres ile ilişkili belirteçlerin rolü: malondialdehit ve paraoksonaz-1 aktivitesi

Abstract

Aim: This study aimed to evaluate the antioxidative and oxidative status of patients with ascending aortic dilatation using malondialdehyde, an oxidative stress marker, and paraoxonase-1 activity, an antioxidant enzyme.

Methods: This cross-sectional study was conducted between August and December 2020. It included 56 consecutive patients (mean age 55.3 ± 8.6 years; range 31 to 67 years; 26 males, 30 females) with ascending aortic dilatation and 33 sex-and age-matched controls (mean age 54.5 ± 10.5 years; range 32 to 67 years; 13 males, 20 females) with normal aortic diameters. All participants were evaluated using transthoracic echocardiography. Malondialdehyde was analyzed using the thiobarbituric acid assay. Paraoxonase-1 activity was measured manually using a spectrophotometer. The relation of ascending aortic dilatation with malondialdehyde levels and paraoxonase-1 activity was identified with correlation analyses.

Results: The patient group had significantly higher mean malondialdehyde than the control group (2.5 ± 1.9 μmoL/mL and 1.7 ± 0.3 μmoL/mL, respectively; p < 0.001). The patient group had significantly lower mean activity of paraoxonase-1 than the control group (18.5 ± 12.9 U/mL vs.30 ± 17.6 U/mL, respectively; p < 0.002). Serum malondialdehyde was negatively correlated with ascending aortic diameter (r = 0.293, p = 0.009). A significant negative correlation was found between the activity of serum paraoxonase-1 and ascending aortic diameter (r = -0.364, p = 0.001). Malondialdehyde levels and paraoxonase-1 activity were independent predictors of ascending aortic dilatation.

Conclusion: The results are in line with the notion that increased malondialdehyde levels indicate lipid peroxidation, and decreased paraoxonase-1 activity indicates impaired antioxidant defense. Using them may help protect against the pathophysiology of ascending aortic dilatation.

Keywords: antioxidant; ascending aortic dilatation; malondialdehyde; oxidative stress; paraoxonase-1

Öz

Amaç: Bu çalışmada, oksidatif stres belirteci malondialdehit ve antioksidan enzim paraoksonaz-1 aktivitesi ile asendan aort dilatasyonu olan hastalarda oksidatif ve antioksidatif durum değerlendirildi.

Yöntem: Bu kesitsel çalışmaya Ağustos 2020-Aralık 2020 tarihleri arasında asendan aort dilatasyonu olan toplam 56 ardışık hasta (26 erkek, 30 kadın; ort. yaş: 55.3±8.6 yıl; dağılım, 31-67 yıl) ve aort çapı normal olan, yaş ve cinsiyet açısından eşleştirilmiş 33 kontrol (13 erkek, 20 kadın; ort. yaş: 54.5±10.5 yıl; dağılım, 32-67 yıl) dahil edildi. Hastaların tümü transtorasik ekokardiyografi ile değerlendirildi. Paraoksonaz-1 aktivitesi spektrofotometre ile manuel olarak ölçüldü. Malondialdehit, tiyobarbitürik asit testi ile ölçüldü. Asendan aort dilatasyonunun malondialdehit ve paraoksonaz-1 aktivitesi ile olan ilişkisini tespit etmek için korelasyon analizleri yapıldı.

Bulgular: Ortalama malondialdehit düzeyleri, kontrol grubuna kıyasla, hasta grubunda anlamlı düzeyde daha yüksek idi (sırasıyla 1.7±0.3 μmoL/mL'ye kıyasla 2.5±1.9 μmoL/mL; p<0.001). Ortalama paraoksonaz-1 aktivitesi, hasta grubunda anlamlı düzeyde daha düşük idi (sırasıyla 30±17.6 U/mL'ye kıyasla 18.5±12.9 U/mL; p<0.002). Serum malondialdehit düzeyleri ve asendan aort çapı arasında pozitif, anlamlı bir ilişki saptandı (r=0.293, p=0.009). Serum paraoksonaz-1 aktivitesi ve asendan aort çapı arasında negatif, anlamlı bir ilişki saptandı (r=-0.364, p=0.001). Malondialdehit düzeyleri ve paraoksonaz-1 aktivitesi, asendan aort dilatasyonunun bağımsız ön gördürücüleri idi.

