Review Article

Implications of serum paraoxonase activity in obesity, diabetes mellitus, and dyslipidemia

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ABSTRACT

Human serum paraoxonase 1 (PON1) is an enzyme with esterase activity, and is physically bound to high-density lipoproteins (HDL). It plays a key role in the action of HDL toward protection of lipoprotein and biological membrane against oxidative damage. It may have a protective role against atherosclerosis by virtue of its action on hydrolyzing lipid peroxides and preventing accumulation of phospholipids in oxidized low-density lipoprotein (LDL). PON1 is hypothesized to be an indicator of the risk of atherosclerosis and coronary artery disease development. Numerous studies have implicated PON1 activity in relation to various endocrine disorders. The current article reviews the clinical perspectives of PON1 activity with regards to obesity, diabetes mellitus with its complications, and dyslipidemia.

Key words: Diabetes mellitus, dyslipidemia, high-density lipoprotein, obesity, paraoxonase

Introduction

Paraoxonase (aryldialkylphosphatase) is an enzyme having both paraoxonase and aryl esterase activity.[1,2] It hydrolyzes aromatic carboxylic acid esters and certain organophosphorous pesticides, especially paraoxon and nerve gas.[3,4] Plasma paraoxonase (PON) activity in human population demonstrates polymorphic distribution due to an amino acid substitution in the active site of the enzyme, giving rise to low-, intermediate-, or high-activity isoenzymes.[5-8] The polymorphic variation in serum PON activity may affect the metabolism of organophosphates in individuals at high risk of acute organophosphorous intoxication or of organophosphorous-induced delayed polyneuropathy.[9]

Human PONs are high-density lipoprotein (HDL) associated enzymes. PON is located in a subfraction of HDL containing apo A-I and clusterin (Apo J). PON is anchored to HDL by its hydrophobic N terminal end and Apo A-I.[10,11] PON1 and PON3 are expressed in the liver. After secretion into blood, they bind to HDL particles;[12,13] PON2 is expressed widely in a number of tissues but is not present in the blood.[14] The genes encoding the PON family (PON1, PON2, and PON3) are all located on the long arm of chromosome 7 (7q21.3-q22.1).[15]

Paraoxonase: Actions and Alteration in Various States

It plays a significant role in delaying/inhibiting the oxidation of both low-density lipoprotein (LDL) and HDL particles.[16,17] By virtue of its actions like prevention of accumulation of lipid peroxides in LDL, stimulation of breakdown by hydrolysis of lipid peroxides, and protection against lipoprotein oxidation, PON1 has a protective role

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against atherosclerosis and cardiovascular disease Figures 1 and 2.[14,15,18] PON2 and PON3 both have antioxidant properties and hydrolyze aromatic and long-chain aliphatic lactones, but lack paraoxonase or arylesterase activities.[19,20] Similar to PON1, PON3 too protects against LDL oxidation and inflammation,[13] reflecting its atheroprotective effect. Shih *et al*. reported that elevated PON3 expression significantly decreases atherosclerotic lesion formation and adiposity in male mice,[21] signifying the important role of PON3 in protection against obesity and atherosclerosis.

PON1 activity is decreased in patients with diabetes mellitus (DM),[22] cardiovascular complications,[23] hypercholesterolemia, and renal failure.[24] Some environmental, pharmacological or other factors may change the activity of PON1. The factors that induce the activity of PON1 are drugs such as statins, fibrates, aspirin, glucocorticoids, and phenobarbital, which are classical inducers of PON1 activity.[1,25-27] Some environmental chemicals abolish its activity.[28] PON1 activity is also decreased by smoking, alcohol, fat-rich diet, and aging.[1-4,12-17,25-32] Few studies had shown that PON1 activity is slightly higher in the female gender.[7,27]

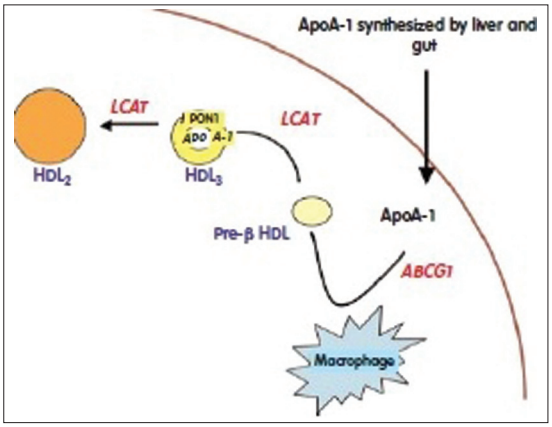

Figure 1: High-density lipoproteins (HDL) is maturated from pre-β-946; migrating HDL to HDL3 by the action of lecithin-cholesterol acyltransferase and then to HDL2 which is large and rich in paraoxonase 1

