

# Remnant-Like Particle Cholesterol, Triglycerides, and Insulin Resistance in Nonobese Japanese Type 2 Diabetic Patients

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**OBJECTIVE** — The aim of the study was to investigate the relationships between remnant-like particle (RLP) cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — A total of 86 nonobese Japanese type 2 diabetic patients (72 men and 14 women, aged 40–83 years, BMI 20.1–26.6 kg/m<sup>2</sup>) were studied. BMI, HbA<sub>1c</sub> levels, and fasting concentrations of plasma glucose, serum lipids (RLP cholesterol, total cholesterol, HDL cholesterol, and triglycerides), and serum insulin were measured. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR). The subjects were divided into two groups according to the value of HOMA-IR. Values >2.5 were indicative of the insulin-resistant state, and values <2.5 were indicative of the insulin-sensitive state.

**RESULTS** — The insulin-resistant group had significantly higher RLP cholesterol and triglyceride levels and lower HDL cholesterol levels compared with the insulin-sensitive group. Univariate regression analysis showed that insulin resistance was positively correlated with BMI ( $r = 0.254$ ,  $P = 0.019$ ), HbA<sub>1c</sub> levels ( $r = 0.278$ ,  $P = 0.011$ ), RLP cholesterol levels ( $r = 0.315$ ,  $P = 0.004$ ), and triglyceride levels ( $r = 0.332$ ,  $P = 0.002$ ) and was negatively correlated with HDL cholesterol levels ( $r = -0.301$ ,  $P = 0.006$ ) in our diabetic patients. Multiple regression analysis showed that insulin resistance was independently associated with serum triglyceride levels, which explained 13.5% of the variability of insulin resistance in our nonobese Japanese type 2 diabetic patients.

**CONCLUSIONS** — These results indicate that 1) nonobese Japanese type 2 diabetic patients with insulin resistance are characterized by high RLP cholesterol and triglyceride levels, and low HDL cholesterol levels; and 2) the level of serum triglycerides is an independent predictor of insulin resistance in these patients.

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**Abbreviations:** CHD, coronary heart disease; CV, coefficient of variation; HOMA-IR, insulin resistance index of the homeostasis model assessment; RLP, remnant-like particle.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances

Cardiovascular disease, particularly coronary heart disease (CHD), is the most important cause of morbidity and mortality in type 2 diabetic patients. There are some data supporting the idea that insulin resistance might play a role in increasing the risk of CHD (1–5). Fasting hypertriglyceridemia and/or low HDL cholesterol concentrations are reported to be associated with insulin resistance (1–4). Reaven et al. (5) demonstrated that individuals with small dense LDL particles are insulin-resistant. All of these lipid abnormalities have been identified as risk factors for CHD in type 2 diabetic patients. Remnant lipoproteins, derived from VLDLs and chylomicrons, are considered atherogenic (6). Kugiyama et al. (7) recently demonstrated that fasting remnant lipoprotein levels predict coronary events in patients with CHD. There is little data on the relationship between insulin resistance and remnant lipoprotein levels in humans.

Abbasi et al. (8) were the first to show that remnant lipoproteins are increased in nondiabetic subjects with insulin resistance compared with those with normal insulin sensitivity. Type 2 diabetes, another state that is associated with insulin resistance, frequently shows high levels of remnant lipoproteins (9), suggesting that remnant lipoprotein levels are associated with insulin resistance in type 2 diabetic patients. To the best of our knowledge, however, the relationship between insulin resistance and remnant lipoproteins is not yet fully investigated in type 2 diabetic patients. A major problem is that remnant lipoproteins per se are associated with triglycerides, and therefore, it is difficult to investigate the relationships between insulin resistance and both remnant lipoproteins and triglycerides independent of each other. It is well recognized that the degree of obesity affects insulin sensitivity in humans (10). For that reason, we recruited nonobese Japanese type 2 diabetic patients and studied the relationships between insulin resistance and both remnant-like particle (RLP) cholesterol and

