R192Q Paraoxonase Gene Variant is Associated with a Change in HDL-Cholesterol Level during Dietary Caloric Restriction in Nondiabetic Healthy Males

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Paraoxonase (PON), an HDL-associated enzyme, may protect against the development of atherosclerosis. Single nucleotide polymorphisms of PON have been reported to be associated with an incidence of coronary heart diseases. We investigated the effect of PON R192Q variants on serum lipid profile after caloric restriction in nondiabetic healthy males. After caloric restriction for 12 weeks, the levels of high-density lipoprotein cholesterol (HDL-C) increased in the subjects carrying RR genotype, but not in the QR and QQ genotypes. The changes in HDL-C from the baseline values in the RR genotype were significantly different from those in the QR and QQ genotypes. Although the changes in lipoprotein lipase activity were not different among three genotypes, we observed a significant difference in the changes in hepatic lipase (HL) activity after caloric restriction, namely, a decrease in the RR genotype and an increase in the subjects carrying the Q allele. In addition, the changes in fasting insulin levels significantly correlated with those in HDL-C levels in the RR genotype, not in the QR and QQ genotypes. PON R192Q polymorphism could affect HDL-C levels after caloric restriction presumably due to decreased HL activity and altered insulin resistance. J Atheroscler Thromb, 2003; 10: 57-62.

Key words: Paraoxonase, High-density lipoprotein, Insulin, Hepatic lipase

Introduction

Coronary heart disease (CHD) is a principal cause of mortality and morbidity in industrial countries. Several studies have shown dietary intervention, such as a reduction of lipid intake reduced an incidence of CHD mainly due to changes in blood lipids profile (1-3). Caloric restriction had been known to improve not only diabetic status or insulin resistance but also lipid profile such as decrease in serum triglycerides (TG), resulting in beneficial changes in metabolic risk factors for CHD (4,5).

The increased levels of HDL-C have been reported to be associated with the decreased risk for CHD (6). HDL has been accepted to protect against atherosclerosis mainly by transport of excess cholesterol from peripheral tissues to liver. Another mechanism for antiatherogenesis of HDL, antioxidative property, has been recently focused on. HDL is reported to prevent the oxidation of low-density lipoprotein (LDL) (7), which has been known to be a pivotal event in atherogenesis. PON is a calcium-dependent esterase that exists on HDL particles and is known to catalyze hydrolysis of organophosphates, and is widely distributed among organs such as liver, kidney, intestine, and serum (8). Mackness et al (8) described that paraoxonase (PON) degenerates peroxidized lipids in oxidized LDL. The variant of the PON gene coding for the replacement of arginine by glutamine at codon 192 (R192Q) has been associated with increased risk for CHD.
in diabetic patients (9). R192Q genotype reportedly affected serum lipid levels and another genotype, L54M, was reported to be associated with insulin resistance and the levels of serum TG and HDL-C (10). In addition, several studies have shown an association between increased oxidative stress and decreased insulin action (11), and Cheung et al. (12) reported that antioxidant vitamin E modulated HDL-C levels during lipid-lowering therapy. Therefore, PON might have metabolic effects, besides antioxidative activity, concerning the risk factors for atherosclerosis.

In light of such evidence, we aimed at investigating whether PON R192Q genotype affect serum lipid levels during caloric restriction in non-diabetic males.

Materials and Methods

Subjects
Male soldiers or employees at the Nerima Base of the Japan Ground Self Defense Force were examined by blood and physiological examinations in periodical medical checks. The subjects voluntarily participated in this study with an inclusion criterion: body mass index (BMI) ≥ 22 kg/m², exclusion criteria: cardiovascular and cerebrovascular diseases, acute and chronic inflammatory diseases, neoplastic diseases, diabetes mellitus, any endocrine diseases, renal dysfunction, gastro-intestinal diseases, liver dysfunction except for slight elevations of aspartate aminotransferases (up to 60 IU/l), abnormal data in fasting blood glucose (greater than 6.7 mmol/l) and significant excretion of urine glucose. Subjects with a history of weight change (≥ 2 kg) in the last 6 months and taking routine medication were also excluded. This resulted in a study population of 71 subjects, who read, understood, and answered a questionnaire and informed consent forms which was approved by the committee on Human Research and Medical Sciences of National Defense Medical College.

