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Original article

PARAOXONASE 1 ENZYME ACTIVITY AND MYELOPEROXIDASE CONCENTRATION IN INDIVIDUALS WITH ANGIOGRAPHICALLY CONFIRMED CORONARY ARTERY DISEASE

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Abstract

Introduction: PON1 and MPO are key regulators of HDL function. While PON1 exerts antiatherogenic protection by limiting lipid oxidation, MPO promotes HDL oxidation and the formation of dysfunctional, pro-inflammatory HDL.

Aim: This study aimed to evaluate the relationship between PON1 catalytic activity and MPO concentration with the development and severity of atherosclerosis and coronary artery disease (CAD) in patients from the Republic of North Macedonia.

Material and methods: This cross-sectional study included subjects undergoing percutaneous coronary angiography with or without stenting due to monitoring of stable angina or induced ischemia. The catalytic activity of the PON1 enzyme and the concentration of the MPO enzyme were analyzed. The PON1 catalytic activity was measured spectrophotometrically, MPO levels were measured with a human MPO ELISA test kit.

Results: A total of 165 subjects (106 CAD, 59 non-CAD) were analyzed. CAD patients had significantly lower PON1 activity, whereas MPO levels did not differ. MPO/PON1 ratio and HDL×PON1 index clearly discriminated CAD from non-CAD. CAD patients showed lower HDL and ApoA1 and higher glucose and Lp(a). Across CAD severity stratification (no stent, stent, restenosis), LDL and triglycerides were similar, while Lp(a) increased and HDL×PON1 declined, indicating progressive HDL dysfunction and oxidative imbalance.

Conclusion: Our findings suggest that CAD was associated with lower PON1 activity, reflecting dysfunctional and pro-oxidative HDL despite similar LDL levels. Lp(a) increased with atherosclerosis severity and was highest in patients with restenosis, highlighting the value of combined biochemical testing for enhanced cardiovascular risk stratification and early identification of susceptibility in the Macedonian population.

Keywords: coronary artery disease; HDL cholesterol; PON1; MPO

Introduction

Paraoxonases belong to one enzyme family group and include three non-similar isoforms: PON1, PON2 and PON3. The genes for all three enzymes are located one next to other on the long arm of chromosome 7.

Among the paraoxonase enzymes, PON1 has been studied most extensively and is considered the most important [1]. This is largely due to the studies conducted by Mackness *et al.* who described the role of the enzyme PON1 in association with high-density lipoprotein (HDL) in reducing the accumulation of lipid peroxides in low-density lipoprotein (LDL)[2-4]. The protective role of HDL against LDL oxidation has been linked to paraoxonase-1 (PON1), an enzyme bound to HDL that inhibits the buildup of lipid peroxides in LDL particles[4-6].

The above findings highlighted the potential link between PON1 enzyme, HDL, and the prevalence of coronary artery disease in patients, and stimulated research interest in PON1 activity, mainly to try to clarify more precisely the physiological mechanisms of the enzyme[7,8] and the additional influence of single nucleotide polymorphisms of PON 1 gene on the activity of the enzyme itself[6].

On the other hand, the myeloperoxidase (MPO) enzyme is also associated with HDL functionality, but with opposed effect, meaning promoting oxidative stress and atherosclerosis. While circulating MPO levels are low in healthy individuals, they are significantly elevated in the plasma or serum of patients with acute coronary syndrome and in those at increased risk of major adverse cardiovascular events[9,10].

PON 1 enzyme identification, classification and structure

PON1 was originally described by Abraham Mazur and Norman Aldridge in the 1940s–1950s as an "A"-esterase but later was renamed as paraoxonase due to its ability to detoxify the organophosphate compound paraoxon, a toxic metabolite of parathion commonly used as an agricultural insecticide[11-13].

