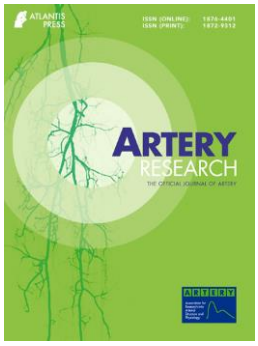

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

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To cite this article: Maryam Teimouri, Hashem Nayeri (2018) Association of serum paraoxonase activity with lipid profile, APO-A and APO-B in subjects with different levels of HDL, Artery Research 24:C, 32–39, DOI: https://doi.org/10.1016/j.artres.2018.10.227

To link to this article: https://doi.org/10.1016/j.artres.2018.10.227

Published online: 3 December 2019

Artery Research (2018) 24, 32—39

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

Association of serum paraoxonase activity with lipid profile, APO-A and APO-B in subjects with different levels of HDL

Maryam Teimouri, Hashem Nayeri*

Department of Biochemistry, Falavarjan Branch, Islamic Azad University, Isfahan, Iran

Received 15 September 2018; received in revised form 15 October 2018; accepted 22 October 2018
Available online 9 November 2018

KEYWORDS
High-density lipoprotein;
Coronary heart disease;
Paraoxonase-1;
Lipoproteins;
ApoA;
ApoB

Abstract *Background:* Coronary heart diseases are inversely related to plasma high-density lipoprotein (HDL) level. Paraoxonase-1 (PON1) is mainly associated with HDL and plays a vital role in protection of low-density lipoprotein (LDL) and HDL. The aim of this study was to investigate the association between paraoxonase activity (PON1) with lipid profile, apoA-I, apoB and apoB/apoA-I ratio in subjects with different level of HDL cholesterol (HDL-C).
Methods: 135 subjects, 20—60 years old, contributed to this study. The subjects were divided into three groups (45 in each group) with different levels of HDL-C (High, Normal and Low). For each group, the activity of PON1 was measured using paraoxon as a substrate. Moreover, the serum level of lipid profile, ApoA and apoB were measured. The statistical analysis was performed using SPSS software.
Results: PON-1 activity and apoA-I level were decreased in subjects with lower level of HDL-C ($P < 0.001$). ApoB and apoB/apoA-I ratio were higher in subjects with lower level of HDL-C ($P < 0.001$). Serum PON-1 activity was positively correlated with TC, TG, apo A-B, and LDL-C levels ($P < 0.01$).
Conclusions: In conclusion, determination of serum PON1 activity and lipoproteins may play important role in earlier prediction of CAD and help to design a therapeutic for treatment of CAD toward PON1 activity regulation.

* Corresponding author.
E-mail address: hnaieri@gmail.com (H. Nayeri).

https://doi.org/10.1016/j.artres.2018.10.227
1872-9312/

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide.[1] It has long been known that concentration of plasma high-density lipoprotein cholesterol (HDL-C) has an inverse correlation with the incidence of CHD, indicating that HDL-C prevents development of atherosclerosis. LDL-C (low-density lipoprotein cholesterol) oxidation is responsible in initiation and progression of atherosclerosis. HDL-C anti-inflammatory and antioxidant function inhibit the oxidation of (LDL-C).[2,3] Hydrolase enzymes including paraoxonase (PON) 1, lecithin-cholesterol acyltransferase (LCAT) and platelet activating factor acetyl hydrolase (PAF-AH) are responsible for antioxidant activity of HDL-C. PON1 is one of the enzymes associated with HDL.[4]

Paraoxonases (PON, EC 3.1.8.1) are hydrolytic enzymes consisting of PON1, PON2, and PON3 with aryldialkylphosphatase activity. Human serum paraoxonase (PON1) is a calcium-dependent enzyme with broad-spectrum activities such as esterase, peroxidase, and lactonase activity.[3,5] PON1 is mainly synthesized in the liver and released into the bloodstream binds to the HDL-C. Moreover, secretion of the PON1 from the liver is facilitates by HDL-C. In addition, HDL-C stabilizes the PON1 and furnishes a hydrophobic environment that is needed for PON1 function. PON1 exhibits anti-inflammatory, anti-oxidative, anti-atherogenic, anti-diabetic, anti-microbial and organophosphate-hydrolyzing properties.[6–8] Anti-atherogenic properties of PON1 is induced by its lipolactonase activity, which reduces uptake of oxidized low-density lipoprotein (Ox-LDL) by macrophages, inhibits biosynthesis of cholesterol, and stimulates HDL-mediated cholesterol efflux from macrophages.[7–10] Furthermore, it has been shown that PON1 hydrolyzes homocysteine (Hcy)-thiolactone and prevents homocysteinylation of HDL, LDL, and other proteins.[11] Apolipoprotein (apo) A-I (apoA-I), the major protein in HDL, binds to the PON1 and stabilizes this enzyme. Binding of apoA-I to PON1 selectively stimulates PON1 lactonase activity.[12] Previous studies demonstrated that PON1, PAF-AH, and LCAT protect LDL-C from oxidative modification and consequently prevent lipid-peroxide accumulation on LDL-C. Studies have shown that plasma PON1 activity is decreased in several diseases, including coronary artery diseases (CAD),[13] diabetes mellitus,[14] obesity,[15] and renal failure.[16]

