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Relationship between serum triglyceride levels and endothelial function in a large community-based study

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ABSTRACT

Background and aims: It is established that low-density lipoprotein cholesterol is an independent risk factor for cardiovascular events. Recently, circulating triglycerides level has been focused on as a risk factor for cardiovascular events. In this study, we evaluated the associations between triglycerides and endothelial function in a general population.

Methods: We analyzed data for 4887 subjects who were enrolled in the FMD-Japan registry. We investigated cross-sectional associations between serum triglyceride levels and endothelial function assessed by measurement of flow-mediated vasodilation (FMD).

Results: Serum triglyceride levels were correlated with FMD ($r = -0.12$, $p < 0.001$). Subjects were divided into six groups based on serum triglyceride levels. FMD was significantly decreased with an increase in serum triglyceride levels (≤0.71 mmol/L, 7.0 ± 3.5%; 0.72–0.94 mmol/L, 6.3 ± 3.5%; 0.95–1.19 mmol/L, 6.0 ± 3.1%; 1.20–1.48 mmol/L, 5.8 ± 3.2%; 1.49–2.02 mmol/L, 5.7 ± 3.1%; ≥2.03 mmol/L, 5.5 ± 3.0%; p for trend <0.001). After adjustment for age, sex, and cardiovascular risk factors, including high-density lipoprotein cholesterol, serum triglyceride levels of more than 1.20 mmol/L were independently associated with the low quartile of FMD (1.20–1.48 mmol/L, odds ratio (OR) 1.41, 95% confidence interval (CI) 1.09 to 1.82; 1.49–2.02 mmol/L, OR 1.31, 95% CI 1.00 to 1.70; ≥2.03 mmol/L, OR 1.48, 95% CI 1.13 to 1.95) using serum triglyceride levels of less than 0.71 mmol/L group as the reference.

Conclusions: These findings suggest that triglycerides are an independent predictor of endothelial function. Lowering circulating triglyceride levels may improve endothelial function, leading to a decrease in cardiovascular events.

Clinical trial registration information: URL for Clinical Trial: http://UMIN; Registration Number for Clinical Trial: UMIN000003409

1. Introduction

Endothelial dysfunction is the initial step of atherosclerosis, resulting in cardiovascular complications [1,2]. It is clinically important to evaluate the condition of endothelial function, which

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provides additive information for risk stratification. Flow-mediated vasodilation (FMD) of the brachial artery, which is an index of endothelium-dependent vasodilation, provides useful information on endothelial function [3–11]. Evaluation of FMD is noninvasive and FMD is a good reflection of nitric oxide production. Furthermore, previous studies have shown that endothelial function assessed by FMD is an independent predictor of cardiovascular events [12–16].

Total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) are well-established independent predictors for cardiovascular events [17]. Although the risk of cardiovascular disease can be reduced through pharmacological interventions, including statin therapy, patients with dyslipidemia have high residual risk of cardiovascular events [18–20]. Clinical and epidemiological studies have shown a link between circulating triglyceride levels and cardiovascular disease [21–24]. In the Asia Pacific Cohort Studies Collaboration, serum triglyceride levels were shown to be independently associated with risk of coronary heart disease [25]. However, in some studies, this association was lost after adjustment of HDL-C [26,27]. Therefore, an independent association between circulating triglyceride levels and cardiovascular disease has been controversial.

Several investigators have reported univariate associations between circulating triglyceride levels and endothelial function [7,28]. However, subjects in previous studies were limited to small numbers of subjects or highly selected subjects. In addition, it remains unclear whether circulating triglyceride levels are an independent risk factor for endothelial dysfunction. The purpose of this study was to evaluate the relationship between circulating triglyceride levels and endothelial function in a general population.

2. Materials and methods

2.1. Subjects

A total of 5433 Japanese adults aged 17–86 years who underwent health-screening examinations with agreement for measurement of vascular function were enrolled in the Flow-mediated Dilation Japan Registry between 1 April 2010 and 31 August 2012 at three general hospitals in Japan. All employees have an obligation to undergo health screening every year under the regulations of the Society-managed Health Insurance Union in Japan. In accordance with the regulations, we performed health-screening examinations. Among the 5433 participants, information on the serum triglyceride levels was available for 4887 participants. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg, on at least 3 different occasions in a sitting position, or currently taking antihypertensive medication. Diabetes mellitus was identified using the American Diabetes Association criteria [29]. Dyslipidemia was identified using the third report of the National Cholesterol Education Program [17]. We defined smokers as those who were current smokers. This study was approved by the ethical committees of Hiroshima University. All subjects gave written informed consent for participation in the study.

2.2. Study protocol

We measured vascular responses to reactive hyperemia in the brachial artery in all participants. Subjects were instructed to abstain from eating, alcohol, smoking and caffeine at least 12 h prior to the measurements. Measurements were performed while subject was supine position in a quiet, dark, air-conditioned room (constant temperature of 22°C–25 °C). Venous blood samples were obtained from the left antecubital vein. The observers were blind to the purpose of this study. Levels of serum total cholesterol, triglycerides, HDL-C, and LDL-C were enzymatically measured (JCA-BM6010). Glucose levels were measured by the glucose oxidase immobilized oxygen electrode method (GA08II; A&T, Yokohama, Japan). We investigated cross-sectional associations between serum triglyceride levels and FMD.

2.3. Measurement of FMD

A high-resolution ultrasonography (UNEXEF18G, UNEX Co, Nagoya, Japan) was used to evaluate FMD. The protocol for measurements of FMD has been described in detail previously [30]. Briefly, the longitudinal image of the brachial artery was assessed before and after generation of vascular response to reactive hyperemia by a 5 min period of forearm occlusion to evaluate FMD. FMD was defined as the maximal percentage change in vessel diameter from the baseline value.

2.4. Statistical analysis

Results are presented as mean ± SD. All reported probability values were 2-sided, and a probability value of <0.05 was considered to be statistically significant. Categorical variables were compared by means of $\chi 2$ test. Continuous variables were compared by using analysis of variance (ANOVA) for multiple groups. Relations between variables were determined by Spearman's correlation coefficients analysis. Crude and adjusted odds ratios of low quartile of FMD (less than 3.9%) according to serum triglyceride levels were calculated by using the lowest triglycerides group (less than 0.71 mmol/L) as the reference. The data were processed using the software package Stata version 9 (Stata Co., College Station, Texas, USA).

3. Results

3.1. Baseline clinical characteristics

The baseline characteristics of the 4887 subjects are summarized in Table 1. Of the 4887 subjects, 3821 (78.2%) were men and 1066 (21.8%) were women. One thousand ninety-six subjects (22.4%) had hypertension, 2275 (46.6%) had dyslipidemia, 310 (6.3%) had diabetes mellitus, and 851 (17.4%) were current smokers. The mean value of FMD was 6.0 ± 3.3%. Of the 4887 subjects who were evaluated, 122 (2.5%) had known coronary heart disease and 45 (0.9%) had known stroke.

3.2. Relationships between FMD and cardiovascular risk factors

FMD was negatively correlated with age, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, glucose, and brachial artery diameter and was positively correlated with HDL-C (Table 2). There was a significant relationship between FMD and triglycerides ($r = -0.12$, $p < 0.001$; Fig. 1).

3.3. Relationships between serum triglyceride levels and cardiovascular risk factors

Univariate regression analysis revealed that serum triglyceride levels were significantly correlated with age, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, HDL-C, LDL-C, and glucose (Table 2). Participants were categorized into six groups based on serum triglyceride levels (Table 1). Age, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, LDL-C, glucose, and