The risk factors associated with ultrasonic tissue characterization of carotid plaque in type 2 diabetic patients

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ABSTRACT

Aims: Little is known about the related factors of plaque echogenicity in diabetic subjects.
Methods: This was a single-center, retrospective, study investigating a subgroup of patients of a previously published trial. We enrolled 179 middle-aged and older Japanese type 2 diabetic patients with carotid plaque, and examined the parameters related with echogenicity of carotid plaque evaluated by gray-scale median (GSM).
Results: Proportion of males and body mass index (BMI) were significantly higher and HDL-cholesterol was significantly lower in the patients with low GSM ($<$48) plaques ($n = 89$) as compared to those without it ($n = 90$). A multiple logistic regression analysis with gender, BMI, and HDL-cholesterol as independent variables and the presence of low GSM plaques as an objective variable showed that male (odds ratio (OR) 2.36, 95% CI 1.05–5.31, $p = 0.037$) and BMI (OR 1.12 [1.01–1.24], $p = 0.029$) were independently associated with low GSM plaques. Another multiple logistic regression analysis with gender, BMI, and low-HDL–cholesterolemia (HDL-C $<$40 mg/dl) as independent variables showed that low-HDL–cholesterolemia (OR 2.30 [1.03–5.13], $p = 0.042$) and BMI (OR 1.11 [1.00–1.22], $p = 0.046$) were independently associated with low GSM plaques.
Conclusions: Our study suggests that gender, BMI and low-HDL-cholesterol are important determinants of the content of the vascular wall in diabetic subjects.

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1. Introduction

Cardiovascular disease (CVD) based on atherosclerosis is the most important cause of mortality in subjects with diabetes mellitus. Therefore, the early detection of high-risk group for CVD and subsequent rapid intervention, are important in the management of diabetic patients.

Previous studies have revealed that the presence of carotid plaque, which can be assessed quickly, non-invasively, and economically with high-resolution ultrasound, is regarded as a reliable marker for systemic atherosclerosis and cardiovascular event (Nambi et al., 2010). In ultrasonography, plaques of carotid artery have been assessed by two important indicators; one is plaque size and the other is its echogenicity. Thickness of carotid plaque, one of the most common indices of plaque size, has been an established surrogate marker for systemic atherosclerosis, and it has been shown to be a reliable marker of risk for cardiovascular disease

(CVD) (Nambi et al., 2010; O'Leary et al., 1999). Recently, plaque echogenicity, a simple and reliable tool in predicting plaque composition, has also been shown to be a reliable marker of risk for CVD: several studies have shown that patients with echolucent plaques have higher risk for CVD than patients with echogenic ones (Grønholdt, Nordestgaard, Schroeder, Vorstrup, & Sillesen, 2001; Hirano et al., 2010; Honda et al., 2004). Furthermore, we have also shown that plaque echogenicity evaluated by gray-scale median (GSM) analysis, together with plaque thickness, could improve the prediction ability of CVD events in type 2 diabetic patients without history of CVD (Irie et al., 2013). These findings indicate that both thickness and echogenicity of carotid plaque are useful in identifying diabetic patients with high risk of CVD events and that insight into risk factors that determine the thickness and echogenicity of carotid plaque will be able to inform preventive strategies for cardiovascular disease.

It is well known that plaque thickness is associated with traditional coronary risk factors such as hyperglycemia, dyslipidemia, hypertension, and obesity, inflammation, and oxidative stress. However, the determinants of plaque echogenicity are less well established, while several studies have reported that plaque echogenicity is also related to lipid status, body mass index, and some inflammation markers (Andersson et al., 2009; Libby & Aikawa, 2002;

Nishi et al., 2002). Especially, little is known about the related factors of plaque echogenicity in diabetic subjects.

The aim of the present study is to clarify the parameters related with the echogenicity of carotid plaque, using the baseline data collected in the previous study.

2. Materials and methods

2.1. Subjects

The data presented in this report were collected as part of the baseline characteristics of 287 diabetic patients in the previous study that evaluated whether the assessment of plaque echogenicity using GSM can be a predictor of future CVD events (Irie et al., 2013). Outline of the eligibility criteria of the original cohort was as follows: (1) age ≥40 years at the time of enrollment, and (2) diagnosed with type 2 diabetes based on the criteria of the Japan Diabetes Society (Japan Diabetes Society, 2007). Exclusion criteria were (1) history of ischemic stroke, coronary heart disease, or peripheral artery disease, (2) elevated liver enzymes (GOT or GPT ≥2.5 times the normal range), (3) renal insufficiency (serum creatinine ≥2.0 mg/dl). Detailed eligibility criteria of the original cohort were described in the previous publication (Irie et al., 2013). Screening of the study patients was performed consecutively during the registration period (from April 2007 to December 2009) at the outpatient diabetes clinic of Osaka Police Hospital.

Since statins were reported to affect plaque composition (Katakami et al., 2005; Watanabe et al., 2005), those who had been receiving statins (n = 108) were excluded from the current study. After all, a total of 179 middle-aged and older Japanese type 2 diabetic patients with carotid plaque were enrolled.