PON-1 activity is more closely related to the HDL-C concentration. Moreover, reduced PON1 activity is considered as a major cause of HDL-C dysfunction and atherosclerosis development. In addition, it has been reported that plasma PON-1 activity is related to variation of plasma concentrations of triglyceride (TG), LDL-C, apoA-I, and apolipoprotein B100 (apoB).[17–19]

Duo to the significant role of HDL-C characteristics in CHD development, studies about HDL-C related enzymes such as PON1 and its association with lipid profile and lipoproteins levels seem to be necessary. Therefore, this study was performed to study correlation between serum PON1 activity and lipid profile apoA-I, apoB, and apoB/apoA-I ratio in subjects with different levels of HDL.

Materials and methods

135 men aged 20–60 years (body mass index (BMI) $\leq$30 kg/m^2) participated in this study. Inclusion criteria included no infections, allergies, thyroid dysfunction, diabetes mellitus, kidney and liver diseases, familiar hypercholesterolemia and sign of cardiovascular or inflammatory diseases, and use of corticosteroid or lipid-lowering drugs. Demographic information about life style, medication, and family history were acquired through interviews with subjects and all participants were asked not to change, as much as possible, their lifestyle, dietary habits and physical activity levels during the intervention. The Ethics Committee of Isfahan Cardiovascular Research Center (ICRC), a WHO collaborating center approved this study protocol, and all participants provided written informed consent.

Individuals were categorized into three groups with different levels of HDL- C, group 1 (n = 45): HDL-C $\leq$35 mg/dl; group 2 (n = 45): 35> HDL-C $\leq$55 mg/dl; group 3 (n = 45): HDL-C >55 mg/dl.

Biochemical measurements

A blood sample was taken in the morning after 12–14 h fasting. Samples were centrifuged for 15 min at 3000 rpm (1792× *g*) and stored at −20 °C until analysis. Serum levels of FBS, and lipid profiles such as total cholesterol (TC), triglyceride (TG), HDL-C, and LDL-C were analyzed enzymatically by commercial laboratory kits (Pars Azmoon, Iran) in a fully automated analyzer, Hitachi 917 (Japan). ApoA-I and apoB were measured by immunoturbidometric methods using an automated analyzer (Hitachi 917, Kyoto, Japan) and commercial kits (Pars Azmoon, Iran).

Serum PON1 activity

Serum PON1 activity was measured using commercial enzyme assay kit (Taligene Pars, Isfahan, Iran). In this assay, PON1 catalyzed the cleavage of paraoxon resulting in p-nitrophenol formation. The p-nitrophenol formation was assayed by monitoring the increase in absorbance at 412 nm (25 °C) by using spectrophotometer (UV-2600, Shimadzu, Kyoto, Japan).

Statistical analysis

Statistical analyses were performed by SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). One-way ANOVA was performed to compare mean values between three groups with different HDL-C levels; once the differences existed among the means, the pairwise multiple comparisons were determined by Tukey HSD, as the post hoc range tests. Bivariate linear regression models were used to investigate the unadjusted relationships between outcome variables (i.e., HDL-C level, paraoxonase activity, and apoB to apoA-I) and explanatory variables (i.e., ALT, AST, LDL, HDL, Cholesterol, TG, FBS, apoB, and apoA-I), respectively (Model #1 in Tables 2–6). To investigate the effect of

Table 1 General characteristics and biochemical laboratory data in subjects with three levels of HDL.

