

Paraoxonase1, its Q192R polymorphism and HDL-cholesterol in relation to intensive cardiac care unit stay in ischemic heart disease

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AIMS AND OBJECTIVES: The present study was evaluated the atheroprotective potential of paraoxonase1 (PON1) and its Q192R polymorphism, to determine whether this polymorphism, which is responsible for differential PON1 activity plays any role in the pathogenesis, severity and extent of coronary artery disease (CAD).

MATERIALS AND METHODS: This hospital-based cross-sectional study investigated 60 diagnosed cases of CAD and 60 age and gender matched controls. All were assessed for serum PON1 activity, PON1 Q192R polymorphism and for classical cardiovascular risk factors. Individual serum phenotyping for PON1 Q192R polymorphism was determined by double substrate hydrolysis assay. Severity of CAD was assessed by the length of intensive cardiac care unit (ICCU) stay.

RESULTS: Serum PON1 activity is significantly reduced in cases of CAD (92.6 ± 31.13 IU/L when compared with controls (105.26 ± 32.53 IU/L). Furthermore, serum arylesterase activity is reduced in CAD patients (90.31 ± 23.26 kU) when compared with the control subjects (101.61 ± 28.68 kU). Serum PON1 and arylesterase activities are significantly negatively correlated with the length of ICCU stay ($r = -0.393$ and $r = -0.374$ respectively). There is no significant difference in the occurrence of CAD and length of ICCU stay among the PON1 phenotypes ($P = 0.92$). Logistic regression analysis after adjustment of established risk factors revealed no significant association between CAD risk and PON1 Q192R polymorphism (odds ratios: 1.179 [95% confidence intervals: 0.507-2.744], $P = 0.702$).

SUMMARY AND CONCLUSIONS: The current study demonstrates that the activity of the PON1 enzyme may be

more important factor than the PON1 Q192R polymorphism in the severity and extent of CAD.

Key words: Coronary artery disease, paraoxonase1, paraoxonase1 Q192R polymorphism

Introduction

Ischemic heart disease (IHD) is a major public health concern and the single leading cause of mortality and morbidity in economically developed countries and is now rapidly assuming serious threat in developing countries like India.^[1]

The oxidized low density lipoprotein (oxLDL) is believed to play a central role in atherogenesis. The best known anti-atherogenic function of high density lipoprotein (HDL) is in the reverse cholesterol transport, besides its anti-inflammatory, anti-oxidant and antithrombotic properties.^[2] However, it appears that coronary artery disease (CAD) risk is not just merely related to the static plasma HDL-cholesterol (HDL-C) levels, but with the functional characteristics of HDL.^[3,4] Human serum paraoxonase1 (PON1) is present in serum entirely anchored to HDL particles containing apo A-1 and apo J.^[5] PON1 has now been reported to have inverse relationship to the risk of cardiovascular diseases (CVD). PON1 hydrolyses a variety of oxidized and modified lipids including oxLDL. PON1 also protects HDL from oxidation and preserves its anti-oxidant function.^[6] *PON1* gene contains two coding region polymorphism: one at position 192 (Glutamine [Q] to arginine [R] substitution) and another

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at position 55 (leucine [L] to methionine [M] substitution).^[7,8] PON1 Q192R polymorphism constitutes the molecular basis for interindividual variability. Paraoxon hydrolytic activity is greatest in PON1 RR homozygotes and least with PON1 QQ homozygote individuals.^[9] Heterozygotes have intermediate activity. Furthermore, it has been hypothesized that PON1 polymorphism offer differential genetic susceptibility toward risk of CVD. This gave us the insight to investigate PON1 activity and polymorphism in diagnosed cases of IHD and control subjects.