PON1 is a calcium-dependent hydrolase that can be found among various mammalian species. Structurally PON1 is a glycoprotein with about 354-355 amino acids and a molecular mass in the range of 43-45 kDa, as described in structural studies[14]. The enzyme displays multiple catalytic functions, including lactonase, arylesterase, and paraoxonase activities[15]. Although PON1 shows its enzymatic activity on oxidized lipids, the exact physiological substrates for PON1 are still not well known[16]. PON1 is synthesized predominantly in the liver, which represents its primary site of expression. Following secretion into the circulation, the enzyme is mainly associated with HDL, where it contributes to antioxidant and anti-atherogenic functions. PON1 belongs to a group of HDL-associated enzymes, including lecithin–cholesterol acyltransferase (LCAT) and platelet-activating factor acetylhydrolase (PAF-AH), which collectively mediate the antioxidant properties of HDL.

Structure and functionality of MPO enzyme

By structure, MPO is a heme peroxidase cyclooxygenase enzyme. It is a glycosylated homodimeric protein and it is composed of two monomers and has a molecular weight of 146 kDa. Each monomer consists of a 14.5 kDa light chain and a 58.5 kDa glycosylated heavy chain, that contain a prosthetic heme derivative and a calcium-binding site necessary for enzymatic reactions[17,18].

Daugherty *et al.* reported that MPO co-localizes with macrophages in human atherosclerotic lesions[19].

It has been shown that MPO is involved in the development and progression of atherosclerosis. High blood MPO levels are associated with established CVD and identify individuals who are at increased risk for CAD and cardiovascular events[20,21]. HDL is the primary target for oxidative modification in patients with established coronary artery disease (CAD). HDL isolated from aortic lesions in patients with CAD contains high levels of 3-chlorotyrosine and 3-nitrotyrosine, two abnormally oxidized amino acids that are characteristic of the MPO activity. Oxidation of HDL selectively impairs the ability of the lipoprotein to remove cholesterol from cells, rendering the lipoprotein atherogenic[20,22].

During inflammatory conditions, myeloperoxidase (MPO) is released from the azurophilic granules of polymorphonuclear neutrophils and monocytes into the extracellular environment. MPO generated hypochlorous acid (HOCl) induces oxidative modification of HDL within atherosclerotic lesions, impairing ABCA1-mediated cholesterol efflux through site-specific chlorination of tyrosine residues on apolipoprotein A-I (apoA-I). These oxidative changes convert HDL into a pro-inflammatory particle and contribute to the formation of dysfunctional HDL. Oxidative damage to HDL-associated proteins and lipids disrupts normal HDL maturation and alters its biological functions, thereby promoting atherogenesis. Notably, the HDL-associated enzyme paraoxonase-1 (PON1) has been shown to limit MPO-induced HDL modification and apoA-I cross-linking, thereby preserving both the anti-inflammatory properties of HDL and its capacity to mediate cholesterol efflux[23].

Materal and method

Study population

The study included 106 patients with confirmed coronary artery disease (CAD), treated with percutaneous coronary intervention (PCI) with or without stenting, as indicated, due to inducible ischaemia and/or stable CAD. The control group consisted of 59 randomly selected patients during the same period, matched for gender and age, admitted to hospital due to chest pain, in whom absence of atherosclerotic CAD and/or other structural heart disease was confirmed during patient's diagnostic workup.

All patients were treated at the University Clinic for Cardiology, "Mother Teresa" Clinical Centre, Skopje.

Patients were a genetically homogeneous group, all of them with Caucasian origin and from the same geographical area, R.N. Macedonia, but were part of two different ethnic groups. Patients who had major cardiovascular events, acute coronary syndrome, renal failure (creatinine >3.0 mg/dL), and a history of malignant diseases in the previous 5 years were excluded. Also, exclusion criteria were acute inflammatory processes at inclusion (e.g., infections, autoimmune diseases).

The study was approved by the Ethics Committee of the Faculty of Medicine – Skopje, and patients participated in the study after giving a read and signed written informed consent. The study was conducted in accordance with the principles stated in the Declaration of Helsinki.

Clinical characteristics of the study population

The study group comprised a total of 165 patients, of whom 106 were classified as CAD, i.e. the study group, and 59 were classified as a control group (non-CAD). The mean age of all patients was 63.68 years, with 27% being women. Diabetes mellitus was present in 40%, and 70% of the study participants were smokers. Demographically, 134 patients were Macedonian, while the rest of the patients were of the minority ethnical groups present in the country.