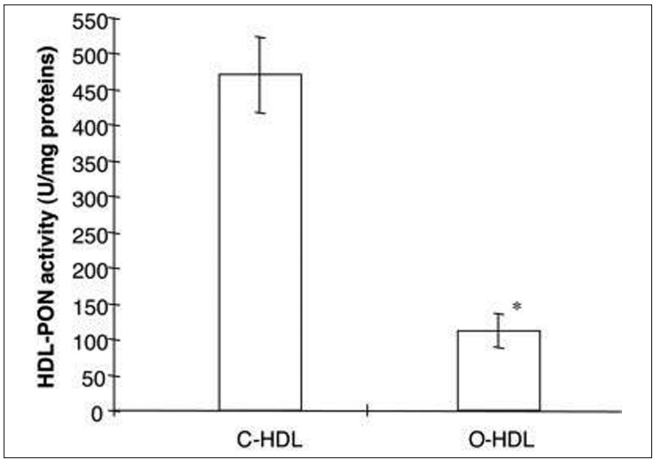

Figure 3: Values of paraoxonase activity in high-density lipoproteins isolated from plasma of control and obese subjects

Paraoxonase 1 Activity in Obesity

Obesity is associated with several alterations in the lipid metabolism, leading to changes in lipoprotein levels and composition,[33,34] and greater risk of cardiovascular disease. Oxidative stress is increased in obese subjects compared with healthy controls[35] Figure 3. Ferretti *et al*. reported significantly lower PON activity in obese subjects compared with control subjects.[36] A relationship was found between HDL-PON and lipid hydroperoxides in HDL and LDL of control and obese subjects, which suggests that subjects with lower PON activity are more exposed to oxidative damage Figure 4. In obese adults, diminished levels of PON1 activity is correlated with low levels of HDL-cholesterol.[36,37] Body mass index is an independent predictor of PON1 activity.[38] In another study involving childhood subjects, there was decreased PON1 activity in obese compared with normal weight peers.[39] The aryl esterase activity had significant positive correlation with adipokine levels and

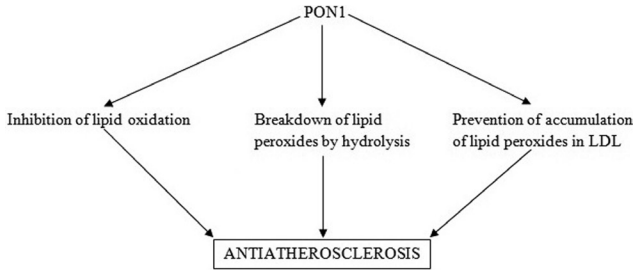

Figure 2: Anti-atherosclerotic properties of PON1. (PON1: Paraoxonase 1, LDL: Low-density lipoprotein)

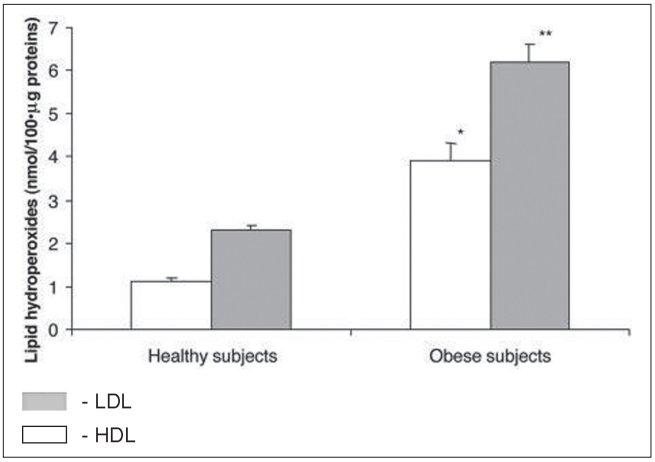

Figure 4: Levels of lipid hydroperoxides in high-density lipoproteins (HDL) and low-density lipoprotein (LDL) isolated from plasma of control and obese subjects. Data are expressed as the mean ± SEM. **P* < 0.001 vs. lipid hydroperoxides in HDL from control subjects; ***P* < 0.001 vs. levels of hydroperoxides in LDL from control subjects

negative correlation with leptin concentrations. These results confirm that obesity is associated with oxidative damage of lipoproteins and may explain the increased cardiovascular risk in obese people. Orlistat treatment in obese subjects increases PON1 activity and PON/HDL ratio besides altering the lipid profile.[40]