Materials and Methods

This was a hospital-based cross-sectional study. A total of 60 patients diagnosed as having IHD were included in the study as cases. Confirmation of diagnosis was carried out with history of typical chest pain and specific electrocardiogram (ECG) abnormalities for IHD. Control population consisted of 60 healthy subjects matched for age, gender and attending the routine health check-up in out-patient department. Written valid informed consent was obtained from all subjects. The study was approved by the institutional ethical committee.

The patients with chest pain admitted in the emergency department had undergone physical examination and classical 12 lead ECG taken in supine position according to classical recommendations.^[1] History of major systemic illness in the past is obtained by health questionnaire. Signs of old myocardial infarction (MI) are detected by resting ECG. Subjects with previous history of IHD, diabetes, hypertension, renal or hepatic disease, patients on exogenous hormone therapy were excluded. After confirmation of diagnosis, decision is taken by the treating physician for the necessity of admitting the patient in the intensive cardiac care unit (ICCU). After improvement in health, patients are transferred to the general wards. The following criteria used for transferring the patient from ICCU to the general ward.

- Stabilization of vital parameters such as pulse rate, blood pressure etc.
- Repeat ECG showing no evidence of fresh infarct
- Improvement in the general condition of the patient.

The length of ICCU stay in hours was taken as one of the crude measurement of severity of ischemic attack.

All fine chemicals purchased from Sigma Chemical Co. Fasting venous blood collected aseptically from all subjects in the morning. Fasting blood sample collected in fluoride bulb (collected within 24 h in IHD cases) was analyzed within a few hours for estimation of plasma glucose while the remaining blood was allowed to clot in plain bulb. Serum was collected by slow speed centrifugation of clotted blood which was then used for estimation of biochemical parameters. Serum analyzes were estimated using ERBA Smartlab Autoanalyzer.

Serum paraoxonase (PON1) activity assay

1 unit of paraoxonase activity produces 1 nmol of p-nitrophenol and the activity is expressed as U/L based on the molar absorption coefficient (18050 M/cm) at 405 nm at pH 8.0. Intra- and inter-assay coefficients of variation (CVs) are 3.3% and 4.7% respectively. Paraoxon is neurotoxic substance. Therefore safety measures included use of face mask, preparation of required quantity of working reagent in one setting of analysis and treatment of waste water receptacle and pipettes with 2 N NaOH.

Serum arylesterase activity assay

1 unit of arylesterase activity is equal to 1 mM of phenylacetate hydrolyzed per min. The activity is expressed as kU/L, based on the extinction co-efficient of phenol of 1310 M/cm at 270 nm, pH 8.0 and 25°C after correction for non-enzymatic hydrolysis. Intra- and inter-assay CV are 2.4% and 3.7% respectively.

Lipid and lipoprotein measurement

Serum total cholesterol (TC), triglycerides (TG) and HDL-C levels were determined using commercially available kits (Star Diagnostics, India). The LDL-cholesterol (LDL-C) levels were calculated using Friedewald formula.^[10]

Paraoxonase polymorphism

Individual serum was phenotyped for PON1 polymorphism by plotting the salt stimulated paraoxonase activity versus arylesterase activity which shows trimodal distribution of study population.

Statistical analysis

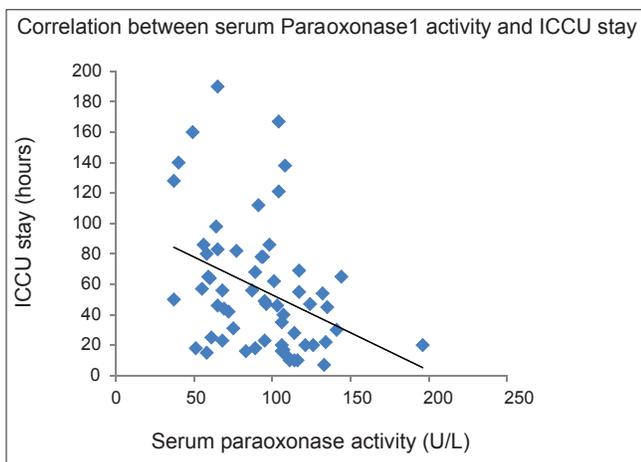
Results are presented as mean \pm standard deviation. The continuous variables tested for normality with Shapiro-Wilk test. Student's unpaired *t*-test used for statistical analysis between cases and controls for numerical variables in Gaussian distribution. The strength of association between two parameters is expressed by the Pearson's correlation co-efficient. Allele frequency is evaluated for Hardy-Weinberg equilibrium. χ^2 test and Fisher's exact test were performed to compare the frequencies of PON phenotypes between subjects with and without IHD. The logistic regression analysis is used for prediction of risk of IHD contributed by various risk factors. The three models prepared in the logistic regression for the analysis of data are as follows:

Model I: Age, sex, body mass index, smoking status, fasting plasma glucose level, TC, TG, HDL-C, LDL-C (known risk factors).

Model II: All parameters in Model I + Basal PON1 activity.

Model III: All parameters in Model I + PON1 polymorphism.

Subjects are divided into PON1 QQ homozygotes and PON1 R carriers for regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) are calculated. $P < 0.05$ is considered as statistically significant. All analyses are carried out with the statistical software Mstat 12 (Systat Software INC, USA) student version.



**Figure 1a: Correlation studies ($r = -0.393$, $P = 0.0043$).
ICCU stay = Intensive coronary care unit stay**

Results

Table 1 shows that among the clinical and lipid parameters, the levels of HDL-C in IHD cases were significantly elevated than in control group. Fasting blood glucose levels were found significantly elevated in cases than in control subjects. Moreover, significantly lower paraoxonase and arylesterase activities were found in cases than in controls.

Figure 1 shows that serum PON1 and arylesterase activity is significantly negatively correlated with duration of ICCU stay.

Figure 2 shows that by plotting the graph of the ratio of salt stimulated paraoxonase activity to arylesterase activity versus cumulative frequency of individuals; it shows the trimodal division of the study population by the antimodes at 3.7 and 5.5 [shown by arrows in Figure 2a]. According to these antimodes, the study population

Table 1: Clinical and biochemical parameters of IHD cases and controls

Parameters	Cases	Controls	P value
Age (years)	59.08 \pm 12.39	60.2 \pm 11.83	0.615
Sex (male/female)	31/29	31/29	1.0
Body mass index (kg/m ²)	23.57 \pm 03.37	23.21 \pm 2.75	0.521
Blood glucose level (mmol/L)	6.01 \pm 1.2	5.54 \pm 1.05	0.024*
Total cholesterol (mmol/L)	4.73 \pm 0.86	4.93 \pm 0.86	0.127
Triglyceride (mmol/L)	1.88 \pm 0.37	1.96 \pm 0.37	0.163
High density lipoprotein-cholesterol (mmol/L)	0.87 \pm 0.11	0.95 \pm 0.18	0.006**
Very low density lipoprotein-cholesterol (mmol/L)	0.86 \pm 0.2	0.80 \pm 0.2	0.154
Low density lipoprotein-cholesterol (mmol/L)	3.0 \pm 0.85	2.72 \pm 0.88	0.081
Paraoxonase activity (U/L)	92.6 \pm 31.13	105.26 \pm 32.53	0.031*
Arylesterase activity (U/L)	90.31 \pm 23.26	101.61 \pm 28.68	0.019*