Sonuç: Çalışma sonuçlarımız, lipid peroksidasyonunu gösteren artmış malondialdehit düzeylerinin ve bozulmuş antioksidan savunmasını gösteren azalmış paraoksonaz-1 aktivitesinin, asendan aort dilatasyonunun patofizyolojisinde rol oynayabileceği görüşünü desteklemektedir.

Anahtar sözcükler: antioksidan; asendan aort dilatasyonu; malondialdehit; oksidatif stres; paraoksonaz-1

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INTRODUCTION

Ascending aortic dilatation (AAD) is a common clinical disease. Aortic aneurysms are caused by a 1.5-fold increase in the normal diameter of the ascending aorta. As it is a clinically silent entity, one of the main reasons for mortality in adults is an ascending aortic aneurysm (AscAA) (1). Familial predisposition, hemodynamic force, aortic transmural inflammation, destructive remodeling, and oxidative stress in the extracellular matrix have contributed to the pathophysiology of AAD (2–4).

In general, histopathological analyses of AscAAs reveal medial degeneration which is caused by the loss of smooth muscles and disrupted elastic lamina (4, 5). Matrix metalloproteinases (MMPs) contribute to cystic medial degeneration and aortic wall remodelling. Scavengers of reactive oxygen species (ROS) reacting with ROS and other free radicals reduced MMP-9 expression in macrophage foam cells in aortic plaque (6). This reduced antioxidant activity and increased oxidative stress may affect the development of AscAAs.

Free oxygen radicals are neutralized by antioxidant systems to restore the optimal balance in living organisms. An impaired balance between the antioxidant and oxidant systems leads to oxidative stress, which causes tissue damage through protein oxidation and lipid peroxidation (7). The most destructive effect of lipid peroxidation caused by oxidative stress occurs in cell membranes. Malondialdehyde (MDA), which is a highly reactive compound, is one of the main secondary results of lipid peroxidation, and it is a reliable indicator of oxidative stress (8).

The paraoxonase (PON) family contains three antioxidant isoenzymes: PON-1, PON-2, and PON-3. It has proven anti-inflammatory and antioxidant properties. The PON multigene family is clustered on the human chromosome 7 long arm (q21–q22) (9). PON-1, an endogenous antioxidant enzyme, is initially synthesized and secreted in the liver. It has been proposed that PON-1 contributes to the antioxidant system mainly by downregulating lipoprotein-oxidized phospholipids (10).

Studies have shown that MDA is membrane-permeable, leading to intracellular impairment and deformation. Therefore, it may be a valuable oxidative stress marker (8). Current studies have also demonstrated that the concentration of PON-1 is reduced in cardiovascular diseases, hypercholesterolemia, and diabetes, all of which are related to increased oxidative stress (11,12). In this study, it is hypothesized that increased systemic and vascular oxidative stress might contribute to pathogenesis of ADD. Therefore, we aimed to evaluate the antioxidative and oxidative status of AAD patients using MDA and PON-1 activity.

MATERIALS AND METHODS

This case-control, cross-sectional study was done at Goztepe Prof. Dr. Suleyman Yalcin City Hospital at Istanbul Medeniyet University, Department of Cardiology, between August and December 2020. It included 56 consecutive patients with AAD (26 males and 30 females with a mean age of 55.3 ± 8.6 years and a range of 31 to 67 years) and 33 sex- and age-matched controls with normal aortic diameters (20 females and 13 males with a mean age of 54.5 ± 10.5 years and a range of 32 to 67 years). Those with an age ≥ 18 years and a diagnosis of ADD based on transthoracic echocardiographic examination were included in the study. The following individuals were excluded: those who had congenital heart disease, congestive heart failure, documented coronary artery disease, having a prosthetic valve or a bicuspid aortic valve, Marfan syndrome, myocarditis, moderate-to-severe valve disease, renal dysfunction, pericarditis (creatinine > 1.5 mg/dL), cardiomyopathies, acute and chronic inflammatory diseases, active and chronic infections, acute and chronic liver disease, hemolytic disorders, previous stroke, connective tissue diseases, malignancies, and the use of antioxidant supplements or antioxidant vitamins. In this study, each participant submitted written informed consent. The Ethics Committee (2021/0016) of Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul Medeniyet University, approved the study protocol. This study followed the Declaration of Helsinki principles.