Variables	Group 1	Group 2	Group 3	P-value (G1-G2)	P-value (G1-G3)	P-value (G2-G3)
Age	42 ± 11 P-value = 0.413[a]	39 ± 10	42 ± 13	0.364	0.704	0.196
BMI (kg/m^2)	25.59 ± 3.64 P-value = 0.135[a]	24.79 ± 3.00	24.04 ± 3.88	0.289	0.056	0.289
ALT (IU/L)	40.71 ± 29.45 P-value = 0.317[a]	33.45 ± 22.56	32.54 ± 23.29	0.203	0.169	0.870
AST (IU/L)	28.84 ± 15.99 P-value = 0.153[a]	22.93 ± 10.04	26.00 ± 13.83	0.055	0.376	0.300
LDL (mg/dl)	109.83 ± 29.85 P-value < 0.001[a,b,c]	104.98 ± 26.57	85.21 ± 29.95	0.002	<0.001	0.439
Chol (mg/dl)	197.67 ± 33.77 P-value < 0.001[a,b,c]	173.77 ± 32.61	161.91 ± 34.83	0.106	<0.001	0.001
TG (mg/dl)	200.88 ± 81.42 P-value < 0.001[a,b,c]	120.22 ± 53.80	104.31 ± 49.24	<0.001	<0.001	0.252
FBS (mg/dl)	98.72 ± 10.73 P-value = 0.153[a]	95.58 ± 7.92	97.10 ± 9.71	0.458	0.432	0.123
PON1 activity (IU/L)	28.97 ± 19.30 P-value = 0.031[a,b,c]	42.06 ± 24.48	44.56 ± 39.25	0.036	0.015	0.688
Apo B (mg/dl)	114.60 ± 45.52 P-value = 0.153[a]	117.92 ± 46.07	105.70 ± 42.52	0.725	0.353	0.203
ApoA-I (mg/dl)	127.07 ± 9.19 P-value < 0.001[a,b,c]	179.73 ± 16.60	207.01 ± 34.45	<0.001	<0.001	<0.001
ApoB/apoA-I	0.97 ± 0.49 P-value < 0.001[a,b,c]	0.67 ± 0.28	0.52 ± 0.21	<0.001	<0.001	0.047

Note. ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Triglyceride; FBS: Fasting Blood Sugar Levels; Apo: Apolipoprotein; Group 1: HDL ≤35 mg/dl; Group 2: 35 > HDL ≤55 mg/dl; Group 3, HDL >55 mg/dl. Means ± Standard deviations are presented.

[a] Using one-way ANOVA.

[b] Using Tukey HSD test.

[c] Significant at level of 5%.

potential confounders (i.e., age and BMI) in regression models, the multivariate linear regression analyses were performed (Model#2 in Tables 2–6). These analyses estimated the effect of explanatory variables (β) on outcomes, and 95% confidence interval (CI) for βs. All tests were two-sided and the significant level was considered at 5%.

Results

Table 1 represents general characteristics and biochemical parameters (age, MBI, ALT, AST, FBS, LDL, HDL, TG, Cholesterol, PON1 activity, apoB, apoA-I, and apoB/apoA-I) of all subjects. As observed in Table 1, age of all subjects was matched in the three groups. Moreover, there was no significant difference in the mean level of ALT, AST, BMI, FBS, and apoB. The mean LDL-C value in group 3 was lower compared with that in group 1 ($P < 0.001$). Group 1 subjects had higher cholesterol levels in comparison with group 2 and 3. However, there was no significant difference in cholesterol levels among group 1 and 2. Group 1 had higher level of TG in comparison to group 2 and 3. The serum PON1 activity was lower in group 1 compared with those in groups 2. Serum apoA-I level was significantly increased in parallel with increasing of serum HDL-C level. ApoB/apoA-I ratio was decreased with HDL-C level increasing and was higher in the low HDL-C group.

Table 2 shows effects of clinical biomarkers (LDL, Cholesterol, TG, PON1, apoA-I, and apoB/apoA-I) on HDL in three experimental group. As seen in Table 2, there was a negative relationship between serum HDL-C levels with cholesterol level in group 2. Moreover, serum HDL-C level was positively effects on apoA-I level in group 2 and 3. As shown in Table 3, the expected direct association of paraoxonase activity with apoA-I and serum HDL-C status in group 1 was presented. Furthermore, by reducing potential confounders such as age and BMI, positive relationship between serum HDL-C level and paraoxonase activity was observed in group 3. Additionally, linear regression model was performed to investigate effects of lipid profiles, paraoxonase activity, and ApoA-I on ApoB/apoA-I ratio (Table 4). ApoB/apoA-I ratio had a direct outcome on LDL, cholesterol and TG among three groups ($P < 0.001$). Negative associations between ApoB/Apoa1 ratio and HDL-C were observed (Table 3). Tables 5 and 6 show correlations between clinical biomarkers (ALT, AST, FBS, LDL, HDL, TG, Cholesterol, PON1 activity, apoB, apoA-I, and apoB/apoA-I) and HDL level, ApoB/apoA-I ratio, and PON1 activity in all subjects. As shown in Table 5, serum HDL-C level increased LDL-C, cholesterol, apoA-I and PON1 activity, and HDL-C level decreasing evaluated TG, apoB, and apoB/apoA-I ratio. In addition, serum PON1 activity was directly associated with serum HDL-C level and apoA-I. Moreover, results indicate a significant negative effect of apoB/apoA-I

