OBSERVATIONS

Association Between the Connexin37 Polymorphism and Peripheral Arterial Disease in Subjects With Type 2 Diabetes

Connexin37 is one of the major connexins expressed in the endothelium, monocytes, and macrophages and plays important roles in atherogenesis (1). The COOH-terminus of this protein is a substrate for specific kinase or protein partners and thereby functions as a regulatory domain (2). Because the C-to-T substitution at nucleotide 1019 in the connexin37 gene causes a proline-to-serine substitution in the regulatory COOH-terminus, and affects its function, this polymorphism is likely associated with the pathogenesis of atherosclerosis. Indeed, this polymorphism has been shown to associate with the risk of coronary artery disease (3). In this study, we investigated whether this polymorphism is associated with an ankle-brachial blood pressure index (ABI), a noninvasive and established method of assessing peripheral arterial disease (PAD), which leads to poorer quality of life and higher mortality in type 2 diabetic patients (4,5).

All Japanese type 2 diabetic patients (diagnosed by diabetologists based on World Health Organization criteria) who visited the outpatient clinics of five participating hospitals (Osaka University Medical Hospital, Ehime Prefectural Central Hospital, Ehime Prefectural Imabari Hospital, Ishibashi Clinic, and Naka Kinen Clinic) were asked to participate in this study, and 2,288 subjects were enrolled. The genotypes of the connexin37 C1019T polymorphism were determined with a fluorescence- or colorimetry-based allele-specific DNA-primer probe assay system (Toyobo Gene Analysis). The prevalence of the connexin37 C1019T genotypes was as follows: CC, 64.6%; CT, 31.1%; and TT, 4.3%. The genotype distribution was in Hardy-Weinberg equilibrium. ABI was measured automatically using the Form PWV/ABI device (Colin, Komaki, Japan). According to generally used guidelines (5), we diagnosed the subjects based on each ABI value as follows: ≤0.90, low ABI (diagnosed as PAD); 0.91–1.30, normal ABI; >1.30, noncompressive. We thereby excluded the subjects with ABI >1.30 (n = 27).

We performed a statistical analysis in 2,261 type 2 diabetic subjects: 35.5% male, mean ± SD 60.6 ± 10.0 years of age, 6.0 ± 6.4 years duration of diabetes, 50.0% cigarette smokers, 24.0 ± 3.4 kg/m^2 BMI, 6.9 ± 1.3% A1C, 60.9% hypertensive (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or having been treated for hypertension), and 62.2% dyslipidemic (serum total cholesterol ≥220 mg/dl, serum triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl, or having been treated for dyslipidemia). Low ABI was identified for 51 subjects, and the prevalence of low ABI was significantly higher in subjects with TT genotype than CC or CT genotype (7.2 vs. 2.0%; P = 0.0008). There were no differences among the genotypes for the other parameters including sex, age, duration of diabetes, history of smoking, BMI, A1C, presence of hypertension, and presence of dyslipidemia. Furthermore, a multiple logistic regression analysis revealed that the TT genotype was a risk factor for low ABI independently of traditional risk factors (odds ratio 3.78 [95% CI 1.61–8.89]; P = 0.0023).

Because a negative ABI cannot completely rule out PAD, further studies are required to reach a conclusion. This study, however, suggests that the *connexin37* C1019T polymorphism is associated with PAD in Japanese type 2 diabetic patients.

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patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation (Executive Summary). Circulation 2006;113:1474–1547