All participants underwent a detailed physical examination and electrocardiography, and they were questioned about their medical history and the drugs they used. The following formula was used to calculate the Body Mass Index (kg/m^2) = [Weight in kg]/[Height in m]. In this study, those who had a diastolic blood pressure of ≥ 90 mmHg and systolic blood pressure

Table 1. Baseline demographic and clinical characteristics of the study population

		AAD (+) (n=56)			AAD (-) (n=33)			*p*	
Age, years		55.3	±	8.6	54.5	±	10.5	0.924	m
Sex	Female	30		(53.6)	20		(60.6)	0.518	x^2
	Male	26		(46.4)	13		(39.4)		
BMI, kg/m^2		26.5	±	2.9	26.9	±	2.8	0.504	t
Risk factors									
Smoking, n (%)		11		(20)	8		(24)	0.609	x^2
Hypertension, n (%)		20		(35)	12		(36)	0.197	x^2
Diabetes mellitus, n (%)		19		(34)	6		(18)	0.110	x^2
Hyperlipidemia, n (%)		17		(31)	14		(42)	0.248	x^2
Medical treatment									
ACEI/ARB, n (%)		17		(30)	8		(24)	0.617	x^2
Beta-blocker, n (%)		27		(48)	9		(27)	0.070	x^2
Aspirin, n (%)		11		(20)	5		(15)	0.612	x^2
Statin, n (%)		12		(21)	6		(18)	0.733	x^2
CCB, n (%)		16		(29)	2		(6)	*0.011*	x^2
Insulin, n (%)		3		(5)	3		(9)	0.502	x^2
OAD, n (%)		8		(14)	4		(12)	0.765	x^2

[t]Independent samples *t*-test / [m]Mann-Whitney U test / x^2 Chi-square test. AAD: ascending aortic dilatation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CCB: calcium channel blocker, OAD: oral antidiabetic drug.

of ≥ 140 mmHg on three consecutive measurements or those who took antihypertensive drugs were diagnosed with hypertension. We defined diabetes mellitus as using antidiabetic drugs, going on a diabetic diet, or having a fasting blood glucose level of ≥ 126 mg/dL. Those who smoked during diagnosis were considered smokers, irrespective of frequency and quantity. Hyperlipidemia means a triglyceride level of ≥ 150 mg/dL or a total cholesterol level of ≥ 200 mg/dL.

In this study, all participants were administered an M-mode, two-dimensional, comprehensive Doppler echocardiographic examination by the same skilled echocardiographer, who was blinded to the study protocol. Echocardiographic examinations were conducted using a commercially available device with a 2.5 MHz–3.5 MHz transducer (Philips iE33 xMATRIX echocardiography system; Philips Healthcare Inc., MA, USA). The M-mode was used to calculate the left ventricular ejection fraction (LVEF) from the parasternal long axis. Devereux's equation was used to calculate left ventricular mass (LVM): LVM (g) $= 0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD3)]\} + 0.6$, where LVEDD is the left ventricular end-diastolic diameter, IVSd is the interventricular septum dimension, and PWd is the posterior wall dimension. The LVM index was defined as the LVM divided by BSA (LVM/BSA, g/m^2) or by height^2 (13). The severity and presence of aortic regurgitation were identified with color and pulsed Doppler examinations. The guidelines of the American Society of Echocardiography (ASE) were followed to measure the proximal ascending aortic diameter with M-mode echocardiography in the parasternal long-axis view. This shows that the aortic diameter is maximized through the forefront method in a vertical plane to the aorta's long axis (14). In this study, AAD means an ascending aortic diameter of ≥40 mm.

Blood samples from all participants were collected after they fasted for 12 or more hours and kept at -80 °C for analysis. Synthetic paraoxon was used as a substrate to assay plasma PON-1 activity. The primary ratio of substrate hydrolysis to p-nitrophenol was used to identify the activity of PON-1. Its absorbance was controlled at 412 nm in the assay mixture, which contained 2.0 mM $CaCl_2$, 20 mL of plasma, and 1.0 mM paraoxon in 100 mM Tris-HCl buffer (pH 8.0). One PON-1 activity unit means 1 nmoL of 4-nitrophenol, which was made under the study conditions mentioned above (15). The levels of lipid peroxidation in the serum samples were measured based on the thiobarbituric acid reaction using the method of Buege and Aust. We used this