Correlations between leptin levels[38] as well as adiponectin levels and PON1 activity have been previously proven in obese adults[41] Figure 5. There are several mechanisms of adipokines influencing PON1 activity. Beltowski found that rats treated with leptin had decreased PON1 activity.[42] These mechanisms may be the following: leptin as a hydrophobic peptide can bind to HDL[43] and inhibit directly the PON1 enzyme. On the other hand, leptin enhances oxidative stress[44,45] through the generation of reactive oxygen species (ROS)[42] and stimulates the secretion of inflammatory cytokines[46] and other acute phase proteins which have diminishing effect on PON1 enzyme activity by the inhibitory effect on hepatic PON1 synthesis.[47] Leptin also enhances the production of serum amyloid A protein[48] which can replace apolipoprotein-A1 (apo A-I) in HDL. Apo A-I plays a major role in stabilizing the structure of PON1. Leptin may have modulatory effect through the alteration of the lipid content in HDL particles;[49] inverse correlation has been observed between leptin, HDL, and apo A-I in human subjects.[50] Adiponectin might accelerate the reverse cholesterol transport and increase apo A-I–mediated cholesterol efflux through enhancing HDL assembly in the liver.[51,52] Another study in male mice has demonstrated that elevated PON3 expression significantly decreases atherosclerotic lesion formation and adiposity.[21] Women with polycystic ovarian syndrome (PCOS) and obesity were found to have high insulin resistance and significantly lower PON1 levels.[53,54] These findings suggest that decreased PON1 activity in PCOS patients might contribute to increased insulin resistance and attendant atherosclerotic heart disease. Table 1 gives the summary of studies demonstrating the relationship between lower PON activity in obesity and associated increase in cardiovascular risk. Analysis of the studies on PON1 activity in obesity leads to the conclusion that obesity is associated with 50–60% reduction in PON activity, accompanied by significant fall in LDL and increase in HDL. This reflects in higher atherosclerotic potential. Studies have not yet analyzed the corresponding fall in PON with the incremental body mass index.

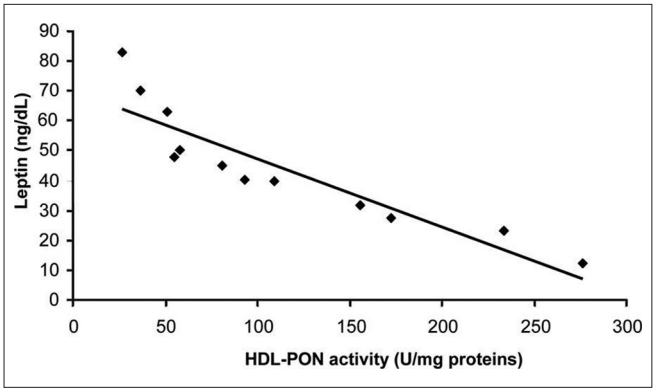

Figure 5: Correlation between the levels of HDL-PON activity and leptin in the plasma of obese subjects ($r = -0.90$; $P < 0.001$; $n = 12$)

Table 1: Summary of studies mentioning low paraoxonase 1 activity in obesity and associated increase in cardiovascular risk

Study	Country	Patients enrolled	Conclusion
Ferreti *et al*.[35]	Italy	43	Increase in oxidative stress in LDL and HDL of obese subjects is associated with a decrease in HDL-PON activity. The lower paraoxonase activity and the compositional changes in HDL and LDL could contribute to the greater risk of cardiovascular disease associated with obesity
Bajnok *et al*.[37]	Hungary	75	Serum levels of resistin showed a positive correlation with serum PON1 and a negative correlation with numerous parameters of the metabolic syndrome (i.e. adiposity, blood pressure, levels of leptin, free fatty acid, glycosylated hemoglobin, and lipid peroxidation). BMI is an independent predictor of PON1 activity
Koncsos *et al*.[38]	Hungary	31	Altered levels of leptin, adiponectin, and PON1 activities may be useful markers besides the general risk factors in childhood obesity
Bajnok *et al*.[40]	Hungary	74	PON1 activity shows negative association with markers of metabolic syndrome. Adiponectin is an independent variable of serum PON1, which may contribute to the anti-atherosclerotic effect of adiponectin
Beltowski *et al*.[41]	Poland	-	Hyperleptinemia induced by exogenous leptin administration markedly decreases plasma PON1 activity and induces oxidative stress. These lead to atherogenesis in hyperleptinemic obese individuals
Shih *et al*.[110]	USA	-	Elevated PON3 expression significantly decreases atherosclerotic lesion formation and adiposity in male mice
Garin *et al*.[54]	Switzerland	873	The metabolic syndrome is characterized by smaller, denser lipoprotein particles that increase their susceptibility to oxidative modifications and diminished serum paraoxonase-1, which is a major determinant of the antioxidant capacity of high-density lipoproteins. These may be contributory factors to the increased presence and severity of coronary disease in such patients