* $P < 0.05$, ** $P > 0.01$, *** $P > 0.001$. IHD: Ischemic heart disease

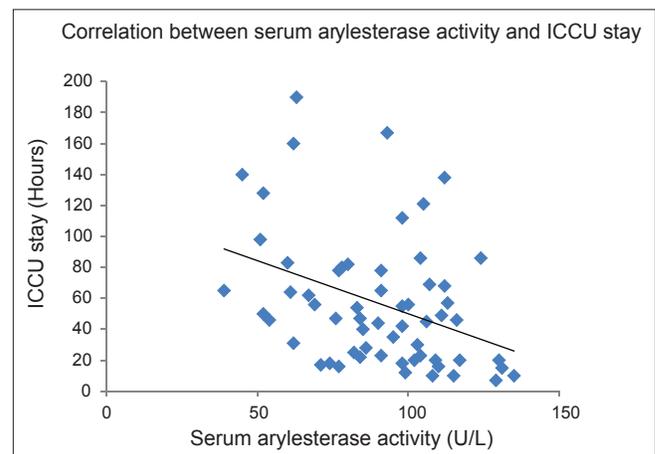


Figure 1b: Correlation study ($r = -0.374$, $P = 0.003$)

is divided into 44 individuals with QQ phenotype, 56 individuals with QR phenotype and 20 individuals with RR phenotype [Figure 2a and b]. The distribution of PON1 phenotypes in cases showed that there are 21 (35%) patients with QQ phenotype, 30 (50%) with QR phenotype and 9 (15%) with RR phenotype. Similarly, controls are divided into three phenotypes as 23 (38.33%) with QQ, 26 (43.33%) with QR and 11 (19.33%) with RR phenotype. There is no significant difference in the distribution of PON1 phenotypes in patients and controls [Table 2].

As shown in Table 3, ICU stay among individuals with PON1 phenotypes is statistically not significant ($P=0.92$).

Model I of logistic regression is prepared with the known risk factors. When PON1 activity is added in this Model I, the significance of the model increases (from $P=0.021$ for Model I to 0.015 for Model II) and it also increases the risk prediction reflected by Naglekerke R^2 value from 0.201 to 0.224 showing weak independent association of serum PON1 activity toward CAD risk (OR: 0.989 [95% CI: 0.975 ± 1.003], $P=0.121$). Similarly, when Model III is prepared for analysis of the predictive power of PON1 polymorphism, there is no significant association between PON1 polymorphism and IHD risk (OR: 1.179 [95% CI: 0.507-2.744], $P=0.702$) [Table 4] after adjustment for all risk factors. Furthermore, the significance of the model and risk prediction does not change when compared with Model I showing no association of PON1 polymorphism in CAD risk.

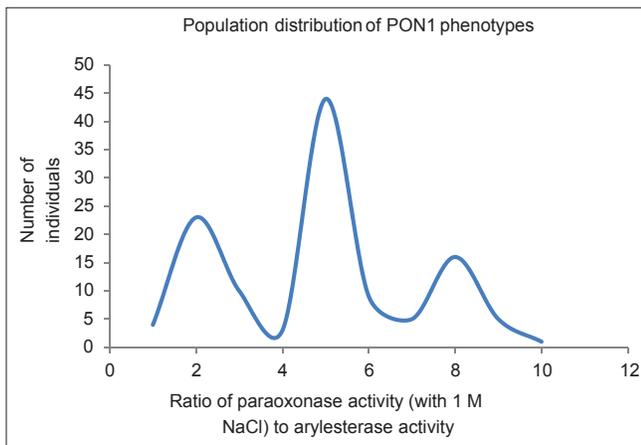


Figure 2a: Paraoxonase polymorphism by two substrate hydrolysis assay (By plotting the graph of the ratio of salt stimulated paraoxonase activity to arylesterase activity versus cumulative frequency of individuals, it shows the trimodal division of the study population by the antimodes at 3.7 and 5.5)

Discussion

The cardioprotective function of HDL could be mostly attributed to the enzymes associated with HDL.^[11] HDL-associated PON1 enzyme is found to be involved in destroying lipid peroxides. The present study shows statistically significant lower levels of paraoxonase activity in cases than in controls ($P=0.031$). Low PON1 activity observed in IHD cases in the present study is consistent with the study done by Navab *et al.* and Ayub *et al.* who have found significantly lower activity and concentration of serum PON1 in cases than control group. Furthermore, they observed no significant variation in PON1 activity even 6 weeks after MI.^[12,13]

