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Remnant-like particles and coronary artery disease in familial hypercholesterolemia

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ABSTRACT

Background: Although remnant-like particle cholesterol (RLP-C) has been associated with coronary artery disease (CAD) in the general population, few data exist regarding this issue in patients with familial hypercholesterolemia (FH). The aim of our study was to investigate the association between RLP-C and the presence of CAD in patients with FH.

Methods: We examined 282 patients with FH (144 males, mean age, 41 ± 17 years) whose RLP-C levels were measured. We assessed the baseline characteristics, including lipid levels, other conventional risk factors for cardiovascular events, the presence of CAD, and the serum RLP-C levels.

Results: Serum RLP-C levels significantly correlated with serum triglyceride (TG) levels (Pearson's $r = 0.631$, $p < 0.001$). We observed that a larger proportion of individuals in the higher tertiles of serum RLP-C had a larger number of diseased coronary arteries ($p < 0.001$ for the trend of multi-vessel disease). Logistic regression analysis, after adjusting for age, sex, hypertension, diabetes, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and lipoprotein (a) [Lp(a)], revealed that RLP-C was significantly associated with CAD [odds ratio (OR): 1.08, 95% confidence interval (CI): 1.00–1.16, $p = 0.046$]; however, adding serum TG levels into the logistic regression model nullified this association (OR: 1.07, 95% CI: 0.98–1.17, $p = 0.141$), whereas Lp(a) was independently associated with CAD (OR: 1.02, 95% CI: 1.00–1.03, $p = 0.015$).

Conclusions: Serum RLP-C levels were significantly associated with the presence and severity of CAD in patients with FH. However, the clinical usefulness of measuring RLP-C levels beyond that of measuring TG levels should be further assessed.

1. Introduction

Familial hypercholesterolemia (FH; OMIM #143890) is characterized by the triad of (1) primary low-density lipoprotein (LDL) hypercholesterolemia, (2) tendon xanthomas, and (3) premature coronary artery disease (CAD) [1,2]. Although all FH individuals are at a high risk of CAD due to the lifelong burden of LDL cholesterol (LDL-C) accumulation, there remains a great diversity in phenotype [3–5]. Identifying individuals at a higher risk of cardiovascular events among the patients with FH and then aggressively addressing modifiable risk factors in this already high-risk group could be beneficial with respect to health outcomes and cost.

Remnant-like particles (RLPs), derived from very-low-density lipoproteins and chylomicrons, are considered atherogenic lipoproteins.[6] RLP cholesterol (RLP-C) has been shown to be associated with cardiovascular events in patients with metabolic syndrome, type-2 diabetes, and CAD [7–9]. However, few data exist regarding this issue in FH patients with increased RLP-C levels. Thus, the aim of our study was to investigate the association between RLP-C levels and the presence of CAD in patients with FH.

2. Methods

2.1. Patient population

A total of 284 consecutive patients who fulfilled the clinical criteria for FH determined by the Japan Atherosclerosis Society[10] and whose RLP-C levels had been measured between January 2006 and December 2016 were retrospectively assessed (males: n = 144; mean age = 41 ± 17 years, mean LDL-C = 254 ± 60 mg/dL).

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Table 1
Baseline characteristics.

Variable	All	Coronary artery disease		p-Value
	(n = 282)	Yes (n = 88)	No (n = 194)	
Age (years)	41 ± 17	49 ± 14	38 ± 17	< 0.001
Men	144 (51%)	61 (69%)	83 (48%)	< 0.001
Hypertension	68 (24%)	47 (53%)	21 (12%)	< 0.001
Diabetes	34 (12%)	22 (25%)	12 (9%)	< 0.001
Smoking	86 (30%)	46 (52%)	40 (22%)	< 0.001
Body mass index (kg/m^2)	24.3 ± 3.1	24.1 ± 3.8	24.4 ± 3.0	0.2456
TC (mg/dL)	336 ± 66	346 ± 71	332 ± 63	0.113
LDL-C (mg/dL)	254 ± 60	265 ± 64	249 ± 58	0.0478
HDL-C (mg/dL)	53 ± 15	46 ± 13	56 ± 15	< 0.001
TG (mg/dL)	112 [74–166]	149 [105–201]	96 [64–147]	< 0.001
Lp(a) (mg/dL)	23.6 [13.2–42.4]	34.7 [16.7–57.3]	21.8 [12.3–35.8]	< 0.001
RLP-C (mg/dL)	6.8 [5.1–9.7]	8.4 [6.0–11.9]	6.3 [4.7–8.7]	< 0.001

TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol, TG, triglyceride; Lp(a), lipoprotein (a); RLP-C, remnant-like particle cholesterol.