PON: Paraoxonase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BMI: Body mass index

Paraoxonase 1 Activity in Diabetes Mellitus

PON1 activity has been studied in patients with metabolic syndrome and insulin resistance, and some contradictions were found between the studies performed in non-diabetic subjects. In non-diabetic Swiss population, the significantly reduced serum PON1 concentrations and activities were associated with metabolic syndrome defined according to the World Health Organization (WHO) guidelines.[55] Yamada *et al*. have shown that there was a positive correlation between the Homeostasis Model Assessment (HOMA) index and HDL-corrected PON1 activity in non-diabetic Japanese subjects.[56] In another study on Turkish population, PON1 activities were not different between non-diabetic subjects with and without metabolic syndrome.[57] Additionally, Beer *et al*.[58] found that PON1 activities and concentrations were not different in diabetic patients compared to subjects with impaired fasting glucose and controls, although postprandial hyperlipemia was associated with changes in serum PON1 in diabetic subjects. In the same study, significantly low serum PON1 concentrations in the postprandial period were demonstrated, attributed to postprandial hypertriglyceridemia, whereas the decrease in PON1 activity was not statistically significant. There was no difference in the postprandial PON1 response between diabetic and non-diabetic groups. In another study,[59] PON1 activity was not significantly altered compared with normoglycemic controls, although oxidized LDL levels were significantly higher in glucose-intolerant and newly diagnosed diabetic subjects.[59] All these studies suggest that PON1 activity loss may occur later in the course of diabetes mellitus and hyperglycemia, rather than in the stage of insulin resistance.

Serum PON1 activity is significantly decreased in type 1 and type 2 diabetics compared to the healthy control subjects.[60-62] Ferretti *et al*. reported significantly lower PON1 activity in type 1 diabetic patients compared to healthy controls. They hypothesized that the decreased ability of HDL to protect erythrocyte membranes could be related to lipid composition of HDL and to this low PON1 enzyme activity[61] Figure 6. Diabetes is associated with oxidative damage.[63] The higher plasma levels of lipid peroxidation products in diabetic patients[64] are ascribed to higher susceptibility of plasma lipoproteins to oxidation[65,66] and decrease of plasma antioxidant defenses.[67] Altered myocardial substrate/ fat metabolism leads to diabetic cardiomyopathy.[68] Apart from decreased PON activity,[37,69,70] abnormal HDL composition and altered HDL subclasses distribution are also found in type 1 diabetes patients.[71,72]

The compositional changes in HDL lead to its altered

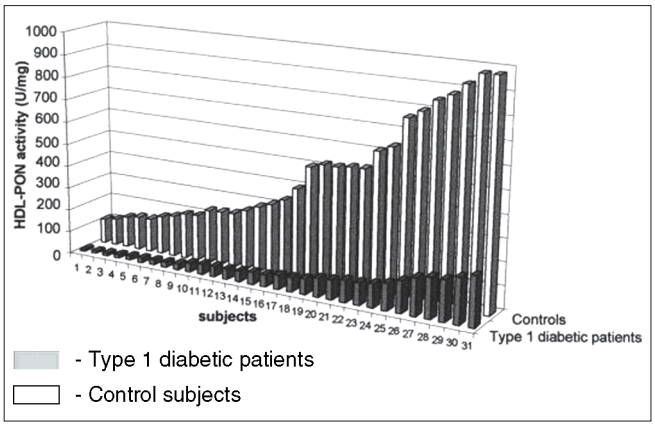

Figure 6: Activity of PON associated with HDL (HDL-PON) isolated from control subjects and type 1 diabetic patients. Activity is expressed as units per milligram of HDL protein

functional activities resulting in lower protection exerted by HDL from diabetic patients against LDL oxidation and a decreased capacity to induce cholesterol efflux from biological membranes.[17,73-76] Binding of PON to HDL is affected. There is also a conformational change in PON and altered availability of substrates within the hydrophobic region of HDL in which PON is active. It also gives rise to an increase in susceptibility to organophosphate poisoning.[9] Low serum PON activity cannot detoxify these compounds via hydrolysis. This leads to higher susceptibility to neural damage by these environmental toxins due to low PON activity in diabetes, resulting in an increase in organophosphate-induced delayed polyneuropathy in diabetic subjects.

