Original article

Impact of nonfasting triglycerides/high-density lipoprotein cholesterol ratio on secondary prevention in patients treated with statins

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A B S T R A C T

Background: Some studies have demonstrated that low-density lipoprotein cholesterol (LDL-C) lowering therapy is one of the most important strategies to prevent coronary artery disease. Also, serum triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) are recognized as independent risk factors of cardiovascular diseases. The aim of this study was to investigate whether the nonfasting TG/HDL-C ratio could affect the incidence of cardiovascular events after percutaneous coronary intervention (PCI) even in patients treated with statins.

Methods and results: One thousand one hundred seventy consecutive patients were enrolled, all of whom underwent successful PCI for acute coronary syndrome or stable angina and continued statin treatments after PCI. They were equally divided into three groups on the basis of a nonfasting TG/HDL-C ratio 3 months after PCI. Among these groups, the incidence of major adverse cardiac events (MACE) was measured during a maximum of 5 years after PCI. MACE was defined as cardiac death, nonfatal myocardial infarction, revascularization due to new stenosis or restenosis. Kaplan–Meier analysis demonstrated that patients with higher TG/HDL-C ratio had a significantly higher incidence of MACE than other groups (p < 0.001). In addition, Cox proportional hazards regression analysis indicated that the nonfasting TG/HDL-C ratio was significantly correlated with the incidence of MACE.

Conclusion: The nonfasting TG/HDL-C ratio was a valuable predictor of cardiovascular events after PCI in patients treated with statins.

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Introduction

Cardiovascular disease is a major health problem that can lead to adverse prognosis and high health care costs [1]. Many clinical studies have demonstrated that low-density lipoprotein cholesterol (LDL-C) lowering therapy is one of the most useful strategies to prevent cardiovascular diseases [2–6]. The Japanese guidelines for secondary prevention of coronary artery disease (CAD) have proposed controlling the level of LDL-C to less than 100 mg/dl [7]. Also, 2016 European Society of Cardiology and European Atherosclerosis Society guidelines for the Management of Dyslipidemias recommend decreasing LDL-C level to less than 70 mg/dl for very high-risk patients [8]. Furthermore, statins have been regarded as first-line therapy for lowering the LDL-C level, and 2013 American College of Cardiology/American Heart Association (AHA/ACC) guidelines recommend fixed-dose statin strategies instead of targeted goals to lower blood cholesterol [9,10].

However, some clinical studies have shown that residual cardiovascular risk factors can remain even in patients with appropriate LDL-C levels or those who have been treated sufficiently with statins [11–13]. Other studies also reported that low high-density lipoprotein cholesterol (HDL-C) levels were associated with a high incidence of cardiovascular events among patients with CAD [14,15]. In addition, 2013 AHA/ACC guideline did not make any specific recommendations on the treatment of elevated triglycerides (TG), but some previous studies have demonstrated that serum TG can affect the morbidity or mortality of cardiovascular diseases [9,16–18]. Furthermore, it is known that patients with hypertriglyceridemia frequently have low plasma levels of HDL-C [19].

Therefore, the TG/HDL-C ratio, which can reflect TG and HDL-C simultaneously, has been increasingly recognized as a powerful predictor of cardiovascular diseases in both primary prevention and secondary prevention [20].

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However, there have been few studies to evaluate the correlation between a low TG/HDL-C ratio and cardiovascular events reduction in patients treated with statins. Moreover, there have been several studies using a nonfasting TG/HDL-C ratio. For this reason, the aim of this study was to investigate whether the nonfasting TG/HDL-C ratio could affect the incidence of cardiovascular events after percutaneous coronary intervention (PCI) even in patients treated with statins.

Methods

Study population

In this study, the clinical records of 1170 consecutive patients, who underwent successful PCI for acute coronary syndrome (ACS) or stable angina pectoris between January 2005 and December 2015 and continued statin treatments without taking fibrates, were examined. However, patients with the following conditions or health histories were excluded from this study: residual stenosis in major coronary artery branches, residual heart failure of more than New York Heart Association class 2, past histories of coronary bypass surgery, malignant tumors, kidney dysfunction needing dialysis treatment, or uncompensated liver cirrhosis. Furthermore, those who had experienced cardiovascular events within 3 months after PCI were likewise excluded to avoid the influence of PCI procedure or subacute thrombosis. The ethics committee of our hospital approved the study protocol, and all patients prior to entry gave written informed consent.