The study protocol was approved by the committee on human research ethics of Osaka Police Hospital. Written informed consent was obtained from all the participants after a full explanation of the study.

2.2. Clinical and biochemical analysis

Blood samples were collected after an overnight fast for analysis of serum concentrations of glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and HbA1c. Dyslipidemia was defined as LDL cholesterol ≥120 mg/dL, HDL cholesterol <40 mg/dL, Triglycerides ≥150 mg/dL, or current use of lipid-lowering agents in accordance with the standards of the Japan Diabetes Society (Japan Diabetes Society, 2007). Hypertension was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg or current use of anti-hypertensive agents. Renal function was evaluated by urinary albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR).

2.3. Ultrasound examination

B-mode ultrasonography of the carotid artery, using an ultrasound machine (Toshiba SSA-790CE; Toshiba Medical Systems, Tokyo, Japan) with a 7.5-MHz linear transducer, was performed by experienced laboratory physicians. Scanning of the common carotid artery (CCA), the carotid bulb (CB), and the internal carotid artery (ICA) in the neck was performed bilaterally in three different longitudinal projections (anterior, lateral, and posterior, which corresponded to ~60°, 90°, 150° for the right carotid artery and ~210°, 270°, and 300° for the left carotid artery marked on the Meijer's Arc) as well as transverse projections. We assessed the carotid artery structures according to the guideline of the Japan Society of Ultrasonics (Terminology and Diagnostic Criteria Committee & Japan Society of Ultrasonics in Medicine, 2009). Carotid plaque was defined as a focal structure encroaching into the arterial lumen or demonstrating a thickness >1.0 mm as measured from the media–adventitia interface to the intra-lumen interface.

Measurement of the plaque thickness was performed in the CCA, the CB, and the ICA separately, and the greatest value among them was used as the representative value for each individual. Reproducibility analysis of 20 pairs of replicate measurements yielded absolute mean differences of 0.03 ± 0.05 mm for plaque thickness. The inter-observer coefficient of variation for measurement of plaque thickness was 0.7%.

The plaque echogenicity was evaluated using a parameter the gray-scale median (GSM) in a gray-scale range of 0 (black) to 255 (white). A single reader (Y. I.), unaware of the clinical characteristics of the patients, performed GSM analysis using Adobe Photoshop software (Adobe Systems, version 7.0, San Jose, CA, USA). According to the criteria reported previously, the standardization of the B-mode image was performed by using a curve option, so that the GSM for the blood ranged from 0 to 5 and for the adventitia from 185 to 195 (Sabetai et al., 2000). The carotid plaque was manually delineated and the GSM of its pixels was read from the entire delineated area. In case there were multiple plaques in one individual, all the plaques present were subject to GSM measurement and the lowest value among them was used as the representative value for each individual. The intra-reader coefficient of variation for GSM measurements was 5.8% for 140 consecutively replicated measurements.

2.4. Statistical analyses

All values are reported as means ± SD, median (range), or real numbers of subjects with the percentage in parentheses. The data were compared by the χ^2-test, the unpaired t-test for parametric data, or the Mann–Whitney U test for nonparametric data between the subjects with and without low GSM (= lower than median value of the study subjects) plaques. A multiple logistic regression model regarding determinant factors for the presence of low GSM plaques was performed, where variables with a significance level < 0.05. Association between plaque thickness and variables was analyzed by Pearson's correlation after all non-normally distributed variables were logarithmically transformed. The significant (p <0.05) variables in Pearson's univariate analysis were selected for multivariate regression analysis.

For all tests, p <0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS statistics Version 21 software program (SPSS Inc.).

3. Results

3.1. Patient characteristics

The baseline characteristics of subjects are shown in Table 1. Among a total of 179 subjects (males, 82%; age, 65 ± 7 years (mean ± SD); diabetes duration, 12 ± 9 years; HbA1c, 7.5 ± 1.2%.), 144 (80%) patients had hypertension and 107 (60%) had dyslipidemia.

3.2. Correlation between plaque echogenicity and cardiovascular risk factors

When all subjects were divided into two groups based on the median of GSM value of their carotid plaques (subjects with low GSM [<48] values [n = 89] and those with high GSM [≥48] values [n = 90]), proportion of males and body mass index (BMI) were significantly higher and serum HDL cholesterol levels were significantly lower in the subjects with low GSM (<48) plaques as compared to those without it. There were no significant associations between the presence of low GSM plaques and the other parameters. A multiple logistic regression analysis with gender, BMI, and serum HDL-C levels as independent variables and the presence of low GSM plaques as an objective variable showed that male sex (odds ratio (OR) 2.36, 95% CI 1.05–5.31, p = 0.037) and BMI (OR 1.12, 95% CI 1.01–1.24, p = 0.029) were independently associated with the presence of low GSM plaques. Another multiple logistic regression analysis with gender, BMI, and the