**Table 1—Clinical profile of insulin-resistant and insulin-sensitive diabetic patients**

Clinical characteristics	Insulin-resistant	Insulin-sensitive	P
n	39	47	—
Sex (M/F)	30/9	42/5	—
HOMA-IR	3.53 ± 0.12	1.52 ± 0.07	<0.001
Age (years)	61.4 ± 1.2	60.5 ± 1.6	0.322
BMI (kg/m <sup>2</sup> )	23.2 ± 0.3	22.6 ± 0.3	0.064
HbA <sub>1c</sub> (%)	7.4 ± 0.2	6.9 ± 0.2	0.071
Fasting glucose (mmol/l)	9.4 ± 0.3	7.4 ± 0.3	<0.001
Fasting insulin (μU/ml)	8.8 ± 0.4	4.6 ± 0.2	<0.001
Total cholesterol (mg/dl)	195 ± 6	193 ± 4	0.414
LDL cholesterol (mg/dl)	118 ± 5	119 ± 3	0.436
Triglycerides (mg/dl)	143 ± 12	98 ± 6	<0.001
RLP cholesterol (mg/dl)	5.9 ± 0.5	4.4 ± 0.3	0.003
HDL cholesterol (mg/dl)	48 ± 2	54 ± 2	0.015

Data are n or means ± SEM.

triglyceride levels independently using simple and multiple regression analyses.

## RESEARCH DESIGN AND METHODS

A total of 86 Japanese type 2 diabetic patients who visited our clinic were recruited for the present study. Type 2 diabetes was diagnosed based on World Health Organization criteria (11). Their age and BMI levels (mean ± SEM) were 60.9 ± 1.0 years and 22.9 ± 0.2 kg/m<sup>2</sup> (range 20.1–26.6), respectively. They were all nonobese (12). The duration of diabetes was 9.4 ± 0.7 years (range 1–32) and the HbA<sub>1c</sub> level was 7.1 ± 0.2% (range 5.5–13.9%). There were 38 patients who were taking sulfonylureas, and the rest were being treated with diet alone. All subjects had ingested at least 150 g carbohydrates for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease, and none were taking medications that affected lipid metabolism. They did not consume alcohol or perform heavy exercise for ≥1 week preceding the study.

Blood was drawn the morning after a 12-h fast. Plasma glucose was measured with the glucose oxidase method and serum insulin was measured using a two-site immunoradiometric assay (Insulin Riabead II, Dainabot, Japan). Coefficients of variation (CVs) were 4% for insulin >25 μU/ml and 7% for insulin <25 μU/ml, respectively. There was no detectable cross-reactivity of proinsulin in the insulin assay. RLP cholesterol was measured by the method reported by Nakajima et al. (13). Triglyceride, total cholesterol, and HDL cholesterol levels were also measured. The

range of triglyceride levels was 34–346 mg/dl in our present study. The LDL cholesterol level was calculated using the Friedewald formula (14).

The estimate of insulin resistance by the homeostasis model assessment (HOMA-IR) was calculated with the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l) ÷ 22.5 (15). The HOMA-IR value (mean ± SD) of normal tolerant subjects was 1.6 ± 0.9, and we defined the values >2.5 as an insulin-resistant state and the values <2.5 as an insulin-sensitive state (4,16). The threshold value for insulin resistance (2.5) in our study is similar to that (2.77) in nonobese subjects with no metabolic disorders, reported by Bonora et al. (17).

## Statistical analysis

Data are presented as means ± SEM. Statistical analyses were conducted using StatView 5 software (Statview, Berkeley, CA). The means of two groups were compared with Student's *t* test. Simple (Spearman's rank) correlation coefficients between HOMA-IR and measures of variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with HOMA-IR. *P* < 0.05 was considered significant. In our multivariate analysis, *F* values ≥4 were considered significant.