There are propositions that other enzymes associated with HDL surface, such as plasma platelet-activating factor acetylhydrolase, lecithin cholesterol acetyl transferase (LCAT), and cholesteryl ester transfer protein (CETP),[77] might be involved in the alterations of the protective effect exerted by diabetic HDL against oxidative damage of biological membranes. In fact, previous studies have shown, in diabetic patients, modifications of the activities of enzymes involved in the antioxidant role of HDL, such as LCAT.[78] Moreover, a PON-independent inhibition of LDL oxidation by HDL has been observed by Graham *et al*.[79]

A larger proportion of the PON protein could be inactive in diabetes either because of the presence of an endogenous circulating inhibitor or perhaps because of increased glycosylation of PON. The loss of the strong correlation between PON concentration and glycation of apo A-I in healthy subjects[10] and in all the diabetic populations might indicate a disruption in the interaction between PON and the HDL particle. PON1 activity is lower in type 1 and type 2 diabetic patients, coupled with higher triglyceride levels, compared to non-diabetic control subjects although PON

serum levels are not significantly different. Unlike type 1 diabetes, HDL and apo A-I levels have been found to be lower in type 2 diabetic patients.[37] There is a contradiction in the literature about the correlation between glycated hemoglobin (HbA1c) and PON1 activity. A negative correlation was found in both types of diabetes,[62] although no significant association was reported between HbA1c and PON1 activity in a study performed in type 1 diabetes patients.[60] There was also a negative correlation between PON1 activity and presence of vascular complications.[62] The lower serum PON1 activity was found in diabetic patients with macrovascular complications than in those with microvascular complications. In a recent study,[80] reduced PON1 activity in type 2 diabetic patients was found to be associated with a significant increase in the risk of cardiovascular disease (CVD) which leads to the conclusion that PON1 activity could be a predictor of CVD in type 2 diabetes.[80] Serum PON1 activity in diabetic patients with neuropathy was significantly lower than in patients without diabetic neuropathy.[80] Additionally, serum PON1 activity was decreased in patients with myocardial infarction.[81] Both PON1 and arylesterase enzyme activities were lower in diabetic foot patients compared to healthy control subjects.[82] Studies investigating the relationship between diabetes complications and PON1 polymorphisms have shown variable results. Flekac *et al.* reported that L55M and Q192R polymorphisms are more common in diabetes and are associated with macroangiopathy[62] Figure 7. PON1-55 MM and PON1-192QQ genotypes were associated with poorer diabetes control than LL and RR genotypes. Better diabetes control was found in patients with LL genotype than with MM, and similarly, in those with RR genotype versus QQ ($P < 0.05$). Chiu *et al.* have shown that L55M polymorphism, not Q192M, was an independent determinant for beta-cell function in glucose-tolerant Whites.[83] In Turkish population, PON1-R192 variant was found as an independent genetic risk factor more than three times in the development of complications in diabetes[84] and RR genotype may be a risk factor for cardiac complications in type 2 diabetes patients.[85] Association of LL genotype and the development of diabetic retinopathy has been reported by Mackness *et al.*[86] Figure 8. Oxidized LDL has been shown to be cytotoxic to retinal capillary endothelial cells and pericytes, leading to development of retinopathy in diabetes.[87] PON1 activity was significantly low in patients with non–insulin-dependent diabetes mellitus and retinopathy compared to patients without complication, but was not different between patients with and without proteinuria.[88] The authors have reported serum PON activity as one of the factors for retinopathy. Other studies have reported lower PON1 activity in diabetic subjects with nephropathy.[37,86] In another study by Abbott *et al.*, paraoxonase activity was lower in both type 1 and type 2 diabetic subjects. This decrease was unrelated to differences in paraoxonase phenotype distribution or its serum concentration. Rather, the difference in paraoxonase activity was explained by its specific activity, which was lower in diabetics, indicating either the presence of a circulating inhibitor or disturbance of the interaction of paraoxonase with HDL, affecting its activity. Paraoxonase specific activity was lowest in patients with peripheral neuropathy.[37] Table 2 gives the summary of studies demonstrating the relationship between lower PON activity in diabetes and its complications. Analysis of the studies on PON1 activity in diabetes leads to the conclusion that diabetes is associated with 10–15% reduction in PON activity. The fall in PON1 activity is significantly more when diabetes is accompanied by microvascular complications, especially neuropathy and nephropathy resulting in higher risk for atherosclerosis.