Table 2 The effect of lipid profiles, paraoxonase activity, and ApoA-I, and ApoB/apoA-I on HDL, by using linear regression model, in subjects with different levels of HDL.

Variables		Model #1				Model #2			
		r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value
LDL (mg/dl)	Group 1	0.13	0.02	−0.01 (−0.03, 0.01)	0.429	0.19	0.04	−0.01 (−0.04, 0.01)	0.387
	Group 2	0.28	0.08	−0.01 (−0.02, 0.09)	0.074	0.32	0.10	−0.01 (−0.02, 0.09)	0.190
	Group 3	0.13	0.02	−0.03 (−0.09, 0.04)	0.426	0.20	0.04	−0.03 (−0.10, 0.04)	0.418
Chol (mg/dl)	Group 1	0.03	0.01	−0.001 (−0.02, 0.02)	0.793	0.19	0.02	−0.001 (−0.02, 0.02)	0.836
	Group 2	0.38	0.15	−0.26 (−0.40, 0.11)	0.012[a]	0.32	0.16	−0.06 (−0.002, 0.11)	0.042[a]
	Group 3	0.04	0.01	−0.01 (−0.06, 0.07)	0.160	0.20	0.02	−0.01 (−0.07, 0.08)	0.177
TG (mg/dl)	Group 1	0.02	0.04	−0.01 (−0.04, 0.01)	0.216	0.12	0.02	−0.004 (−0.11, 0.10)	0.944
	Group 2	0.08	0.01	−0.02 (−0.05, 0.08)	0.603	0.22	0.05	−0.003 (−0.07, 0.07)	0.932
	Group 3	0.20	0.01	−0.01 (−0.10, 0.09)	0.883	0.24	0.06	−0.01 (−0.04, 0.01)	0.251
PON1 activity (IU/L)	Group 1	0.21	0.04	−0.03 (−0.07, 0.02)	0.209	0.28	0.08	−0.03 (−0.07, 0.02)	0.252
	Group 2	0.13	0.02	0.02 (−0.03, 0.07)	0.398	0.24	0.06	0.01 (−0.04, 0.07)	0.655
	Group 3	0.12	0.01	−0.01 (−0.05, 0.02)	0.468	0.24	0.06	−0.02 (−0.06, 0.02)	0.291
ApoA-I (mg/dl)	Group 1	0.59	0.01	−0.01 (−0.05, 0.02)	0.468	0.64	0.20	0.004 (0.001, 0.01)	0.004[a]
	Group 2	0.42	0.18	0.02 (0.01, 0.03)	0.004[a]	0.46	0.40	0.05 (0.03, 0.07)	<0.001[a]
	Group 3	0.41	0.35	0.04 (0.02, 0.06)	<0.001[a]	0.45	0.40	0.05 (0.03, 0.07)	<0.001[a]
ApoB/apoA-I	Group 1	0.10	0.09	−0.02 (−0.04, 0.001)	0.050	0.14	0.02	−0.03 (−0.14, 0.07)	0.518
	Group 2	0.01	0.01	−0.002 (−0.06, 0.06)	0.948	0.24	0.06	−0.02 (−0.08, 0.05)	0.646
	Group 3	0.30	0.01	−0.03 (−0.12, 0.07)	0.556	0.32	0.10	−0.02 (−0.04, 0.01)	0.052

Note. HDL: High-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Triglyceride; FBS: Fasting Blood Sugar Levels; PON1: Paraoxonase; Apo: Apolipoprotein.
Model #1: Bivariate Linear regression model, including one continuous explanatory variable.
Model #2: Linear regression model, adjusted for potential confounders, such as Age and BMI.
r: Linear correlation; R^2: Coefficient of determination in regression model; β: Regression coefficient; CI: Confidence Interval.
[a] Significant at level of 5%.

Table 3 The effect of lipid profiles, paraoxonase activity, and ApoA-I, and ApoB/apoA-I on paraoxonase activity, by using linear regression model, in subjects with different levels of HDL.