The collected samples for analysis (blood) from the study group were analyzed for the following biochemical parameters: HDL, LDL, total cholesterol (TC), Lp(a), ApoB, ApoA1, glucose, triglycerides (TG). Samples were measured immediately after blood collection using standard routine methods at the University Institute of Clinical Biochemistry Clinical Centre "Mother Teresa" -Skopje.

MPO enzyme concentration was successfully measured in 151 patients, of whom 95 patients belonged to CAD group and 56 to non-CAD group. Measurements of the PON1 enzyme activity was obtained for 99 patients, 63 belonging to CAD group and 36 in non-CAD group.

Samples Analysis

All blood samples were collected in the morning following an overnight fasting period. From the collected samples, serum was obtained using tubes without anticoagulant, after a 30-minute rest of the sample. Plasma was obtained using tubes containing anticoagulant, sodium citrate, followed by centrifugation at 3000 rpm for its separation, for 10 minutes at 4 ºC.

Measurement of PON1 arylesterase activity

PON1 arylesterase activity was measured by using Arylesterase/Paraoxonase kit by Zeptometrix (Buffalo, USA). This kit uses the catalytic activity of arylesterase/paraoxonase over phenyl acetate, which results in phenol formation. The rate of formation of phenol was measured by monitoring the increase in absorbance at 270 nm at 25ºC on an automated Perkin Elmer Wallac 1420 Victor2 (USA). The working reagent consists of 20 mM Tris/HCl buffer, pH 8.0, containing 1 mM CaCl2 and 4 mM phenyl acetate as the substrate. Samples diluted 1:3 in buffer were added and the change in absorbance was recorded following a 20 sec lag time. One unit of arylesterase activity is equal to 1 μM of phenol formed per minute. The activity is expressed in kU/L, based on the extinction coefficient of phenol of 1310 M-1cm-1 at 270 nm, pH 8.0, and 25ºC. Blank samples containing water were used to correct for non-enzymatic hydrolysis. A purified PON standard included in the kit was used during measurements.

Measurement of MPO enzyme concentration

Serum MPO levels were measured by human MPO ELISA kit (Hycult Biotechnology, Uden, Netherland) as per manufacturer's protocol. The kit is a ready-to-use solid-phase sandwich enzyme-linked immunosorbent assay. In the first step, samples and standards are incubated in microtiter wells coated with antibodies recognizing human MPO. A wash step follows, after incubation of 60 minutes at room temperature. Next biotinylated tracer antibody is added to bind the captured human MPO. Another incubation of 60 minutes at room temperature follows, and there is a second wash step. After washing, streptavidin-peroxidase conjugate is added that will bind to the biotinylated tracer antibody. After an additional incubation of 60 minutes at room temperature and a wash step, tetramethylbenzidine (TMB) substrate is added. After an incubation of 30 minutes at room temperature, oxalic acid is added to stop the enzyme reaction. Then the absorbance is measured at 450 nm with a spectrophotometer Perkin Elmer Wallac 1420 Victor2 Microplate Reader. A standard curve is obtained by plotting the absorbance (linear) *versus* the corresponding concentrations of the human MPO standards (log). Human MPO concentration of the samples can be determined from the standard curve.

Results

Table 1 illustrates the demographic and clinical characteristics of patients classified according to CAD, presence of stent, restenosis, smoking status and diabetes.

Table 1. Profile of the patient group in the study

	CAD	non-CAD
Gender (Male)	80(72%)	31(28%)
Gender (Female)	26(48%)	28(52%)
Smoking	31(70%)	13(30%)
Stent	36(100%)	0(0%)
Restenosis	46(100%)	0(0%)
Diabetes	36(72%)	14(28%)

CAD group was characterized predominantly by a male population, a higher frequency of active smokers, and a significantly greater frequency of diabetes. All patients in CAD group

had undergone angiography, of whom 36 patients had only one stent and 46 patients had restenosis. These findings reflect a high-risk cardiovascular patient profile and are consistent with known epidemiological determinants of coronary artery disease.

The statistical significance of the biochemical parameters was analyzed using one-way ANOVA statistical method, in relation to different patient groups according to CAD and non-CAD classification. The results are shown in Table 2.