2.2. Biochemical analysis

Blood samples were drawn for assays after overnight fasting either before administering lipid-lowering treatment or after the discontinuation of medication for at least 4 weeks. Serum levels of total cholesterol (TC), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were determined enzymatically (Qualigent, Sekisui Medical) using automated instrumentation according to previously described assays [11]. RLP-C was measured using an immunoseparation assay as described previously [12]. Genomic DNA was isolated from peripheral blood white blood cells according to standard procedures and was used for polymerase chain reaction analyses. We sequenced the coding regions of FH-associated genes [LDL receptor and proprotein convertase subtilisin/kexin type 9 (*PCSK9*)]. The genotype of all the participants in this study was determined as previously described [13].

2.3. Clinical assessments

Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or treatment with antihypertensive medications. The presence of diabetes was defined as previously described by the Japan Diabetes Society [14]. Smoking status was defined according to current smoking habits. CAD was defined as a lumen diameter stenosis of > 50% in a major coronary artery [15]. Patients were classified according to the number of diseased vessels: 1-vessel disease, 2-vessel disease, and 3-vessel disease (patients with disease in 3 vessels or left main trunk disease).

2.4. Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consents were obtained from all subjects for inclusion in the study.

2.5. Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as counts and percentages. For values lacking a normal distribution, the median and interquartile range were reported. Mean values of continuous variables were compared using the Student's *t*-test for independent data, and median values were compared using the nonparametric Wilcoxon–Mann–Whitney rank sum test. Categorical variables were compared using the χ^2 test. Multivariate analysis of independent predictors of adverse outcomes was performed using the logistic regression model. Variables with $p < 0.10$ on univariate analysis were selected for multivariate analysis in consideration of potential confounding variables. The Cochran–Armitage trend test was used to assess the trend of multi-vessel disease (2- or 3-vessel disease) according to the tertiles of RLP-C levels. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using R ver. 3.3.2.

3. Results

3.1. Baseline clinical characteristics

The baseline characteristics of the study population are illustrated in Table 1. As expected, the patients with CAD were significantly older than those without CAD. The frequencies of other conventional risk factors such as male sex, hypertension, diabetes, and smoking habits were significantly higher, whereas HDL-C levels were significantly lower in FH patients with CAD than in those without CAD. Under these conditions, serum RLP-C levels were significantly higher in the patients with CAD than in those without CAD.

We identified causative mutations, either within the LDL receptor gene or in *PCSK9*, in 191 (67%) of 284 patients. Details of the mutations were described in Supplemental Table 1. Characteristics according to genetic mutation status are illustrated in Supplemental Table 2. RLP-C levels of patients either with LDL receptor gene mutation of *PCSK9* gene

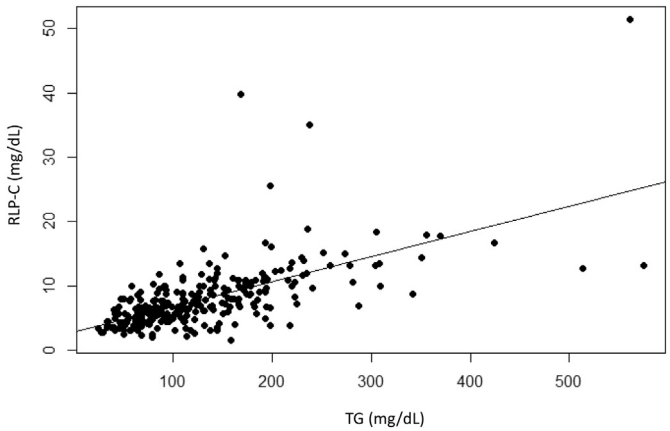

Fig. 1. Correlation between TG and RLP-C levels in patients with FH.
X axis: TG (mg/dL). Y axis: RLP-C (mg/dL). Pearson's r = 0.631, p < 0.001.
TG: triglyceride; RLP-C: remnant-like particle cholesterol.