Variables		Model #1				Model #2			
		r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value
LDL (mg/dl)	Group 1	0.06	0.01	−0.08 (−0.32, 0.16)	0.497	0.30	0.22	−0.07 (−0.30, 0.15)	0.516
	Group 2	0.44	0.01	−0.08 (−0.69, 0.42)	0.651	0.51	0.08	−0.20 (−0.65, 0.31)	0.502
	Group 3	0.11	0.01	−0.08 (−0.59, 0.42)	0.741	0.47	0.09	−0.22 (−0.75, 0.31)	0.403
Chol (mg/dl)	Group 1	0.14	0.01	−0.06 (−0.29, 0.17)	0.614	0.27	0.23	−0.09 (−0.30, 0.12)	0.396
	Group 2	0.34	0.11	0.32 (0.04, 0.60)	0.066	0.42	0.18	0.25 (−0.05, 0.55)	0.100
	Group 3	0.09	0.02	0.17 (−0.28, 0.62)	0.443	0.48	0.07	0.06 (−0.43, 0.54)	0.817
TG (mg/dl)	Group 1	0.12	0.01	0.001 (−0.19, 0.20)	0.993	0.39	0.15	0.66 (−0.06, 1.38)	0.074
	Group 2	0.07	0.07	0.31 (−0.06, 0.67)	0.100	0.43	0.18	0.22 (−0.16, 0.59)	0.249
	Group 3	0.01	0.12	0.74 (0.05, 1.43)	0.077	0.63	0.15	0.66 (−0.06, 1.38)	0.074
HDL (mg/dl)	Group 1	0.19	0.20	0.14 (0.05, 0.23)	0.004[a]	0.32	0.10	−0.24 (−0.67, 0.19)	0.267
	Group 2	0.21	0.02	−0.06 (−0.19, 0.07)	0.378	0.36	0.13	−0.05 (−0.18, 0.08)	0.441
	Group 3	0.13	0.04	−0.27 (−0.69, 0.15)	0.198	0.60	0.36	0.15 (0.07, 0.24)	0.001[a]
ApoA-I (mg/dl)	Group 1	0.22	0.22	0.02 (0.001, 0.04)	0.021[a]	0.32	0.23	0.02 (0.001, 0.04)	0.039[a]
	Group 2	0.15	0.15	0.03 (−0.03, 0.09)	0.345	0.37	0.13	0.03 (−0.03, 0.09)	0.362
	Group 3	0.36	0.36	0.04 (−0.02, 0.09)	0.176	0.49	0.10	0.03 (−0.03, 0.08)	0.285
ApoB/apoA-I	Group 1	0.05	0.05	−0.13 (−0.29, 0.04)	0.136	0.28	0.17	−0.10 (−0.27, 0.07)	0.247
	Group 2	0.24	0.24	−0.28 (−0.06, 0.62)	0.107	0.38	0.06	−0.02 (−0.08, 0.05)	0.646
	Group 3	0.24	0.24	−0.10 (−0.76, 0.55)	0.749	0.42	0.08	−0.18 (−0.84, 0.48)	0.575

Note. HDL: High-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Triglyceride; FBS: Fasting Blood Sugar Levels; PON1: Paraoxonase; Apo: Apolipoprotein.
Model #1: Bivariate Linear regression model, including one continuous explanatory variable.
Model #2: Linear regression model, adjusted for potential confounders, such as Age and BMI.
r: Linear correlation; R^2: Coefficient of determination in regression model; β: Regression coefficient; CI: Confidence Interval.
[a] Significant at level of 5%.

Table 4 The effect of lipid profiles, paraoxonase activity, and ApoA-I on ApoB/apoA-I ratio, by using linear regression model, in subjects with different levels of HDL.