Study Protocol
The subjects entered into a medical supervised diet program. The program consisted of a 1800 kcal/day American Heart Association step 2 diet. Food was selected self-selected with dietitian supervision on macronutrient selection. The subjects were encouraged not to change their usual physical activity, alcohol consumption, and smoking habits during the study. The subjects were in the program for 12 weeks. Three-day food records just before the dietary intervention period and 12 weeks after were checked and daily total caloric intake was calculated. Body weight, waist and hip circumference were measured before and after the study.

Blood sampling
Following 12 hours of fasting, venous blood was obtained from each subject before and after the study period. Blood was collected into vacutainers containing heparin and EDTA-Na₂ as anticoagulant, and placed immediately on ice, and plasma was separated by centrifugation at 3,000x g for 20 min at 4 °C. Aliquots of the plasma samples were subjected to biochemical analyses, and the remainder of each sample was stored at −80°C for further study. Plasma samples for determination of lipase activities were collected 10 min after intravenous administration of 30 I.U. heparin per kg body weight in precooled heparinized tubes. The plasma was separated immediately by centrifugation at 4°C and stored thereafter at −80°C.

DNA extraction and PON genotyping
A genome DNA was extracted from buffy coats as previously described (13). After extraction and purification, purified genome DNAs were stored at −20°C dissolved in distilled water. PON R192Q genotype are determined by the restriction fragment length polymorphism with use of the restriction enzyme AlwI. Polymerase chain reaction (PCR) using primers for amplification of a 99 bp sequence coding for position 192, 5'-TATTGTTCGTGGGACCTGAG-3' and 5'-CAGCCTAAAACCCAAATACATCCTC-3', was performed, and the PCR fragments were digested by AlwI. Allele RR (arginine/arginine) corresponded to 65 and 34 base pairs two fragments, QQ (glutamine/glutamine) to 99 base pairs and QR (arginine/glutamine) to 99, 65 and 34 base pairs three fragments.

Biochemical Analyses
Plasma total cholesterol (TC) and HDL-C, TG and glucose were determined by enzymatic methods using commercially available enzymatic reagents (Kyowa Medics Co, Tokyo, Japan). LDL cholesterol (LDL-C) was estimated using the Friedewald formula (LDL-C=TC - HDL-C - TG/5). Apoprotein (apo) A, AII, B, CII, CIll and E were measured using the electrophoresis assay (Daichi Pure Chemicals Co, Inc Japan). Insulin measurement was performed with use of radioimmunoassay (Diagnostic System Laboratories Inc). The activities of lipoprotein lipase (LPL) and hepatic lipase (HL) were measured by using modifications of previously published methods (14). Both substrates contained, per ml, 2.8 mg glycerol trioleate, 0.14 mCi tri [1-¹⁴C] oleoylglyceride, 20 mg gum arabic and 25 mg bovine serum albumin. The substrate for HL contained a high salt concentration (1 mol/l), and the LPL a low salt concentration (0.15 mol/l). LPL activity was measured after inhibition of the HL activity by pre-treatment of the plasma sample with sodium dodecyl sulphate (0.1 mmol/l). The assays were run at 28°C for 60 min and the reaction was terminated by an organic system. Quantification was achieved by measuring the liberated fatty acids by liquid scintillation counting. The activities of post-heparin plasma lipases are expressed as µmol/ml of free fatty acids liberated per hour.
Statistical Analyses
The values between before and after the study period were analyzed with paired t-test. The values among three groups were analyzed using ANOVA and multiple linear regression. p-values of less than 0.05 were considered significant.