**RESULTS**— Table 1 illustrates the mean values of the clinical characteristics and the clinical profile of insulin-resistant and insulin-sensitive Japanese nonobese type 2 diabetic patients. HOMA-IR values in the patients with insulin resistance and those

with normal insulin sensitivity were 3.53 ± 0.12 and 1.52 ± 0.07, respectively. There was no significant difference in age, BMI, or HbA<sub>1c</sub> levels between the two subpopulations. Fasting glucose and insulin concentrations were significantly higher in the insulin-resistant group than in the insulin-sensitive group. No significant difference was observed in total and LDL cholesterol levels between the two subpopulations. In contrast, the patients with insulin resistance had significantly higher levels of triglycerides (143 ± 12 vs. 98 ± 6 mg/dl, *P* < 0.001) and RLP cholesterol (5.9 ± 0.5 vs. 4.4 ± 0.3 mg/dl, *P* = 0.003) than those with normal insulin sensitivity. The HDL cholesterol level was significantly lower in the insulin-resistant subgroup (48 ± 2 mg/dl) than in the insulin-sensitive subgroup (54 ± 2 mg/dl, *P* = 0.015).

Spearman's rank correlations of insulin resistance with measures of variables were calculated for all of our diabetic patients (Table 2). Insulin resistance was positively correlated with BMI, HbA<sub>1c</sub>, triglycerides, and RLP cholesterol levels. In contrast, HDL cholesterol levels were negatively correlated with insulin resistance. Age and both total and LDL cholesterol levels were not associated with insulin resistance. Multiple regression analyses were carried out using the stepwise procedure.

The analysis included insulin resistance as a dependent variable and candidate risk factors (i.e., BMI, HbA<sub>1c</sub>, triglycerides, and RLP and HDL cholesterol) as independent variables. Insulin resistance was independently predicted by serum triglyceride levels, which explained 13.5% of the variability of insulin resistance in our patients. Other variables (e.g., BMI, HbA<sub>1c</sub>, and RLP and HDL cholesterol) were not independently associated with insulin resistance in our nonobese Japanese type 2 diabetic patients.

**CONCLUSIONS**— Type 2 diabetes is a syndrome characterized by insulin resistance and/or defective insulin secretion (18,19). There seem to be ethnic differences in insulin resistance in type 2 diabetes. Haffner et al. (20) recently showed that in Caucasian populations, 92% of type 2 diabetic patients are insulin-resistant. In contrast, Chaiken et al. (21) previously showed that in African-Americans with a BMI <30 kg/m<sup>2</sup>, 60% of type 2 diabetic patients are insulin-resistant. Using the minimal model approach shown by Bergman et al. (22), our team previously

demonstrated that nonobese Japanese type 2 diabetic patients are divided into two variants: one with primary insulin resistance and the other with normal insulin sensitivity (23–25). Japanese subjects with impaired glucose tolerance had also two discrete forms: insulin resistance and normal insulin sensitivity (26). However, the factors contributing to insulin resistance in nonobese Japanese type 2 diabetic patients are not yet fully clarified. One of the potential factors responsible for insulin resistance is an abnormal lipid profile. We recently demonstrated that nonobese type 2 diabetic patients with insulin resistance had significantly higher triglyceride and lower HDL cholesterol levels than those with normal insulin sensitivity (4). Similar results were reported in Caucasian type 2 diabetic populations (20).

In the present study, we first showed that RLP cholesterol levels were higher in the insulin-resistant group than in the insulin-sensitive group of nonobese type 2 diabetic patients. The idea that RLP cholesterol may be associated with insulin resistance is supported in the recent study by Abbasi et al. (8), which showed that RLP cholesterol levels were elevated in nondiabetic insulin-resistant female volunteers. Thus, these various forms of dyslipidemia are postulated to be associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

Hypertriglyceridemia, low HDL cholesterol, and high RLP cholesterol levels are considered increasing risk factors for CHD. Patients with hypertriglyceridemia have smaller and denser LDL particles and an enhanced degree of postprandial lipemia (1,2,5,27). Both of these changes have also been identified as CHD risk factors (1,27). Low HDL cholesterol itself is reported to promote atherosclerosis by decreasing reverse cholesterol transport or by interfering with the atherogenicity of LDL particles (28). Kugiyama et al. (7) recently demonstrated that RLP cholesterol levels predict coronary events in patients with CHD. Why are the subjects with these abnormal lipid profiles at a particularly high risk for CHD? Although the mechanism behind this association has remained unknown, our present study supports the view that a defect in insulin-mediated glucose disposal plays a major role in increasing the risk of CHD.