Variables		Model #1				Model #2			
		r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value
LDL (mg/dl)	Group 1	0.81	0.63	0.88 (0.66, 1.09)	<0.001[a]	0.82	0.65	0.90 (0.68, 1.13)	<0.001[a]
	Group 2	0.69	0.47	0.54 (0.36, 0.73)	<0.001[a]	0.70	0.25	0.37 (0.09, 0.66)	0.011[a]
	Group 3	0.80	0.66	0.46 (0.35, 0.57)	<0.001[a]	0.81	0.67	0.45 (0.33, 0.56)	<0.001[a]
Chol (mg/dl)	Group 1	0.87	0.38	0.70 (0.41, 1.00)	<0.001[a]	0.87	0.39	0.70 (0.40, 1.00)	<0.001[a]
	Group 2	0.70	0.49	0.54 (0.37, 0.72)	<0.001[a]	0.71	0.18	0.25 (−0.05, 0.55)	0.100
	Group 3	0.62	0.75	0.51 (0.41, 0.60)	<0.001[a]	0.63	0.75	0.51 (0.40, 0.61)	<0.001[a]
TG (mg/dl)	Group 1	0.56	0.09	0.32 (−0.02, 0.66)	0.062	0.58	0.24	0.43 (0.09, 0.77)	0.015[a]
	Group 2	0.39	0.15	0.37 (0.09, 0.66)	0.010[a]	0.46	0.18	0.22 (−0.16, 0.59)	0.249
	Group 3	0.30	0.32	0.46 (0.23, 0.69)	<0.001[a]	0.49	0.33	0.44 (0.20, 0.68)	0.001[a]
HDL (mg/dl)	Group 1	0.67	0.21	−0.27 (−0.43, 0.11)	0.002[a]	0.70	0.28	−0.27 (−0.43, 0.10)	0.002[a]
	Group 2	0.20	0.04	−0.07 (−0.04, 0.19)	0.194	0.37	0.13	−0.05 (−0.18, 0.08)	0.441
	Group 3	0.46	0.01	−0.002 (−0.06, 0.06)	0.948	0.53	0.10	−0.02 (−0.04, 0.01)	0.052
ApoA-I (mg/dl)	Group 1	0.68	0.41	−0.07 (−0.10, −0.04)	<0.001[a]	0.73	0.44	−0.07 (−0.09, −0.04)	<0.001[a]
	Group 2	0.40	0.16	−0.07 (−0.11, −0.02)	0.006[a]	0.54	0.13	0.03 (−0.03, 0.09)	0.362
	Group 3	0.64	0.46	−0.06 (−0.08, −0.04)	<0.001[a]	0.66	0.54	−0.06 (−0.08, −0.04)	<0.001[a]
PON1 activity (IU/L)	Group 1	0.05	0.06	−0.45 (−1.04, 0.15)	0.136	0.21	0.17	−0.36 (−0.98, 0.26)	0.247
	Group 2	0.24	0.06	0.21 (−0.05, 0.46)	0.107	0.37	0.06	−0.02 (−0.08, 0.05)	0.646
	Group 3	0.24	0.01	−0.03 (−0.21, 0.15)	0.749	0.42	0.04	−0.05 (−0.24, 0.14)	0.575

Note. HDL: High-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Trigliserid; FBS: Fasting Blood Sugar Levels; PON1: Paraoxonase; Apo: Apolipoprotein.
Model #1: Bivariate Linear regression model, including one continuous explanatory variable.
Model #2: Linear regression model, adjusted for potential confounders, such as Age and BMI.
r: Linear correlation; R^2: Coefficient of determination in regression model; β: Regression coefficient; CI: Confidence Interval.
[a] Significant at level of 5%.

ratio on serum PON1 activity ($P < 0.032$) and serum HDL-C levels ($P < 0.001$) and apoA-I ($P < 0.001$). On the other hand, there was a significant positive relationship between apoB/apoA-I with ALT ($P < 0.003$), AST ($P < 0.001$), LDL-C ($P < 0.001$), cholesterol ($P < 0.001$), TG ($P < 0.001$) and apoB ($P < 0.001$). In Table 6 by reducing potential confounders such as age and BMI, the more significant results were observed.