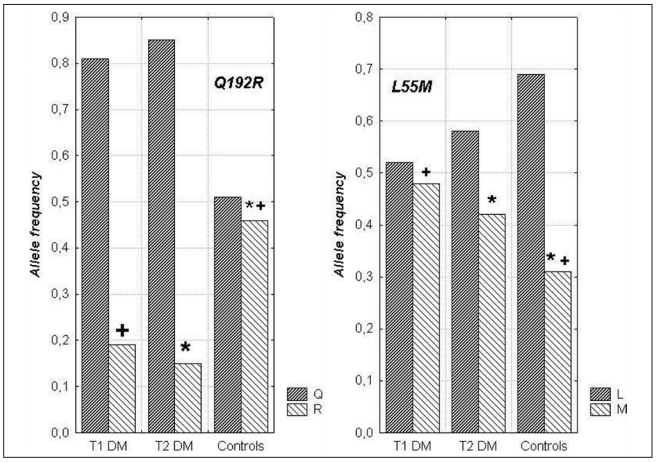

Figure 7: The frequencies of alleles in L55M and Q192R polymorphisms in diabetic patients and healthy subjects. Statistically significant differences ($P < 0.05$): +between T1DM vs. control subjects; *between T2DM vs. control subjects

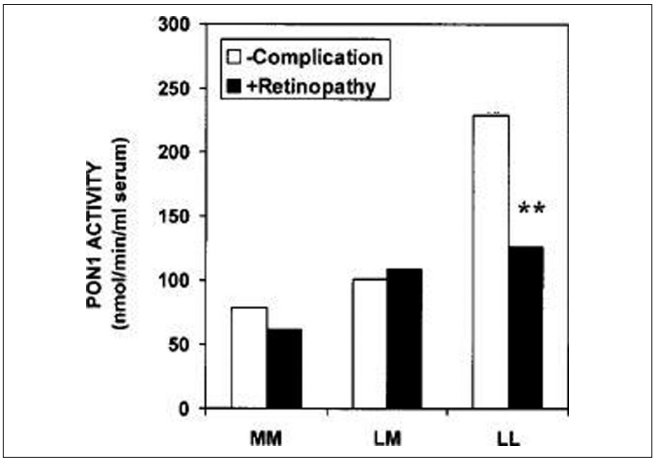

Figure 8: Effects of the PON1-55 genotype on serum PON1 activity in subjects with type II diabetes either with retinopathy or with no complications. LL and MM- Homozygotes, LM- Heterozygotes. $^{**}P < 0.001$

Table 2: Summary of studies demonstrating low paraoxonase 1 activity in diabetes and its complications

Study	Country	Patients enrolled	Conclusion
Abbott *et al*.[37]	UK	136	Low serum paraoxonase activity in diabetic subjects has been associated with increased susceptibility to atherosclerosis, and the present results also suggest an association with peripheral neuropathy
Yamada *et al*.[56]	Japan	237	Insulin resistance or hyperinsulinemia is a factor contributing to the intragenotype variability of paraoxonase activity in a population without overt hyperglycemia
Ferreti *et al*.[60]	Italy	31	Decrease of PON activity in diabetic patients and the lower HDL protective action against membrane peroxidation could contribute to acceleration of arteriosclerosis in type 1 diabetes mellitus
Karabina *et al*.[61]	France	-	Protecting the esterolytic activity of PON1 by antioxidants might be important in preserving its action on phospholipid peroxides and a concerted reaction involving the esterolytic and hydroperoxide reducing activities might be suggested for the action of PON1 in diabetes
Flekac *et al*.[62]	Czech Republic	332	The association of PON1 polymorphisms, lower PON1 activity, and poorer diabetes control found in patients with diabetic macroangiopathy support the idea of genetic factors contributing to the development of vascular disorders in diabetes
Mackness *et al*.[69]	UK	-	Paraoxonase has a physiological role in lipid metabolism and decreases in its activity in diabetes may accelerate atherogenesis
Mackness *et al*.[70]	UK	433	Low PON1 activity may contribute to the increased atherosclerosis found in type 1 diabetes by reducing the ability of HDL to retard LDL oxidation despite the frequently found increased HDL in type 1 diabetes when good glycemic control is established
Valabhji *et al*.[71]	UK	79	Though PON1 activity is low in DM, it does not appear to contribute to the greater risk of CHD in subjects with type 1 diabetes. The PON1 activities of HDL particles relate to the density, size, and composition of the particles
Mackness *et al*.[86]	UK	194	The *PON2* gene may influence *PON1*, and an inter-relationship between the *PON1* and *PON2* genes may influence glycemic control in subjects with type 2 diabetes complicated by retinopathy
Abbott *et al*.[37]	UK	170	Paraoxonase activity was lower in both type 1 and type 2 diabetic subjects. The specific activity was lower in diabetics, indicating either the presence of a circulating inhibitor or disturbance of the interaction of paraoxonase with HDL. Paraoxonase specific activity was lowest in patients with peripheral neuropathy

PON: Paraoxonase, HDL: High-density lipoprotein, DM: Diabetes mellitus, CHD: Coronary heart disease