Age was slightly higher in CAD group with a mean age of 64.72±8.3 (p=0.0428). Older age was expected in CAD group and may partly influence the other risk markers. Statin dose was significantly higher in CAD group (31.42±17.9 mg/day, p=0.0013). This reflects the need for a secondary prevention therapy, meaning a need of administering of more aggressive lipid-lowering medicines in CAD patients. Lp(a) was notably higher in CAD group (40.21±50.2 nmol/l, p=0.0031) and the result is strongly consistent with the fact considering Lp(a) as an independent atherosclerotic risk factor. ApoA1 and HDL were significantly lower in CAD group: ApoA1 (1.23±0.2 g/l, p=0.001), HDL (1.12±0.3 mmol/l, p=0.0011), which suggests impaired HDL quantity and anti-atherogenic capacity. LDL, total cholesterol, triglycerides, ApoB were not significantly different between the groups (p>0.05). This finding likely reflects that the administered statin therapy balances LDL-related markers and it is masking the group differences. Glucose was borderline higher in CAD group (7.46±3.3 mmol/l, p=0.0508), which may indicate metabolic dysregulation and aligns with diabetes/pre-diabetes risk in CAD patients. MPO levels alone showed no difference (28.48±8 mg/ml, p=0.9321), so the MPO levels by themselves may not distinguish CAD *vs*. non-CAD in our study population. PON1 enzyme activity was significantly lower in CAD group (51.82±41.2 kU/l, p=0.0101), and this finding suggests loss of antioxidant/anti-inflammatory HDL function. MPO/PON1 ratio was dramatically higher in CAD group (1.08±0.9, p=0.0101) and indicates a shift toward pro-oxidative dominance, reinforcing an atherogenic environment. The created composite score HDLxPON1 was significantly lower in CAD group (57.56±49.6, p=0.0009). This composite score underlines reduced functional quality of HDL, rather than merely lower HDL levels. ApoA1/HDL was borderline higher in CAD group (1.11±0.12, p=0.0530), possibly reflecting compositional changes in HDL. ApoB/ApoA1 ratio showed borderline significance (0.75± 0.27, p=0.0519) reflecting the balance between the harmful and protective lipoproteins, indicating tendency for atherosclerosis in CAD group.

Table 2. Biochemical parameter statistical relevance between CAD and non-CAD

	CAD	**non-CAD**	**All patients**	**Sample size**	**ANOVA**
	Mean (StDev)	**Mean (StDev)**	**mean (StDev)**	**(CAD/non-CAD)**	**p**
Age	64.72(±8.3)	61.83(±9.4)	63.68(±8.8)	106/59	0.0428
Satins (mg/day)	31.42(±17.9)	21.95(±17.7)	28.03(±18.3)	106/59	0.0013
Glucose (mmol/l)	7.46(±3.3)	6.57(±2.1)	7.15(±2.8)	103/58	0.0508
Lp(a) (nmol/l)	40.21(±50.2)	16.51(±15.2)	32.19(±43.2)	84/43	0.0031
ApoB (g/l)	0.92(±0.3)	0.9(±0.2)	0.91(±0.3)	101/57	0.7213
ApoA1 (g/l)	1.23(±0.2)	1.36(±0.3)	1.28(±0.2)	99/57	0.001
HDL (mmol/l)	1.12(±0.3)	1.28(±0.3)	1.17(±0.3)	103/53	0.0011
LDL (mmol/l)	1.83(±0.9)	1.89(±0.8)	1.85(±0,9)	99/56	0.7001
TC Total Cholesterol (mmol/l)	3.7(±1.3)	3.45(±0.8)	3.7(±1.1)	103/55	0.8718
TG (mmol/l)	1.17(±0.7)	1.18(±0.7)	1.18(±0.7)	97/56	0.9699
AST (U/l)	22.7(±16.8)	22.29(±8.2)	22.56(±14.3)	104/58	0.8622
MPO (mg/ml)	28.48(±8)	28.35(±9.7)	28.4(±8.8)	95/56	0.9321
PON1 (kU/l)	51.82(±41.2)	74.99(±43.9)	60.25(±43.5)	63/36	0.0101
MPO/PON1	1.08(±0.9)	0.47(±0.4)	0.87(±0,8)	65/32	0.0004
HDLxPON1	57.56(±49.6)	100.12(±71.9)	73.52(±62.1)	60/36	0.0009
ApoB/ApoA1	0.75(±0.27)	0.67(±0.23)	0.72(±0.26)	98/54	0.0519
ApoA1/HDL	1.11(±0.12)	1.07(±0.12)	1.10(±0.12)	94/51	0.0530