Table 2. Laboratory and echocardiographic findings of the study population

	AAD (+)				AAD (-)					
	Mean±SD			Median	Mean±SD			Median	*p*	
Glucose, mg/dL	101.0	±	17.8	96	98.1	±	13.9	94	0.712	m
Creatinine, mg/dL	0.8	±	0.2	0.8	0.8	±	0.1	0.7	0.486	m
Total cholesterol, mg/dL	205.8	±	35.	208	213.0	±	40.1	203	0.779	m
LDL cholesterol, mg/dL	128.1	±	29	132	134.7	±	37	126	0.382	t
HDL cholesterol, mg/dL	49.9	±	15.8	46	49	±	11.9	49	0.957	m
Triglyceride, mg/dL	129.3	±	68.7	117	135	±	52.1	124	0.347	m
TSH, uUI/mL	1.6	±	1	1.4	1.7	±	0.9	1.4	0.579	m
White cell count x 10^9	6.9	±	1.9	7	6.9	±	1.7	7	0.840	m
Hemoglobin, g/dL	13.2	±	1.4	13	13.4	±	1.2	13	0.408	m
Echocardiographic features										
LV mass, g	176	±	30.9	176	164.3	±	27.9	159.5	0.090	t
LV mass index, g/m^2	95.6	±	17.3	95.5	89.7	±	14.9	86.5	0.118	t
Ascending aorta diameter, mm	43.4	±	2.7	44	30.1	±	3	29	***0.000***	m
LVEF, %	61.6	±	4.2	60	62.6	±	5.2	60	0.446	m
PON-1 activity, U/ml	18.5	±	12.9	13.8	30.0	±	17.6	25.5	***0.002***	m
MDA, µmol/ml	2.5	±	1.9	2	1.7	±	0.3	1.6	***0.000***	m

*Independent samples *t*-test / [m] Mann-Whitney U test / [χ^2] Chi-square test. AAD: ascending aortic dilatation, HDL: high-density lipoprotein; LDL: low-density lipoprotein; LV: left ventricle; LVEF, left ventricular ejection fraction; MDA: malondialdehyde; PON-1: paraoxonase-1; TSH: thyroid-stimulating hormone.

Table 3. Univariate and multivariate logistic regression analysis results

	Univariate					Multivariate				
	OR	95% CI			*p*	OR	95% CI			*p*
PON	0.95	0.92	-	0.98	***0.002***	0.92	0.88	-	0.98	***0.009***
MDA	5.12	1.99	-	10.02	***0.007***	7.96	2.23	-	13.27	***0.002***
Age	1.009	0.963	-	1.058	0.697					
Hypertension	1.771	0.741	-	4.231	0.199					
LV mass	1.023	0.994	-	1.053	0.120					
LVEF	0.952	0.864	-	1.048	0.312					
hs-CRP	1.066	0.974	-	1.167	0.163					

OR: odds ratio; CI: confidence interval; AAD: ascending aortic dilatation; hs-CRP: high-sensitivity C-reactive protein; LV: left ventricle; LVEF: left ventricular ejection fraction; MDA: malondialdehyde; PON-1: paraoxonase-1.

method because we set out for the spectrophotometric measurement of color, which is produced by the reaction to thiobarbituric acid at 535 nm with MDA (16).

Statistical analysis was done using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). We expressed the descriptive data in frequency and number, median (min–max), or ± SD, if applicable. The Kolmogorov–Smirnov test was used to examine the normality distribution of the variables. Quantitative independent variables were analyzed with the Mann–Whitney U test and the *t*-test, while the quantitative dependent variables were analyzed with the Wilcoxon test and paired samples *t*-test. The chi-square test was used to examine qualitative independent variables, and Fisher's exact test was used in place of the chi-square test, which is not appropriate. The correlation between MDA and AAD levels and PON-1 activity was evaluated through Spearman correlation analysis. Multivariate and univariate logistic regression analyses examined the effect sizes. The patients with proximal aortic dilatation with maximum specificity and sensitivity were discriminated, and Receiver Operating Characteristic (ROC) curve was used to calculate the MDA and PON-1 cut-off values. ROC analysis was performed to calculate the positive predictive value (PPV) and the negative predictive value (NPV) of the variables. A p-value of < 0.05 was considered statistically significant.