Results
Distribution of PON R192Q genotypes and baseline characteristics of the subjects are shown in Table 1. The genotype distribution was consistent with that expected from Hardy-Weinberg equilibrium. There was no significant difference in age, smoking status, and an amount of alcohol consumption among three groups. There was no difference in total caloric intake, anthropometrical and biochemical parameters at baseline among all groups (Table 2). Total caloric intake checked just before the end of the study period significantly decreased in all groups compared to the baseline values. After caloric restriction, body mass index (BMI) decreased in the subjects carrying the QQ genotype, but did not significantly change in the subjects carrying the QR and the RR genotypes. Waist/hip ratio (W/H) decreased in the RR and the QR, but not in the QQ genotype.

Table 2 also shows the changes in lipid profile. A significant decrease in TC levels was observed in the QR genotype. Serum TG levels significantly decreased in the QR, but not in the RR and the QQ carriers. The levels of HDL-C significantly increased in the RR genotype after the study, but not in the QR and the QQ genotypes. Apo A1 did not change in all groups, but apo AII significantly decreased in the QR and the QQ genotypes. Apo B decreased after the study in all groups. Apo CII did not change after the study in all groups, but apo CIII decreased in all groups. Apo E showed a significant decrease in the QR and the QQ, but not in the RR genotype. Although blood glucose did not change in all groups, plasma insulin significantly decreased in the RR genotype after the caloric restriction, but not in the QR and the QQ genotypes. LPL activity in post-heparin plasma significantly increased in the RR genotype after the study, but not in the QR and the QQ genotypes. No significant changes in HL activity were found during the study in all groups.

Table 1. PON R192Q genotype distribution and clinical characteristics of the subjects

|                | QQ (n = 21) | QR (n = 40) | RR (n = 10) |
|----------------|-------------|-------------|-------------|
| Number         | 21          | 40          | 10          |
| Age (years)    | 42.0 ± 3.0  | 42.0 ± 6.0  | 46.0 ± 5.0  |
| Alcohol        |             |             |             |
| consumption (g/week) | 192 ± 121  | 177 ± 99    | 174 ± 97    |
| Current smokers| 13          | 24          | 5           |

Values represent mean ± SD.

Table 2. Anthropometrical and biochemical parameters and caloric intake before and after the study

