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The utility of ultrasonic tissue characterization of carotid plaque in the prediction of cardiovascular events in diabetic patients

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ABSTRACT

Objective: The aim of this study was to evaluate whether non-invasive ultrasonic tissue characterization of carotid plaque using gray-scale median (GSM) can be a predictor of future cardiovascular disease (CVD) events in type 2 diabetic patients.
Methods: A total of 287 type 2 diabetic patients with carotid plaque but without CVD were enrolled (male 72%, mean age 65 ± 7 years). We prospectively evaluated the association between GSM, a quantitative parameter of the plaque echogenicity, and CVD.
Results: The median follow-up period was 55 months, and there were 34 new CVD events. The risk of CVD event was significantly higher in the patients with echolucent (GSM ≤ 37) plaque ($n = 67$) as compared to those without ($n = 220$) (HR = 6.99, 95% CI 3.46–14.14, $p < 0.001$). Cox proportional hazards regression analysis showed that the presence of echolucent plaque (HR = 4.55, 95% CI 2.10–19.84, $p < 0.001$) as well as plaque thickness (HR = 1.44, 95% CI 1.01–2.06, $p = 0.005$) were independent predictors of CVD, even after adjustment for other risk factors. Time-dependent receiver-operating-characteristic curve analysis revealed that the addition of plaque thickness to Framingham risk score (FRS) resulted in significant increase in area under the curve (AUC) [from 0.60 (95% CI; 0.49–0.70) to 0.73 (95% CI; 0.63–0.82), $p < 0.05$]. Notably, the addition of plaque echogenicity (presence/absence of echolucent plaque) to the FRS and plaque thickness resulted in further and significant increase in AUC [from 0.73 (95% CI; 0.63–0.82) to 0.82 (95% CI; 0.75–0.88), $p < 0.05$].
Conclusion: Ultrasonic tissue characterization of carotid plaque using the GSM can improve the risk prediction of cardiovascular event in asymptomatic type 2 diabetic patients with carotid plaque.

1. Introduction

Since cardiovascular disease (CVD) remains the main cause of death and impairment of quality of life in diabetic patients, early identification of individuals at high risk for CVD events and subsequent rapid interventions are important. Recently, ultrasound examination of the carotid artery has been in use to non-invasively identify individuals at high risk for CVD. Some studies have shown that the presence/absence of carotid plaque assessed by ultrasound could improve the prediction ability for CVD over and above conventional coronary risk factors [1–5].

It is well known that disruption of an atherosclerotic plaque plays a crucial role in the pathogenesis of CVD event and that plaque disruption is dependent on the content of lipid, neovascular vessel, and inflammatory cells in the atheroma, and the thickness of the fibrous cap [6–9]. Therefore, tissue characterization of a plaque lesion is considered to be useful for identifying patients at high risk for CVD and death. Presently, various modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) are

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being used to detect vulnerable plaque in coronary and carotid arteries [10–12]. However, it is unrealistic to screen all the asymptomatic patients for individuals at high risk for CVD with these tools, since these tests are limited by the potential of significant adverse effects, technical difficulty, availability, and cost.