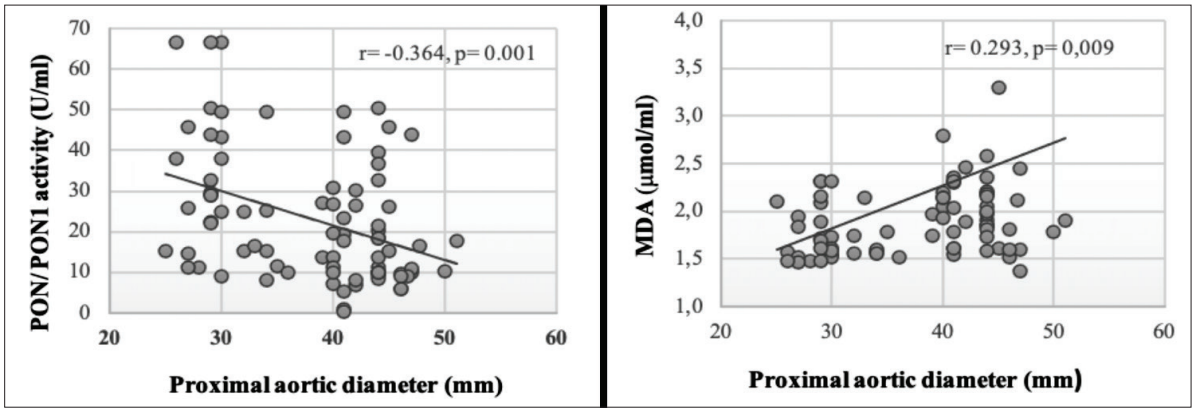

Figure Legends:
Figure 1a-b. Correlation between aortic diameter and serum MDA levels and PON-1 activity. MDA: malondialdehyde; PON-1: paraoxonase-1.

RESULTS

Table 1 shows the baseline clinical and demographic characteristics of the participants. The patient and control groups did not show significant differences in sex, age, hypertension, dyslipidemia, BMI, diabetes mellitus, or smoking status ($p > 0.05$ for all). Furthermore, no significant difference between the groups was found in the type of antihypertensive, antidiabetic, or antihyperlipidemic drugs used ($p > 0.05$ for all).

The echocardiographic and laboratory findings are summarized in Table 2. The AAD group had higher levels of mean serum MDA than the control group (2.5 ± 1.9 µmoL/mL *vs.* 1.7 ± 0.3 µmoL/mL, respectively; $p < 0.001$). The AAD group had significantly lower mean serum PON-1 activity than the control group (18.5 ± 12.9 U/mL *vs.* 30 ± 17.6 U/mL, respectively; $p = 0.002$). The other standard laboratory parameters, LVM, LVM index, and LVEF, did not significantly differ between the groups ($p = 0.090$, $p = 0.118$, and $p = 0.446$, respectively).

A negative significant correlation was found between PON-1 activity and AAD ($r = -0.364$, $p = 0.001$) (Figure 1a). However, the MDA levels were positively and significantly correlated with AAD ($r = 0.293$, $p = 0.009$) (Figure 1b). In the ADD group, PON-1 activity was not correlated with MDA levels.

The dependent variable was the ascending aortic diameter in the analysis of the multivariate logistic regression. Accordingly, the MDA levels (95% confidence interval [CI]: 2.23–13.27; odds ratio [OR]: 7.96) and activity of PON-1 (OR: 0.92; 95% CI: 0.88–0.98) predicted ADD independently (Table 3).

The ROC curve for MDA revealed a cut-off value of ≥ 1.78 µmoL/mL was corraleted with ADD with 75% sensitivity, 69% specificity, 64% PPV, and 58% NPV (AUC: 0.751; 95% CI: 0.641– 0.862; $p < 0.001$) (Figure 2 a). In addition, using a cut-off value of ≤ 21.7 U/mL for PON-1 activity, the specificity, sensitivity, NPV, and PPV were 71%, 65%, 42%, and 63%, respectively (AUC: 0.706; 95% CI: 0.593–0.818; $p = 0.002$) (Figure 2 b).