Even though traditional lipid markers (LDL, total cholesterol, triglycerides) were similar between CAD and non-CAD groups, most likely due to statin therapy, CAD patients showed higher Lp(a), reduced HDL and ApoA1, significantly reduced PON1 activity, evidently elevated MPO/PON1 ratio, impaired HDL functional index (HDL×PON1).

To summarise the results shown in Table 2, patients with CAD were older and received significantly higher statin doses, compared to the non-CAD group. Lp(a) levels were significantly elevated in CAD patients, whereas HDL cholesterol and ApoA1 concentrations were significantly lower. Traditional lipid markers, including LDL, total cholesterol and triglycerides, did not differ between groups, likely reflecting the effect of lipid-lowering therapy.

Notably, PON1 enzyme activity was significantly reduced in CAD patients, while MPO concentrations did not differ. However, the MPO/PON1 ratio and the HDL×PON1 index revealed explicit differences, indicating a shift toward pro-oxidative and dysfunctional HDL profiles in CAD patients.

When we stratified CAD patients in subgroups according to clinical severity of atherosclerosis (no stent, stent, restenosis), shown in Table 3, no significant differences were observed for classical lipid markers - LDL, total cholesterol or triglycerides. This is probably a result of the administered statin therapy that equalized LDL-related markers, masking the classical lipid differences across CAD severity. In contrast, Lp(a) increased progressively across the CAD stratification, reaching the highest values in the restenosis subgroup ($p= 0.0064$). HDL cholesterol and ApoA1 remained lower in all CAD categories compared to non-CAD group ($p<0.01$). This suggests that CAD is characterized not only by lower HDL concentration, but likely by the impaired HDL function that is supported by functional indicators.

Table 3. Biochemical and enzyme parameter statistical significance between stratified CAD and non-CAD groups

	A CAD-no stent	**B CAD-stent**	**C CAD-restent**	**D non-CAD**	**Sample size**	**ANOVA**
	Mean (StDev)	**Mean (StDev)**	**Mean (StDev)**	**Mean (StDev)**	**A/B/C/D**	**p**
Age	66.23(±7.9)	64.4(±8.2)	64.46(±8.5)	61.83(±9.4)	17/43/46/59	0.3036
Statins	27.06(±13.6)	26.9(±14.1)	30.73(±13.3)	21.95(±17.7)	17/43/46/59	0.0439
Glucose	6.75(±1.6)	7.8(±3.7)	7.42(±2.9)	6.57(±2.1)	17/43/43/58	0.1373
Lp(a)	26.81(±33.9)	35.02(±43.2)	49.47(±59.3)	16.51(±15.2)	12/35/37/43	0.0064
ApoB	0.96(±0.3)	0.9(±0.3)	0.91(±0.3)	0.9(±0.2)	16/42/43/57	0.9004
ApoA1	1.23(±0.2)	1.25(±0.2)	1.21(±0.2)	1.36(±0.3)	99/57	0.0095
HDL	1.04(±0.2)	1.14(±0.2)	1.13(±0.3)	1.28(±0.3)	103/53	0.0067
LDL	1.94(±0.7)	1.87(±0.9)	1.75(±0.9)	1.89(±0.8)	99/56	0.8366
TC	3.8(±0.9)	3.7(±1.2)	3.7(±1.3)	3.45(±0.8)	103/55	0.9821
TG	1.23(±0.7)	1.05(±0.6)	1.28(±0.8)	1.18(±0.7)	97/56	0.5202
AST	18.94(±5.8)	21.2(±5.7)	19.4(±5.7)	22.29(±8.2)	104/58	0.256
MPO	31.03(±7.6)	27.11(±7.5)	28.94(±8.6)	28.35(±9.7)	95/56	0.4857
PON1	46.57(±37.8)	54.19(±42.9)	53.46(±43)	74.99(±43.9)	63/36	0.0993
MPO/PON1	1.33(±1)	0.98(±0.8)	1.07(±0.9)	0.47(±0.4)	65/32	0.0047
HDLxPON1	49.85(±50)	66.77(±55.6)	50.68(±55.5)	100.12(±71.9)	60/36	0.0127
ApoB/ApoA1	0.8(±0.32)	0.72(±0.24)	0.76(±0.28)	0.67(±0.23)	98/54	0.1891
ApoA1/HDL	1.17(±0.15)	1.1(±0.09)	1.11(±0.13)	1.07(±0.12)	94/51	0.0528