|                | QQ (n = 21) | QR (n = 40) | RR (n = 10) |
|----------------|-------------|-------------|-------------|
| BMI (kg/m²)    | 26.7 ± 3.0  | 26.1 ± 3.0* | 25.9 ± 2.5  | 27.1 ± 3.7  | 26.0 ± 3.0  |
| W/H ratio      | 0.91 ± 0.06 | 0.91 ± 0.09 | 0.92 ± 0.04 | 0.88 ± 0.04*| 0.92 ± 0.04 | 0.88 ± 0.04*|
| TC (mmol/l)    | 5.64 ± 0.96 | 5.47 ± 0.72 | 5.75 ± 0.92 | 5.50 ± 0.71*| 5.65 ± 0.72 | 5.44 ± 0.93 |
| TG (mmol/l)    | 2.79 ± 2.06 | 2.02 ± 1.02 | 3.01 ± 1.75 | 2.31 ± 1.04*| 1.91 ± 0.81 | 1.59 ± 0.75 |
| LDL-C (mmol/l) | 3.08 ± 1.17 | 3.30 ± 0.74 | 3.21 ± 1.17 | 3.28 ± 0.57 | 3.48 ± 0.70 | 3.26 ± 0.57 |
| HDL-C (mmol/l)| 1.29 ± 0.36 | 1.30 ± 0.36 | 1.12 ± 0.35 | 1.30 ± 0.36 | 1.22 ± 0.34 | 1.37 ± 0.37*|
| ApoAI (mg/dl)   | 145 ± 26   | 140 ± 22    | 141 ± 30    | 138 ± 28    | 148 ± 26    | 149 ± 30    |
| ApoAII (mg/dl)  | 41.0 ± 8.7 | 38.3 ± 6.8**| 41.6 ± 8.5  | 39.2 ± 7.5**| 41.4 ± 9.5  | 40.0 ± 9.1  |
| ApoB (mg/dl)    | 121 ± 23   | 109 ± 12**  | 126 ± 26    | 112 ± 17*   | 126 ± 20    | 109 ± 15**  |
| ApoCII (mg/dl)  | 6.9 ± 2.9  | 6.2 ± 2.0   | 6.8 ± 2.4   | 6.5 ± 2.5   | 5.8 ± 2.7   | 5.3 ± 1.9   |
| ApoCIII (mg/dl) | 21.0 ± 9.8 | 14.3 ± 6.4* | 20.2 ± 7.3  | 15.5 ± 6.4* | 17.2 ± 7.2  | 14.1 ± 7.2**|
| ApoE (mg/dl)    | 8.2 ± 4.7  | 6.5 ± 2.1** | 8.5 ± 2.8   | 7.1 ± 1.8** | 7.2 ± 2.3   | 6.1 ± 1.6   |
| Glucose (mmol/l)| 5.63 ± 0.47| 5.66 ± 0.53 | 5.65 ± 0.63 | 5.87 ± 0.69 | 5.40 ± 0.42 | 5.54 ± 0.25 |
| Insulin (µU/ml) | 9.6 ± 6.0   | 9.3 ± 6.3   | 9.8 ± 8.0   | 7.9 ± 5.6   | 8.9 ± 3.3   | 5.7 ± 2.2**|
| LPL activity (nmol/ml/h) | 22.8 ± 4.8 | 26.4 ± 2.4**| 21.6 ± 4.2  | 24.0 ± 3.6**| 23.4 ± 3.6  | 25.8 ± 5.4  |
| HL activity (nmol/ml/h)  | 18.6 ± 4.8 | 19.8 ± 3.0  | 17.4 ± 4.2  | 18.0 ± 4.2  | 18.6 ± 5.4  | 17.4 ± 4.2  |
| Caloric intake (kcal/day)| 2369 ± 176 | 1902 ± 297  | 2421 ± 175  | 1923 ± 246  | 2463 ± 268  | 1945 ± 208  |

Values represent means ± SD. *p < 0.01, **p < 0.05 compared with the value in week 0
Abbreviations: BMI, body mass index; W/H, waist-hip ratio; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo, apoprotein; LPL, lipoprotein lipase; HL, hepatic lipase
hand, $\%\Delta$HDL-C in the RR genotype was significantly different from those in the QR and the QQ genotypes.

Fig. 2 shows that $\%\Delta$LPL activities were not different among PON R192Q genotype. In contrast, there was a significant difference between $\%\Delta$HL activities in RR and QQ, showing a clear difference in HL activities dependent on PON R192Q genotype.

Fig. 3 shows a relation between $\%\Delta$HDL and $\%\Delta$insulin in each group. A significant correlation was observed in the RR, but not in the QR and the QQ genotypes, indicating a possible link between insulin and HDL-C after caloric restriction in PON RR genotype.

To clarify the determinant of $\%\Delta$HDL-C, we performed linear regression analysis, with $\%\Delta$HDL-C as the dependent variable, and $\%$changes in BMI, W/H ratio, the levels of serum lipids, glucose, insulin and PON genotypes. On univariate regression analysis, $\%$changes in BMI, LDL-C, TG, and PON genotype were associated with $\%\Delta$HDL-C. On multiple regression analysis, $\%$changes in LDL-C, TG, and PON genotype were significantly associated with $\%\Delta$HDL-C (data not shown).

**Discussion**

Our study shows the increased HDL-C in the nondiabetic, relatively obese males only carrying PON RR genotype after caloric restriction and the change in HDL-C levels could be associated with the changes in hepatic lipase activity and fasting insulin levels.