Study design

The patients were monitored carefully with interviews and clinical examinations every 2–3 months and routine blood tests that were performed 3 months after PCI and every 6 months after that. Almost all blood samples were obtained 2–3 h after eating breakfast, but only a few samples were obtained 2–3 h after eating lunch. Also, routine coronary angiography (CAG) was performed 6–8, 12–18, and 48–60 months after PCI, and exercise stress tests were performed every 12 months. During the follow-up, if relapses of some symptoms or a positive result on an exercise stress test were detected, we carried out CAG accordingly. Regarding medical treatment after PCI, lipid-lowering agents such as statins or antiplatelet agents were prescribed either before or just after PCI and continued by the judgment of the attending physicians. The baseline evaluation was performed 3 months after PCI and subjects were equally divided into three groups on the basis of a nonfasting TG/HDL-C ratio. Demographic data including age, gender, body mass index (BMI), the prevalence rate of hypertension and diabetes, smoking rates, the value of LDL-C measured by using a unique surfactant of Kyowa Medix Company (Tokyo, Japan), hemoglobin A1c (HbA1c), uric acid (UA), estimated glomerular filtration rate (eGFR) calculated using the Schwartz formula, and C-reactive protein (CRP) were retrospectively collected from the database. Moreover, the number of ACS patients, the number of deceased vessels, and the usage rate of drug-eluting stents (DES) were also checked. Hypertension was defined as being prescribed oral antihypertensive drugs or blood pressures of higher than 140/90 mmHg at an outpatient visit. Diabetes including impaired glucose tolerance (IGT) was defined as being prescribed oral antidiabetic drugs or an HbA1c level of 6.2 or higher.

The cumulative incidence of major adverse cardiac events (MACE) was investigated during a maximum of 5 years after PCI among the three groups. In this study, MACE was defined as cardiovascular death, nonfatal myocardial infarction, the procedure of revascularization due to new coronary stenosis, and restenosis. Cardiac death was documented as death related to myocardial infarction, congestive heart failure, or arrhythmia. Myocardial infarction was defined as myocardial ischemia with the increase of markers related to myocardial necrosis. Coronary stenosis was defined as 50% or greater narrowing detected by quantitative coronary angiography (QCA) and restenosis was defined as stenosis within both sides of 5 mm of the PCI site. The details of MACE were also evaluated among the three groups. During follow-up periods, the patients who died of the causes other than cardiovascular troubles or who enrolled in another course due to other diseases were processed as censored data. The patients that we could not observe because of change of address were likewise processed as censored cases. However, the patients who had unscheduled CAG but who did not have stenotic lesions continued to be observed.

Furthermore, the correlations between the incidence of MACE and various risk factors including a nonfasting TG/HDL-C ratio were evaluated by using a multivariate analysis. In addition, to exclude the impact of the LDL-C level, the same investigation of the cumulative incidence of MACE was likewise conducted exclusively among patients with a LDL-C level of less than 100 mg/dl in each quantile.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and a p-value of less than 0.05 was considered as being statistically significant. A one-way ANOVA with Tukey post hoc tests and chi-square tests were used to compare the baseline characteristics of patients classified by the TG/HDL-C ratio. The cumulative incidence of MACE was analyzed using Kaplan–Meier method with the log-rank test. In addition, the multivariate Cox proportional hazards regression analysis was performed to investigate the correlation between the TG/HDL-C ratio and MACE after adjustment for conservatively related coronary risk factors such as age, gender, BMI, smoking habit, the value of LDL-C, HbA1c, UA, eGFR, and the use of DES. All data were analyzed using SPSS Advanced Statistics version 24 (Armonk, NY, USA).

Results

The usage rate of strong statins such as atorvastatin, pitavastatin, and rosuvastatin in each quantile was similar (p = 0.742). Also, the usage rate of omega-3 fatty acid in each quantile was 7.9%, 10.3%, and 10.5%, respectively (p = 0.407). Ezetimibe was almost never used in this study (2.1%, 2.1%, and 4.4%, respectively). The median TG/HDL-C ratio of all patients was 2.56 and the median follow-up period was 47 months. The number in Quantile 1 (lower TG/HDL-C ratio), Quantile 2 (intermediate TG/HDL-C ratio), and Quantile 3 (higher TG/HDL-C ratio) was 390 each, and the mean (range) of TG/HDL-C ratio was 1.37 (0.50–2.00), 2.60 (2.02–3.34), and 5.60 (3.35–18.29), respectively. Regarding the differences in the patients’ characteristics, patients in Quantile 1 were older than other groups (p < 0.001). Also, the percentage of males, the BMI, and the prevalence of IGT and smoking rate in Quantile 3 were higher than other groups (p < 0.001), but no difference was noted in the prevalence of hypertension among the three groups. The value of LDL-C, TG, HbA1c, and UA in Quantile 3 was significantly higher (p < 0.001). However, there were no significant differences in the eGFR, CRP, the number of ACS patients, the number of diseased vessels, and the usage rate of DES (Table 1).

During the follow-up period, the observation in 58 patients was discontinued because of a change of house (n = 42), a change to another hospital due to new cancer (n = 10), brain hemorrhage (n = 2), or new renal failure (n = 2). Six patients died of severe infection.
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