The present study showed significantly decreased values of baseline serum arylesterase activity of PON1

Table 2: Distribution of PON1 phenotypes in cases and controls

	QQ (%)	QR (%)	RR (%)	Total (%)
Cases	21 (17.5)	30 (25.0)	9 (7.5)	60 (50.00)
Controls	23 (19.16)	26 (21.66)	11 (9.16)	60 (50.00)
Total	44 (36.66)	56 (46.66)	20 (16.66)	120 (100.00)

$P=0.75$. PON1: Paraoxonase1, QQ: QQ Homozygous phenotype, QR: QR Heterozygous phenotype, RR: RR Homozygous phenotype Q: Q Allele, R: R Allele

Table 3: Duration of ICU stay among PON1 phenotypes

PON1 phenotypes	Number of patients	ICCU stay (h) mean±SD
QQ	21	58.04±4.11
QR	30	54.56±38.93
RR	9	60.44±54.54

$P=0.92$. PON1: Paraoxonase1, ICU: Intensive cardiac care unit, SD: Standard deviation, QQ: Homozygous phenotype, QR: Heterozygous phenotype, RR: Homozygous phenotype, Q: Q Allele, R: R Allele

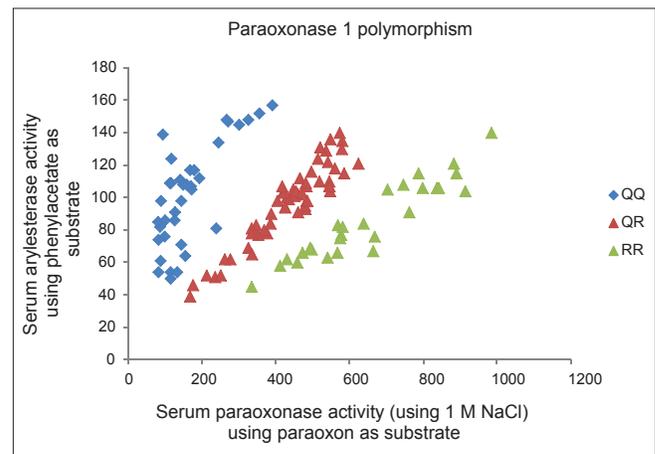


Figure 2b: Paraoxonase1 polymorphism (According to these antimodes at 3.7 and 5.5, the study population is divided into 44 individuals with QQ phenotype, 56 individuals with QR phenotype and 20 individuals with RR phenotype)

Table 4: Logistic regression analysis

Independent variables	Z value	SE	OR (95% CI)	P value
Model I (Naglekerke $R^2=0.201$, $P=0.021$)				
Age	1.811	0.020	1.036 (0.997-1.076)	0.070
Sex	0.693	0.582	1.349 (0.579-3.143)	0.488
Body mass index	-1.137	0.069	0.991 (0.868-1.131)	0.891
Smoking status	0.092	0.695	1.062 (0.295-3.831)	0.927
Plasma glucose level	-1.685	0.010	0.982 (0.962-1.003)	0.092
TC	0.898	0.247	1.203 (0.804-1.799)	0.369
TG	1.026	0.040	0.958 (0.884-1.039)	0.305
HDL-cholesterol	-0.402	0.195	0.918 (0.606-1.392)	0.687
LDL-cholesterol	-0.937	0.169	0.825 (0.552-1.234)	0.349
Model II (Naglekerke $R^2=0.224$, $P=0.015$)				
Age	1.783	0.019	1.035 (0.997-1.076)	0.075
Sex	0.511	0.351	1.252 (0.529-2.962)	0.610
Body mass index	0.028	0.069	0.998 (0.872-1.143)	0.978
Plasma glucose level	-1.597	0.011	1.017 (0.996-1.039)	0.110
TC	0.828	0.185	1.202 (0.778-1.858)	0.408
TG	-0.940	0.047	1.043 (0.955-1.139)	0.347
HDL-cholesterol	-0.395	0.250	1.043 (0.955-1.139)	0.692
LDL-cholesterol	-0.865	0.269	1.212 (0.784-1.873)	0.387
Basal PON1 activity	-1.549	0.007	0.989 (0.975-1.003)	0.121
Model III (Naglekerke $R^2=0.202$, $P=0.032$)				
Age	1.828	0.020	1.036 (0.997-1.076)	0.067
Sex	0.757	0.615	1.396 (0.589-3.309)	0.449
Body mass index	-0.086	0.068	0.994 (0.870-1.136)	0.931
Smoking status	0.111	0.707	1.076 (0.297-3.899)	0.912
Plasma glucose level	-1.704	0.010	0.982 (0.962-1.003)	0.088
TC	0.854	0.245	0.960 (0.585-1.041)	0.393
TG	-0.984	0.040	0.960 (0.885-1.041)	0.325
HDL-cholesterol	-0.361	0.197	0.926 (0.610-1.405)	0.718
LDL-cholesterol	-0.893	0.171	0.832 (0.556-1.245)	0.372
PON1 R carriers	0.383	0.508	1.179 (0.507-2.744)	0.702