Of particular note is the observation that serum triglyceride but not the degree of BMI was independently associated with insulin resistance in our nonobese Japanese type 2 diabetic patients. There are some

data suggesting that elevated triglyceride levels are the preceding factors for the development of insulin resistance in type 2 diabetic patients (29–32). In families with multiple cases of hypertriglyceridemia, increased serum triglycerides levels serve as a risk marker for subsequent development of type 2 diabetes (29). Mingrone et al. (30) reported on two sisters with extreme hypertriglyceridemia and diabetes in whom surgical normalization of serum triglycerides improved glucose tolerance and insulin resistance. We recently reported that treatment with bezafibrate not only lowers serum triglyceride levels, but also improves insulin resistance and fasting glucose levels in type 2 diabetic patients (31). Moreover, we recently demonstrated that physical activity improves serum triglycerides, insulin resistance, and glucose levels without affecting body weight in type 2 diabetic patients (32). Thiazolidinediones, which are being developed for the treatment of insulin resistance and type 2 diabetes, bind with peroxisome proliferator-activated receptor  $\gamma$  and also reduce triglyceride levels in diabetic patients (33).

However, there are self-evident but sometimes forgotten biological realities in the consideration of serum triglycerides as an important factor associated with insulin resistance in nonobese Japanese type 2 diabetic patients. Triglycerides do not exist by themselves in plasma; they exist in association with free and esterified cholesterol, apoproteins, and phospholipids as lipoprotein particles. Triglycerides are carried in all lipoprotein classes. Some lipoproteins are considerably richer in triglyceride than others. Triglyceride-rich lipoproteins include chylomicrons, VLDLs, and their remnants (e.g., RLP cholesterol).

The present study is the first to investigate the relationship between RLP cholesterol and insulin resistance in diabetic patients. With univariate analysis, we found a positive correlation among plasma triglycerides, RLP cholesterol, and insulin resistance; however, with multivariate analysis, we found that plasma RLP cholesterol was no longer an independent factor of insulin resistance. The reason for the results is not known at present, because RLP cholesterol levels per se are associated with triglyceride levels. There was a positive correlation between serum triglycerides and RLP cholesterol in our present study ( $r = 0.879$ ,  $P < 0.0001$ ). The lower prevalence of high RLP cholesterol levels ( $\geq 7.5$  mg/dl) (9) in our patients might have affected the results. In

**Table 2—Correlation of insulin resistance to measures of variables in diabetic patients**

Variables	<i>r</i>	<i>P</i>
BMI	0.254	0.019
HbA <sub>1c</sub>	0.278	0.011
Triglycerides	0.332	0.002
RLP cholesterol	0.315	0.004
HDL cholesterol	-0.301	0.006
Age	-0.024	0.824
Total cholesterol	-0.006	0.954
LDL cholesterol	-0.025	0.818

regard to the prevalence of RLP cholesterol level in diabetic patients, Watanabe et al. (9) were the first to show that ~20% of Japanese diabetic patients had high RLP cholesterol levels. In contrast, only 14% (12 of 86) of diabetic patients had high RLP cholesterol levels in our present study. Hirany et al. (34) recently showed that diabetic patients with macrovascular complications had significantly higher levels of RLP cholesterol and higher RLP cholesterol-to-triglycerides ratios than diabetic patients without macrovascular complications. Alternatively, studies on nonobese populations might underestimate the relationship between RLP cholesterol and insulin resistance in diabetic patients. Further studies using a large number of populations that include high-RLP cholesterol or obese groups will be required to clarify whether the independent contribution of RLP cholesterol to insulin resistance in diabetic patients is significant.

In conclusion, our present study indicates that 1) nonobese Japanese type 2 diabetic patients with insulin resistance are characterized by high RLP cholesterol, high triglyceride, and low HDL cholesterol levels; and 2) serum triglycerides independently contribute to insulin resistance in our nonobese Japanese type 2 diabetic patients.

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