Discussion

The current study investigated correlation between serum paraoxonase activity and lipid profile, apoA-I, and apoB in healthy adult men with different levels of HDL. The results of the present study have indicated that serum PON1 activity in subjects with high HDL-C levels (group 3) was significantly higher in comparison with subjects with normal and low HDL-C levels. Other investigations have shown similar results and demonstrating that PON1 activity contribute to increased levels of HDL-C.[20,21] CHD as a most prevalent and mortal diseases in the world has many independent risk factors such as age, sex, hypertension, smoking, diabetes, elevated plasma level of LDL-C cholesterol (LDL-C >160 mg/dl), and low level of HDL-C (HDL-C <35 mg/dL).[22,23] Although prospective epidemiological studies have indicated that HDL-C is an independent risk factor for CHD, the data have shown that HDL dysfunctionality may be associated with the development of atherosclerosis even at physiological levels of HDL-C.[24,25] A positive correlation between PON1 activity and HDL-C levels has been reported in pervious study. A significant decrease in PON1 activity (arylesterase and paraoxonase) and concentration was observed in CHD patients.[26] In the current study, group 1 (HDL ≤35 mg/dl) had the highest cholesterol, TG, LDL, apoB and apoB/apoA-I. In addition, this group had lower PON1 activity and apoA-I in comparison with other groups. It has been appeared that higher levels of TG, LDL, apoB and apoB/apoA-I leading to HDL dysfunction.[27] Further, in this study, the expected positive correlation between serum PON1 activity, apoA-I and serum HDL-C levels was observed in group 1 and all subjects. Moreover, these data are consistent with pervious study suggested that PON1 activity could influence HDL concentration.[28,29] On the other hand, PON1 activity could effect on plasma concentrations of HDL.[29] Moreover, by reducing potential confounders such as age and BMI, a direct association between serum PON1 activity and serum HDL-C level was observed in subjects with serum HDL-C levels of >55 mg/dl. It is evidenced that PON1 activity is influenced by different factors including environment, pharmacological factors, and lifestyle.[30,31] The PON1 activity and apoA-I level contribute to the HDL-associated antioxidant activity of PON1. Previous study have demonstrated that there is a positive correlation between PON1 enzymatic activity and apoA-I. In fact, arylesterase activity of PON is associated with apoA-I containing HDL. Moreover, lactonase activity of this enzyme increases by binding of PON1 to the apoA-I-HDL-C.[32,33] Lipolactonase activity of the PON1 is stimulated by apoA-I-HDL that inhibits LDL-C

Table 5 Correlations between clinical biomarkers and HDL level, ApoB/apoA-I ratio, and PON1 activity in all subject.

Variables	HDL levels				PON1 activity				ApoB/apoA-I			
	r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value
ALT (IU/L)	0.04	0.01	−0.03 (−0.13, 0.08)	0.652	0.05	0.03	0.06 (−0.15, 0.27)	0.592	0.28	0.08	0.31 (0.11, 0.52)	0.003[a]
AST (IU/L)	0.01	0.01	−0.001 (−0.11, 0.10)	0.990	0.07	0.01	−0.08 (−0.29, 0.13)	0.466	0.37	0.14	0.40 (0.21, 0.60)	<0.001[a]
FBS (mg/dl)	0.08	0.01	−0.04 (−0.14, 0.05)	0.374	0.15	0.02	0.15 (−0.04, 0.33)	0.112	0.06	0.01	0.05 (−0.11, 0.22)	0.056
LDL (mg/dl)	0.32	0.10	0.18 (0.08, 0.28)	<0.001[a]	0.14	0.02	−0.15 (−0.05, 0.34)	0.130	0.43	0.18	0.39 (0.24, 0.54)	<0.001[a]
HDL (mg/dl)					0.19	0.03	0.34 (0.02, 0.67)	0.040[a]	0.45	0.20	−0.82 (−1.11, −0.53)	<0.001[a]
Chol (mg/dl)	0.43	0.19	0.24 (0.15, 0.33)	<0.001[a]	0.17	0.03	0.18 (−0.01, 0.36)	0.063	0.35	0.13	0.32 (0.17, 0.47)	<0.001[a]
TG (mg/dl)	0.47	0.22	−0.26 (−0.36, −0.17)	<0.001[a]	0.03	0.01	0.03 (−0.18, 0.23)	0.794	0.39	0.15	0.40 (0.23, 0.58)	<0.001[a]
PON1 activity (IU/L)	0.19	0.03	0.10 (0.01, 0.20)	0.001[a]					0.04	0.01	−0.04 (−0.22, 0.14)	0.032[a]
Apo B (mg/dl)	0.08	0.01	−0.04 (−0.14, 0.05)	0.387	0.14	0.02	0.14 (−0.04, 0.31)	0.133	0.77	0.59	0.77 (0.66, 0.88)	<0.001[a]
ApoA-I (mg/dl)	0.80	0.64	0.05 (0.04, 0.05)	<0.001[a]	0.23	0.05	0.03 (0.01, 0.05)	0.010[a]	0.61	0.37	−0.02 (−0.02, −0.01)	<0.001[a]

Note. HDL: High-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Trigliserid; FBS: Fasting Blood Sugar Levels; PON1: Paraoxonase; Apo: Apolipoprotein. Bivariate Linear regression model, including one continuous explanatory variable.
r: Linear correlation; R^2: Coefficient of determination in regression model; β: Regression coefficient; CI: Confidence Interval.
[a] Significant at level of 5%.

Table 6 Correlations between clinical biomarkers and HDL levels, ApoB/ApoA1 ratio, and PON1 activity in all subject.