HDL-cholesterol: High density lipoprotein cholesterol, LDL-cholesterol: Low density lipoprotein cholesterol, PON1: Paraoxonase 1, SE: Standard error, CI: Confidence interval, OR: Odds ratio, TC: Total cholesterol, TG: Triglyceride

in cases when compared with control population and significant negative correlation between severity of ischemic attack measured in terms of length of ICCU stay and serum arylesterase activity.

Severity of IHD and PON1 activity

It is assumed that severity of MI is proportional to duration required for the settlement of vital parameters during intensive management. This study expressed significant inverse relationship between PON1 activity and length of ICCU stay of IHD patients. Thus findings of the present study show that PON1 activity as well as arylesterase activity of PON1 is significantly associated with the severity of CAD. Low PON1 activity may reduce the capacity of HDL to prevent oxidation of LDL and may, therefore, lead to IHD. Low PON1 observed in IHD patients may have been present earlier than the coronary event due to its inactivation by increased presence of oxidized lipoproteins in them.

However, the length of ICCU stay among the patients with different PON1 phenotypes does not differ significantly. Granér *et al.* in their study obtained similar results while studying PON1 activity and concentration in relation to their extent of angiographic severity of CAD.^[14] One Indian study conducted by Jayakumari and Thejaseebai explored the role of arylesterase activity of PON1 and HDL-C levels in angiographically confirmed CAD cases.^[15]

Though PON1 activity is significantly decreased in cases than in controls, we observed null relationship between PON1 activity and occurrence of IHD (OR: 0.989, 95% CI: [0.975-1.003], $P = 0.121$) after adjustment of other established risk parameters of IHD. These findings suggest that the low activity of PON1 observed in IHD is due to other risk factors such as advanced age, increased plasma glucose levels, dyslipidemia. Cao *et al.* in their study suggested that the ability of PON1 to protect LDL against oxidation was independent of its esterase activity and the Q192R polymorphism.^[16] Secondly Aviram *et al.* in their study suggested that different active sites are involved in paraoxonase/arylesterase activity and protection against LDL oxidation.^[17] These data suggest that the protective function of PON1 in coronary atherosclerosis is mediated through the mechanism which is independent of polymorphic esterase activity.