Paraoxonase 1 Activity in Dyslipidemia

The positive correlation between PON1, HDL cholesterol, and apo A-I is well known.[37] Saha *et al*. found correlations with triglycerides and apoB as well as HDL.[89] PON genotype is a major determinant of serum lipid and lipoprotein concentrations, particularly HDL-associated parameters.[90] The rise in apo A-I, which plays a protective role against atherosclerosis, was associated with an increase in serum PON1 concentration. On the other hand, human apo A-II is proatherogenic.[91] *In vitro* displacement of PON1 by human apo A-II at physiological concentrations could explain the observation that PON1 was mostly found in HDL particles containing apo A-I but not apo A-II, and thus the lack of anti-atherogenic properties of apo A-II–enriched HDL.[92,93] Studies have demonstrated susceptibility of HDL to atherogenic modifications like glycation and homocysteinylation, induced *in vitro* in the absence of PON1 activity.[94,95] Zech *et al*. have reported that PON1 may first bind to smaller HDL3 particles and then transform into a larger HDL2 particle.[96] Studies performed with both gel filtration and electron microscopic measurements confirmed this hypothesis and PON1 would seem to be present in larger sized HDL2 particle.[97-99]

Some studies have demonstrated that lipid-lowering treatments improve PON1 serum activity. In a recent study[100] performed in 164 patients with type IIb hypercholesterolemia, 3 months of statin treatment (atorvastatin 10 mg/day, simvastatin 10/20 mg/day, and fluvastatin 80 mg/day) significantly increased the PON activity in the three statin-treated groups compared to controls. Paragh *et al*. reported that 3-month treatment with micronized fenofibrate 200 mg/day in patients with coronary heart disease and type IIb hyperlipidemia significantly increased serum PON activity ($P < 0.05$) and improved the antioxidant status.[101] Opposite to this, in another study on normolipidemic rats, fenofibrate treatment dose-dependently decreased plasma PON1 activity by 20–40%[102] Figure 9. In type 2 diabetic patients, gemfibrozil (GEM) 600 mg/bid for 3 months increased PON1 activity,[103] although no difference was observed in PON1 activity with GEM (600 mg/bid) and bezafibrate (400 mg/day) treatments for 8 weeks in type IIb hyperlipidemic patients.[104] Macan *et al*.[105] reported that after GEM treatment, plasma PON1 activity significantly reduced in rats on high-sucrose diet or on control diet compared to rats on diet-only therapy. In conclusion, the decreasing

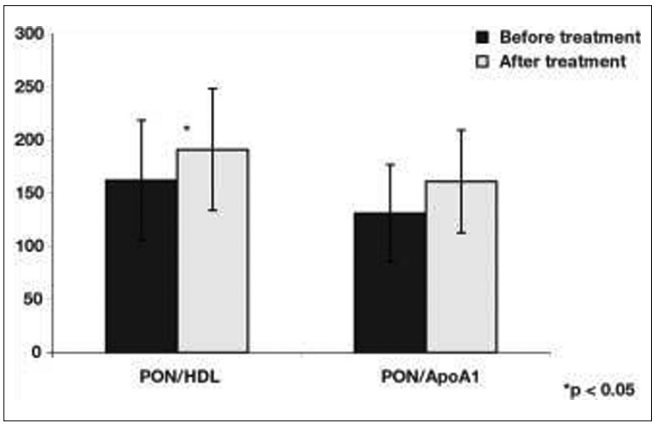

Figure 9: PON/HDL and PON/apo A-I ratio changes before and after micronized fenofibrate treatment. *$P < 0.05$

effect of fenofibrate on PON1 activity may be potentially an adverse effect, which could be masked by the positive changes in plasma lipid profile. Statin intake too is shown to promote PON to decrease LDL oxidation.[106] A recent study has demonstrated that though carriers of CYP2C19*2 alleles exhibited lower levels of platelet inhibition by clopidogrel and higher on-treatment platelet aggregation than noncarriers, there was no significant difference in platelet aggregation among PON1 Q192R genotypes.[107] This leads to the conclusion that PON1 (Q192R) polymorphism does not appear to be a significant determinant of clopidogrel response. Paraoxonase detoxifies homocysteine thiolactone in human blood and is thus hypothesized to delay the development of atherosclerosis. In Tunisian population, coronary

Table 3: Summary of studies demonstrating low paraoxonase 1 activity in dyslipidemia and effect of hypolipidemic agents on serum paraoxonase activity