Carotid arteries as well as the aorta develop foam cell lesions and lipid core plaque at an early age [13]. Interestingly, a recent study reported that the prevalence of lipid-rich plaques in carotid arteries was higher in coronary death than in non-coronary death [14]. Another study using carotid endarterectomy specimens also reported that a soft carotid plaque with a large necrotic core and a marked inflammatory component may be predictive of an increased risk of cerebrovascular events [15]. These findings indicate that the individuals who have vulnerable plaques in their carotid arteries are prone to also have vulnerable plaques in their coronary and/or cerebral arteries, which will lead to CVD events, and thus, the assessment of tissue characteristics of carotid plaques will help to identify the patients with a high risk for CVD event. Indeed, based on a prospective study in 85 asymptomatic type 2 diabetic patients, we have already shown that a quantitative ultrasonic tissue characterization of carotid plaque using integrated backscatter (IBS) analysis can be a predictor of future CVD event [16]. However, the measurement of IBS values requires a specific software package, "Acoustic Densitometry," installed in a SONOS echocardiograph system (Philips Medical Systems), which would limit the widespread use of this approach. In a qualitative evaluation using conventional B-mode ultrasound imaging performed by experienced sonographers, vulnerable plaques, which consist mainly of neovascular vessel, high lipid content, and inflammatory infiltration [8,9], are believed to appear "hypoechoic." On the other hand, stable plaques, which consist mainly of fibrous tissue and calcific components, appear "hyperechoic" [17]. Recently, echogenicity of carotid plaques has become semi-quantitatively evaluable with high-resolution B-mode ultrasound and computer-assisted image processing: the gray-scale median (GSM) of the frequency distribution of gray values of the pixels within the plaque serves as a measure of echogenicity. Since the evaluation of GSM values in carotid plaques requires neither specific software nor a specific ultrasonograph, it can be a more universal and practical approach as compared with IBS analysis.

Based on the background described above, the current study prospectively evaluated whether non-invasive and inexpensive ultrasonic tissue characterization of carotid plaque using GSM can improve the risk prediction of CVD event in asymptomatic type 2 diabetic patients with carotid plaque.

2. Research design and methods

2.1. Subjects

Middle-aged and older Japanese type 2 diabetic patients with carotid plaque but without apparent CVD participated in this study. Patients who fulfilled the following criteria were considered eligible: (1) age $\geq$ 40 years at the time of enrollment, and (2) diagnosed with type 2 diabetes based on the criteria of the Japan Diabetes Society. Exclusion criteria were (1) history of ischemic stroke, coronary heart disease, or peripheral artery disease; (2) elevated liver enzymes (GOT or GPT $\geq$ 2.5 times the normal range); and (3) renal insufficiency (serum creatinine $\geq$ 2.0 mg/dL). 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. All the patients that met eligibility criteria were asked whether they could participate in the present study, and all the patients who agreed to participate were registered. Out of 325 patients who had been registered, four were excluded because of poor image or acoustic shadowing due to severe calcification, and 34 were excluded because of no plaque. After the exclusions, a total of 287 patients were analyzed in this study.

This study was conducted in agreement with the principles of the Helsinki declaration. 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 analyses

Blood samples were collected after an overnight fast for analysis of serum concentrations of glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and HbA1c. Diagnosis of type 2 diabetes was made by the principal investigator in accordance with the standards of the Japan Diabetes Society [18]. Dyslipidemia was defined as LDL cholesterol $\geq$ 120 mg/dL, HDL cholesterol $<$ 40 mg/dL, triglycerides $\geq$ 150 mg/dL, or current use of lipid-lowering agents in accordance with the standards of the Japan Diabetes Society [18]. Hypertension was defined as systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 80 mmHg or current use of antihypertensive agents. The risk of CVD was estimated using the Framingham D'Agostino equations [19]. Risk factors included in the model to assess risk of CVD were gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status.

2.3. Ultrasound examination

B-mode ultrasonography of the carotid artery was performed using an ultrasound machine (Toshiba SSA-790CE; Toshiba Medical Systems, Tokyo, Japan) with a 7.5-MHz linear transducer. All scanning was conducted by experienced laboratory physicians using the same ultrasound system and the same measuring method. Scanning of the extracranial 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 and three different transverse projections. According to the guideline of the Japan Society of Ultrasonics [20], 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. The plaque thickness in the CCA, the CB, and the ICA were measured separately, and the greatest value among them was used as the representative value for each individual. Reproducibility analysis of 20 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 based on the gray-scale median (GSM) in a gray-scale range of 0–255 (0 as the darkest and 255 as the brightest tone). Adobe Photoshop software (Adobe Systems, version 7.0, San Jose, CA, USA) was used for image standardization and calculation of gray-scale values. 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 [21]. Thus the gray-scale values of all pixels would change according to the new linear scale defined by the reference values for blood and adventitia. The plaque was then delineated with a free-hand tool, and the GSM of each plaque 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