Variables	HDL levels				PON1 activity				ApoB/ApoA1			
	r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value	r	R^2	β (95% CI)	p-value
ALT (IU/L)	0.23	0.01	−0.02 (−0.13, 0.09)	0.691	0.22	0.05	0.04 (−0.18, 0.24)	0.746	0.34	0.12	0.34 (0.14, 0.55)	0.001[a]
AST (IU/L)	0.22	0.05	−0.01 (−0.11, 0.10)	0.903	0.23	0.05	−0.08 (−0.29, 0.13)	0.452	0.40	0.16	0.40 (0.20, 0.59)	<0.001[a]
FBS (mg/dl)	0.22	0.05	−0.05 (−0.15, 0.05)	0.346	0.11	0.04	0.14 (−0.05, 0.33)	0.136	0.21	0.05	0.03 (−0.14, 0.20)	0.722
LDL (mg/dl)	0.37	0.13	0.18 (0.08, 0.28)	<0.001[a]	0.20	0.04	0.14 (−0.05, 0.34)	0.150	0.47	0.22	0.39 (0.24, 0.54)	<0.001[a]
HDL (mg/dl)					0.26	0.07	0.40 (0.07, 0.72)	0.018[a]	0.48	0.23	−0.81 (−1.10, −0.52)	<0.001[a]
Chol (mg/dl)	0.48	0.23	0.25 (0.16, 0.34)	<0.001[a]	0.22	0.05	0.17 (−0.02, 0.35)	0.081	0.39	0.015	0.31 (0.16, 0.46)	<0.001[a]
TG (mg/dl)	0.47	0.22	−0.26 (−0.35, −0.16)	<0.001[a]	0.16	0.03	−0.01 (−0.22, 0.20)	0.903	0.43	0.19	0.42 (0.24, 0.59)	<0.001[a]
PON1 activity (IU/L)	0.27	0.07	0.12 (0.02, 0.21)	0.017[a]					0.25	0.06	−0.07 (−0.24, 0.11)	0.002[a]
Apo B (mg/dl)	0.18	0.03	−0.03 (−0.13, 0.07)	0.558	0.18	0.03	0.11 (−0.07, 0.30)	0.232	0.77	0.59	0.77 (0.65, 0.88)	<0.001[a]
Apo A (mg/dl)	0.81	0.65	0.05 (0.04, 0.05)	<0.001[a]	0.28	0.08	0.03 (0.01, 0.05)	0.008[a]	0.63	0.40	−0.02 (−0.02, −0.01)	<0.001[a]

Note. HDL: High-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; LDL: Low-density lipoprotein; Chol: Cholesterol; TG: Trigliserid; FBS: Fasting Blood Sugar Levels; PON1: Paraoxonase; Apo: Apolipoprotein. Linear regression model, adjusted for potential confounders, such as Age and BMI.
r: Linear correlation; R^2: Coefficient of determination in regression model; β: Regression coefficient; CI: Confidence Interval.
[a] Significant at level of 5%.

oxidation and increases the HDL-mediated cholesterol efflux.[10,34] Moreover, results reveled a significant negative correlation between apoB/apoA-I ratio and PON1 activity. In addition, apoB/apoA-I ratio was positively correlated to LDL-C, TG, and cholesterol among three groups and all subjects. As mentioned perversely high cholesterol, TG, LDL, and low levels of HDL-C, are independent predictors of CHD.[25] Moreover, HDL function is reflected by HDL-C levels, PON1 activity, and apoA-I levels. It is suggested that abnormalities in the association between these parameters could explain the development of CHD in individuals with lower HDL-C levels.

Conclusion

In conclusion, we found significantly lower activity of PON1 and apoA- I in subjects with lower levels of HDL-C. Significantly, higher levels of TG, TC, LDL and apoB/apoA-I ratio was observed in subjects with HDL $\leq$35 mg/dl. The protective mechanisms of HDL-C against CHD is a multifactorial procedure that depends on the HDL-C particle size, number, composition, distribution, and PON1 activity. The observed relationship between PON1 activity and lipid profile, apoA-I, apoB, and apoB/apoA-I ratio in subjects with different levels of HCL-C indicating that decreased PON1 activity, apoA-I, and HDL levels and increased TG, TC, LDL, apoB and, apoB/apoA-I ratios could be used for early diagnoses of CHD in adults. However, long-term clinical studies in extended sample size are needed to confirm the relationship of PON1 activity with HDL characteristics and atherogenic index.

Conflict of interest

None declared.

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