Study	Country	Patients enrolled	Conclusion
Balogh *et al*.[71]	Hungary	56	Twice daily administration of 600 mg of gemfibrozil is effective in type 2 diabetic patients with associated hypertriglyceridemia. It favorably lowers lipid levels and improves antioxidant status by increasing serum paraoxonase activity
Saha *et al*.[89]	Singapore	136	In the males, there was a significant negative correlation of serum paraoxonase activity with total ($P < 0.05$) and LDL ($P < 0.01$) cholesterol levels, and positive correlation with HDL cholesterol and apo A-II levels ($P < 0.05$). Serum PON activity had a high positive correlation with serum triglyceride levels in both sexes ($P < 0.001$). Serum apoB level had a positive correlation with the enzyme activity only in females ($P < 0.01$). The high-activity allele (PON) was associated with higher serum triglyceride level ($P < 0.001$) and apoB ($P < 0.001$), while it had lowering influence on total cholesterol ($P < 0.05$) and LDL cholesterol ($P < 0.005$) in men
Hegele *et al*.[90]	Canada	1085	Homozygotes for the low-activity variant of PON had significantly lower levels of plasma apoB-related biochemical variables than heterozygotes and homozygotes for the high-activity variant of PON. Homozygotes for the low-activity variant of PON also had significantly lower ratios of total cholesterol/HDL cholesterol, LDL cholesterol/HDL cholesterol, and apoB/apo A-I than heterozygotes and homozygotes for the high-activity variant of PON. PON is a significant genetic determinant of plasma lipoprotein levels
Mirdamadi *et al*.[91]	Hungary	164	The PON1 phenotype may be a novel predictive factor for the effectiveness of statin treatment on PON1 activity and serum lipid levels
Ferreti *et al*.[94]	Italy	-	There are modifications of lipid composition, apoprotein conformation, and physicochemical properties of HDL incubated in the presence of glucose. These modifications affect the activity of HDL-associated paraoxonase. The modification of order and polarity of glycated HDL and the alterations in paraoxonase activity could potentially contribute to the accelerated atherosclerosis in diabetic patients
Ferreti *et al*.[96]	Italy	332	The enzyme PON contributes to the protective role of HDL against the oxidative damage and against toxicity exerted by homocysteine (Hcy) involved in the development of atherosclerosis. Therefore, significant decrease of the enzyme activity in HDL incubated with Hcy-thiolactone suggests that homocysteinylation could render HDL less protective against oxidative damage and against toxicity of Hcy-thiolactone
Ribas *et al*.[100]	Spain	-	Overexpression of human apo A-II in mice impairs the ability of HDL to protect apoB-containing lipoproteins from oxidation. Further, the displacement of PON1 by apo A-II could explain in part why PON1 is mostly found in HDL particles with apo A-I and without apo A-II, as well as the poor anti-atherogenic properties of apo A-II–rich HDL
Paragh *et al*.[101]	Hungary	52	Three months of treatment with micronized fenofibrate is thought to normalize lipid profile and improve antioxidant status by increasing serum paraoxonase activity in patients with type IIb hyperlipidemia
Kural *et al*.[106]	Turkey	40	Atorvastatin 10 mg/day in dyslipidemic patients decreases the level of oxidative stress (reflected by decrease in auto-antibodies against oxidized LDL) and increases PON activity, especially in patients with HDL levels above 35 mg/dl

PON: Paraoxonase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, APO: apolipoprotein

artery disease was associated with increased homocysteine levels. The low PON1 activity was associated with the PON1 192RR genotypes corresponding with the severity of CAD.[108]

PON1 gene therapy may play a role in the management of dyslipidemia and liver diseases in the future. Injection of plasmid containing the human PON1 gene via rat tail vein could prevent dyslipidemia and hepatic lipid accumulation by increasing antioxidant superoxide dismutase (SOD) and decreasing the serum levels of LDL, total cholesterol, triglyceride, and malondialdehye (MDA). These results indicate that gene therapy with plasmid coated DNA/PON1 might be an effective treatment for hyperlipidemia and liver diseases like hepatosteatosis.[109] Table 3 provides the summary of studies demonstrating the relationship between lower PON activity in dyslipidemia and the effect of hypolipidemic agents on serum PON activity. The summary of studies on paraoxonase activity in dyslipidemia depicts 50–60% higher LDL and 8–10% lower HDL cholesterol in obese subjects, contributing to higher cardiovascular risk. Treatment with hypolipidemic agents results in improvement in PON1 activity.

Conclusion

PON1, by virtue of its antioxidant property, prevents the formation of oxidized LDL and protects phospholipids in HDL from oxidation by inactivating LDL-derived oxidized phospholipids. Serum PON1 levels decrease in states of high oxidative stress like metabolic syndrome, obesity, uncontrolled diabetes, and dyslipidemia. Serum PON1 activity was found to be lower in diabetic patients with macrovascular and microvascular complications. PON1 level is positively correlated with HDL cholesterol and negatively correlated with LDL cholesterol. Numerous polymorphisms in PON1 gene have been described; however, there is still not enough evidence to support the existence of relationship between metabolic disorders and specific polymorphism in PON1 gene.

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