We also observed the reduction in both TG and TC levels in the QR genotype, and no significant changes in TG and TC in the QQ and the RR genotypes. The changes in serum lipid profile, especially TG, were known to be observed after weight loss (15). It is possible that a statistical power
was so weak that the changes in serum TG and TC levels in the QQ and the RR carriers were not statistically significant because apo B levels in all groups decreased.

As reported by several studies, it is controversial how dietary caloric restriction changes the level of HDL-C (15). HDL-C levels are frequently lower in obese than lean subjects, but reportedly did not change or even decreased in acute phase after weight loss in contrast to a rapid reduction in serum TG (15). Several investigators reported that the change in HDL-C levels during weight loss showed biphasic, namely it decreased early and increased late (16). Moreover, there was also known to be much individual difference in the change in HDL-C levels during weight loss. In the present data among combined whole subjects, the levels of serum TG significantly decreased but HDL-C showed no change after diet. However, despite no significant change in serum TG levels, HDL-C levels increased after diet only in the RR genotype, suggesting possible genetic background in modulating HDL-C levels during dietary intervention. Concerning the relation between HDL-C levels and PON genotypes, several reports showed that PON genotypes were associated with markers for insulin resistance in non-diabetic healthy subjects (17–19). In addition, Sakai et al. (20) and Abbott et al. (21) reported that PON activity was associated with HDL-C levels in nondiabetic subjects but not in diabetic patients, implying that PON might exert its effect on HDL metabolism in conjunction with diabetic status or insulin resistance. The present data could support the above hypothesis because there was a significant inverse correlation between the changes in fasting insulin and HDL-C levels only in the RR genotype, but not in the subjects carrying Q allele (Fig. 3).

To gain more insight into the mechanisms for the increased HDL-C levels in the RR genotype during the study, we determined LPL and HL activities, which are key enzymes affecting HDL metabolism (22). LPL activity after the study increased in the QQ and the QR but not in the RR genotype, implying that TG reduction in those genotypes was partly due to increased lipolysis of TG. In contrast, HL activity showed a distinct change from LPL activity after caloric restriction. We observed a significant difference in the changes in HL activity after caloric restriction dependent on PON R192Q genotype (Fig. 2), namely, a decrease in the RR genotype and an increase in the subjects carrying Q allele. Increased HL activity has been reported to be associated with decreased HDL-C levels, especially HDL\textsubscript{2} subfraction (23). Several studies using HL transgenic (24) or knockout mice (25, 26) reportedly supported above findings. Moreover, LPL (16) and HL (27) activity has been reported to decrease and increase in obese subjects respectively. Therefore, increased HDL-C levels in the RR genotype might be due to decreased HL activity after caloric restriction. Although it remains unclear why LPL and HL differently changed after caloric restriction, it is possible that they interact with distinct machineries involving insulin resistance or adiposity. However, since we did not determine cholesteryl ester transfer protein and lecithin:cholesterol acyltransferase, which are pivotal molecules regulating HDL metabolism (28), further studies are needed in future.

Another possible mechanism of the specific change in HDL-C levels in the RR genotype might be associated with the antioxidative effect of PON. Cheung et al. (12) reported that supplementation of antioxidant vitamin E abolished a raising effect of statin and niacin on HDL-C levels. PON protein with the glutamine at amino acid position 192 reportedly have more protective property against oxidative modification of LDL compared to PON with the arginine at the same codon, in contrast to the decreased activity in degradation of paraoxon or other organic phosphates (29). However, the link between antioxidant and metabolic effects of PON remains unclear.

In conclusion, our study demonstrated that PON R192Q genotype was associated with the change in HDL-C and fasting insulin levels after dietary caloric restriction in non-diabetic, relatively obese males and showed possible association between the changes in HDL-C, insulin resistance, and the lipases involving lipid metabolism. These findings could provide one of mechanisms for individual difference in serum lipid response to caloric restriction, and implication for a metabolic role of PON.

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