The vast variability in the PON1 activity in the study population can be explained partly by the PON1 polymorphism. The distribution of PON1 alleles among cases and controls are in Hardy-Weinberg equilibrium. Several studies have hypothesized that PON1 RR phenotype is less favorable variant for the risk of developing CVD. However, in present study, there is no significant difference found in the distribution of PON1 phenotypes among cases and controls ($P = 0.75$). The multivariate study has examined no association between PON1 polymorphism and CAD. Similarly, distribution of homozygous PON1 QQ and PON1 R carriers among the cases and controls is not significant ($P = 0.426$).^[18,19]

In an article in 1993, Adkins *et al.* showed that the differential activity of PON1 phenotypes is due to single nucleotide polymorphism at position 192.^[8] After this, several independent studies have found the association of PON1 RR phenotype at a higher frequency in CAD

in some populations.^[20-25] However, some studies have failed to establish such a relationship.^[26-37] None of the studies have found PON1 R allele negatively correlated with the risk of CAD. Wheeler *et al.* had carried out meta-analysis of previously published 43 studies and concluded that there is a weak association between PON1 polymorphism and CHD (relative risk: 1.15 [95% CI: 1.09-1.22]).^[38] However, this analysis did not take into account the ethnicity and therefore PON1 polymorphism can be the risk factor in particular ethnic groups. These discrepancies in the observations might be due to environmental and methodological factors. Modulation of association between PON1 polymorphism and risk of IHD by gene-environmental and/or gene-gene interactions can be the cause for such diverse results.

Polymorphism in *PON1* gene influence both quality and quantity of PON1 enzyme (PON1 status). The quality of PON1 enzyme determines the catalytic efficiency of hydrolysis of paraoxon. In this study, PON1 activity and not PON1 Q192R polymorphism is significantly different in cases and controls. Furthermore, arylesterase activity of PON1 which is representative of PON1 enzyme concentration is also significantly decreased in cases when compared with control subjects. None of the risk factors of CAD analyzed in the study differ significantly amongst the PON1 phenotypes. This indicates that PON1 enzyme status, i.e. activity and concentration, seems to be the better predictors of coronary events and not the PON1 polymorphism. Mackness *et al.* and Jarvik *et al.* also showed that PON1 status and not *PON1* genotype was associated with CVD.^[39,40]

Regression analysis after adjustment of known risk factors yielded OR of 1.18 (95% CI: [0.507-2.744], $P = 0.702$) for development of IHD in individuals with PON1 R carriers relative to individuals with PON1 QQ homozygotes. The lack of association of PON1 polymorphism and risk of CAD may be due to physiological role of PON1 which may play minor role in early pathogenesis of IHD but more powerful role in interaction with lipid peroxides which are proposed to be its natural substrates. The reason for the lack of association of PON1 polymorphism may also be due to various residual confounding factors not included in the study design.

The poor association between *PON1* Q192R polymorphism and CAD may indicate that this polymorphism is unrelated to coronary atherosclerosis. This polymorphism affects the enzyme activity but this property may be for the artificial substrates like paraoxon and not valid for all substrates.

Thus the findings of the study demonstrate that the atheroprotective effects of HDL may be contributed by PON1 enzyme associated with it. This study strongly suggests that the estimation of HDL-associated PON1 enzyme status provides more valuable information for prediction of risk of future coronary events than static HDL-C levels. Furthermore, the present study shows that the activity of the PON1 enzyme is a more important factor than the *PON1* Q192R polymorphism.

There are several potential limitations to the present study. The study is conducted on small sample size. PON1 polymorphism at codon 192 is done by two substrate hydrolysis assay. *PON1* genotyping, which is more definitive, is not performed in the present study. So the wrong classification of few individuals among three phenotypes can be possible. Also, the actual concentration of PON1 is not directly estimated in the present study. Further studies are needed to characterize the molecular mechanism by which paraoxonase/ arylesterase is involved in cardioprotection. Larger and preferably prospective studies are required to clarify the relationship of PON1 polymorphism and risk of CAD.

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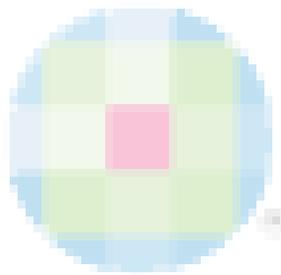
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