DISCUSSION AND CONCLUSION

This study examined antioxidative and oxidative conditions in patients with AAD using MDA and PON-1 activity. Our results showed that MDA levels, the final product of lipid peroxidation, were significantly higher, and the activity of PON-1, the antioxidant enzyme, was significantly lower in patients with ADD than in the controls. In addition, we observed a positive, significant correlation between MDA levels and ADD and a negative, significant correlation between PON-1 activity and ADD. More intriguingly, the results showed that lower PON-1 activity and higher MDA levels independently predicted ADD. To the best of our knowledge, this study is the first to evaluate PON-1 activity and serum MDA levels in ADD patients. Supporting our hypothesis, our results suggest that impaired defense against oxidative stress and increased oxidative stress from higher lipid peroxidation may foster the development of ADD.

Previous studies have found that oxidative stress plays a leading role in the development of aortic aneurysms (2–4). The remodeling of the aortic wall is substantially associated with an impaired balance between MMP and its inhibitors (4–6). By activating a nicotinamide

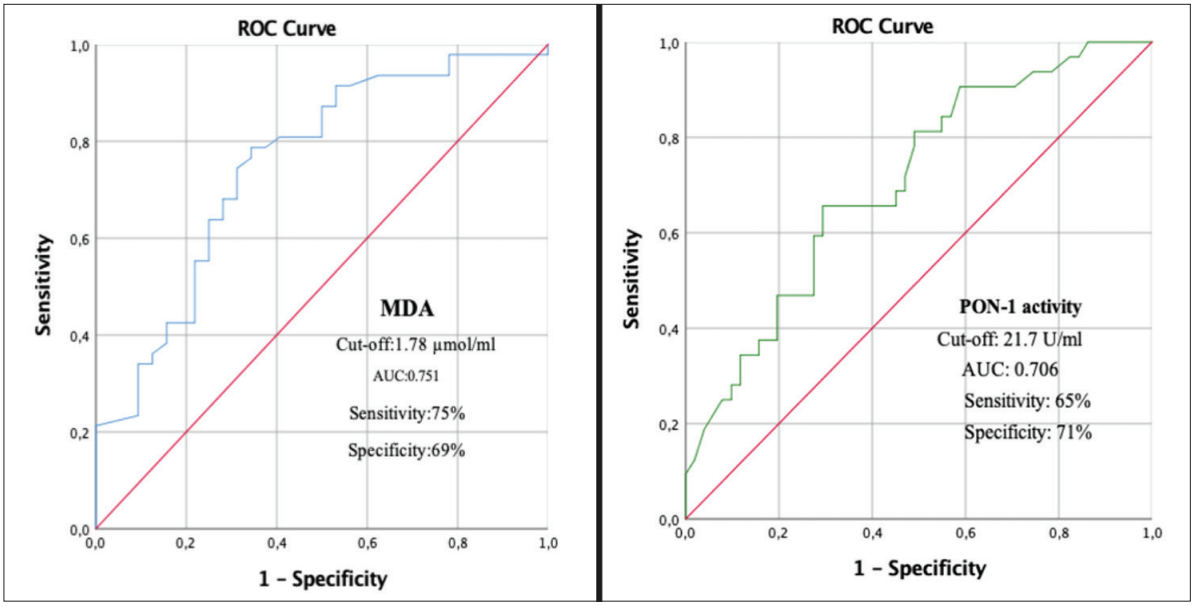

Figure 2a-b. Receiver operating characteristic curve for MDA and PON-1 for predicting ADD. AAD: ascending aortic dilatation; AUC: area under the curve; MDA: malondialdehyde; PON-1: paraoxonase-1.

adenine dinucleotide phosphate-dependent pathway, along with inflammatory cells, vascular smooth muscle cells (VSMCs), mechanical stress, growth factors, and lipid mediators, ROS produced from oxidative enzymes are released in the aorta. ROS upregulate MMPs and VSMC apoptosis, and they alter the delicate equilibrium between the degradation and restoration of the aortic wall (2–6). Recent studies have found a direct effect of ROS on the regulation of the extracellular and cellular components of the aortic wall (17). The major source of ECM proteins in the aorta is VSMCs, and the functional and structural integrity of the proximal aorta requires interaction between VSMCs-ECM proteins and stress of the aortic wall (18). VSMCs in vascular pathologies can dramatically change to synthetic fibroblast-like cells that express several ECM proteases and proteins. Therefore, phenotypic modulation of VSMC enhances the metabolic dysregulation of ECM proteins in reaction to arterial stress. Increased ROS has been proposed to regulate the VSMC phenotype directly through the growth factor of connective tissue (19).