Although MPO concentrations did not vary significantly across the studied groups, PON1 enzyme activity was consistently reduced in CAD patients, even though with no statistical significance between groups ($p=0.0993$). The HDL×PON1 index was significantly lower in stratified CAD groups compared with non-CAD group ($p=0.0127$), indicating impaired HDL functionality. The MPO/PON1 ratio was significantly higher in all CAD

subgroups compared to non-CAD subjects, indicating a pro-oxidative shift. Together, these findings suggest that oxidative imbalance and dysfunctional HDL, rather than LDL levels, are closely associated with CAD presence and restenosis.

Discussion

Atherosclerosis and related cardiovascular diseases are major causes of morbidity and mortality in developed countries. While diabetes, hyperlipidaemia, obesity as metabolic risk factors and smoking are established major risk factors for atherosclerosis [24], emerging studies suggest that the enzyme PON1 and its activity associated with high-density lipoprotein (HDL) may play an atheroprotective role[25,26].

This study highlights the multifactorial nature of coronary artery disease by evaluating both the standard lipid biochemical parameters and some new antioxidative/prooxidative indicators of the HDL functionality. The observed lower levels of HDL, ApoA1 and PON1 enzyme activity in CAD group are consistent with the idea that reduced antioxidant capacity predisposes individuals to lipid peroxidation and subsequent atherosclerotic changes. The HDL-associated enzyme PON1, in particular, plays a key role in hydrolysing oxidized lipids, thereby mitigating oxidative stress and preserving endothelial function.

Furthermore, it is important to consider the potential influence of external factors such as medication use and the presence of comorbidities. For example, the concomitant use of statins and oral antidiabetics, which was observed in the patient population, may affect PON1 and overall lipid metabolism. Future studies should incorporate stratified analyses that account for these factors to clarify their modulatory effects on the antioxidant system[27].

An imbalance between the prooxidant factors such as MPO and protective enzymes, such as PON1, can accelerate the atherosclerotic process.

In addition, the genetic background of the Macedonian population, which in this study was Caucasian but included different ethnic subgroups, suggests that population-specific genetic factors may also modulate CAD risk. Therefore, further studies should aim to compare these findings including the genetic research on various enzyme single nucleotide variants to determine whether the observed associations are consistent across different genetic variations and populations.

Conclusion

In this cohort, traditional lipid markers did not distinguish CAD severity, whereas biomarkers reflecting HDL functionality and oxidative balance were strongly associated with disease presence. CAD patients showed reduced PON1 activity, higher MPO/PON1 ratios, and lower HDL×PON1 composite score, indicating dysfunctional and prooxidative HDL profiles. Lp(a) increased with aggravation of the atherosclerotic disease and was highest in patients where restenosis was observed. These findings suggest that impaired HDL function and oxidative imbalance, rather than the LDL levels, may play a central role in the development and progression of CAD and could represent more informative targets for cardiovascular risk assessment. Coronary artery disease arises from a highly interconnected network of biochemical, genetic, enzymatic and environmental factors. Deciphering this complexity through integrated and comprehensive research is essential for advancing risk prediction, enabling earlier, non-invasive and more accurate diagnosis, driving the development of truly personalized therapeutic strategies that will improve patient outcomes.

Conflict of interest statement. None declared.

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