Oxidative stress is the result of increased ROS, which are the key molecules involved in the signaling pathways of atherogenesis and vascular inflammation. ROS induce oxidative damage to the main biomolecules, such as lipids, proteins, and deoxyribonucleic acid (8). Although all of the main biomolecule classes are affected by free radicals, lipids are the most vulnerable biomolecules (20). Higher lipid peroxidation at the cellular level impairs plasma membrane hemostasis, and this causes the death of many types of cells, including VSMCs (21). Lipid peroxidation induces the release of unsaturated aldehydes, such as acrolein and MDA (8, 20). These aldehydes are thought to mediate inflammation and vascular dysfunction (20). Plasma MDA values are a sensitive indicator of oxidative stress from lipid peroxidation (8). The present study found increased MDA to be a reliable indicator of oxidative stress in ADD patients. This finding shows the role of the aforementioned mechanisms in the pathogenesis of ADD.

Antioxidants are naturally occurring substances that fight against oxidative damage. They also help prevent lipid peroxidation, and they protect nucleic acids, proteins, and carbohydrates (20). There is growing evidence that PON-1 reduces ROS in human endothelial cells, VSMCs, and fibroblasts (22). Furthermore, PON-1 plays a role in inflammation and lipid metabolism by reducing oxidized low-density lipoprotein (LDL), which is the major regulator of atherosclerosis pathogenesis (10). Plasma LDL can be oxidized (ox-LDL) by oxidative radicals, and increased plasma ox-LDL is a proven risk factor of atherosclerosis and endothelial dysfunction (23). It has been demonstrated that ox-LDL increases the expression of chemokines, such as

vascular cell adhesion molecule-1 (VCAM-1), P- and E-selectin, adhesion molecules, endothelial monocyte chemotactic protein-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1) (23). In addition, PON-1 activity has had an inverse association with the formation of atherosclerosis (24).

Although the link between abdominal aortic aneurysms and atherosclerosis is more evident, atherosclerosis may contribute to aortic dilatation (5). In a study, the aneurysmal aortic wall was significantly increased by ICAM-1, MCP-1, and VCAM-1 levels (25). Furthermore, PON-1 prevents the induction of an inflammatory response in cells of the arterial wall (25). Earlier studies found ADD to be a non-inflammatory lesion. Nevertheless, the latest evidence has shown the effect of inflammatory cells infiltration on ADD pathogenesis (26). In our study, consistent with the literature, the ADD patients had significantly lower PON-1 activity than the control group. This indicates that lower PON-1 activity, along with increased peroxidation and vascular inflammation, may contribute to the development of ADD.

PON-1 activity can vary among individuals, depending on genetic and environmental factors, including diet. Abnormal alterations in the parameters of lipids that induce oxidation may attenuate PON-1 activity (24). Some authors have proposed that PON-1 is inactivated through oxidized lipids and interactions with the sulfhydryl group. Therefore, low PON-1 activity indicates higher oxidative stress (24). Reduced PON-1 activity has also been related to higher MDA levels (27). Consistent with these findings, we also found levels of MDA that were higher to a statistically significant degree, as well as lower activity of PON-1 in ADD patients than in the control group. However, the results of this study did not show a significant correlation between MDA levels and PON-1 activity.

We should note that there are limitations to this study. First, the results should be interpreted with caution because it is a cross-sectional study with a relatively small sample. Second, we analyzed serum PON-1 activity in this study; however, we were not able to perform genotyping because of cost limitations. Third, the ascending aortic diameter was measured by echocardiography, and the results could not be verified by another independent technique, including computed tomography and cardiac magnetic resonance imaging. However, the present study is the first to analyze the levels of serum MDA and the activity of PON-1 in ADD patients, an area that has been underresearched.

In conclusion, our results support the notion that increased malondialdehyde levels indicating lipid peroxidation and decreased paraoxonase-1 activity indicating impaired antioxidant defense are likely to contribute to the pathophysiology of ascending aortic dilatation. However, further randomized controlled, large-scale, prospective studies should provide valuable insights into the relation between ascending aortic dilatation and paraoxonase-1 activity and malondialdehyde levels.

Conflict-of-interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

Editing Service

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