Association Between Urinary Albumin Excretion and Plasma 5-Hydroxyindole-3-Acetic Acid Concentration in Men With Type 2 Diabetes

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Serotonin (5-hydroxytryptamine [5-HT]) mediates vasoconstriction and induces the activation of platelets, which may promote atherosclerosis. Plasma 5-HT concentrations have been reported to be high in diabetic patients (1,2); this may be one of the underlying mechanisms of diabetes complications. The 5-HT_{2A} receptor has been identified in glomerular mesangial cells (3), suggesting involvement of 5-HT in the development of diabetic nephropathy through proliferation and matrix sysnthesis in mesangial lesions. Male sex is an independent risk factor for cardiovascular disease (4). Moreover, elevated urinary albumin excretion (UAE) has been reported to be associated with increased risk of cardiovascular mortality (5). Few studies have examined the association between plasma 5-HT concentration and atherosclerosis (6). To our knowledge, a relationship between plasma 5-HT concentration and degree of UAE has never been explored in men with type 2 diabetes. In this study, we evaluated the relationships between plasma 5-hydroxyindole-3-acetic acid (5-HIAA), a derivative end product of 5-HT, concentration and degree of UAE, and markers of subclinical atherosclerosis, such as pulse wave velocity (PWV), ankle-brachial index (ABI), carotid intima-media thickness (IMT), or plaque score in men with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The relationships of plasma 5-HIAA concentrations with degree of UAE and major cardiovascular risk factors were investigated in 205 consecutive men with type 2 diabetes recruited from the outpatient clinic at the Kyoto Prefectural University of Medicine (Kyoto, Japan). Additionally, the relationships between plasma 5-HIAA concentration and PWV or ABI ($n = 160$) and between plasma 5-HIAA concentration and IMT or plaque score ($n = 102$) were investigated in a subgroup of patients.

Plasma 5-HIAA concentrations (normal range 1.8–6.1 ng/ml) were measured by high-performance liquid chromatography. The intra-assay coefficients of variation (CVs) were 2.1, 2.0, and 0.9% for plasma 5-HIAA concentrations of 25.27, 41.30, and 95.09 ng/ml, respectively, and the interassay CVs were 3.9, 3.3, and 2.4% for plasma 5-HIAA concentrations of 7.45, 20.55, and 60.83 ng/ml, respectively. UAE was measured with an immunoturbidimetric assay. A mean value for UAE was determined from three urine collections. Patients were excluded if they were taking any medications that might affect plasma 5-HIAA concentrations (e.g., 5-HT receptor blockers). Approval for the study was obtained from the local research ethics committee, and informed consent was obtained from all participants. Brachial-ankle PWV and ABI were measured using a Colin Waveform Analyzer (form PWV/ABI; Colin Medical Technology, Komaki, Japan) (7). B-mode ultrasonographic imaging of the carotid artery was performed as previously described (8). Because plasma 5-HIAA concentration and UAE showed skewed distributions, log transformation of these values was carried out before performing correlation and regression analysis. The relationships between log (plasma 5-HIAA concentration) and log UAE, PWV, ABI, IMT, or plaque score, as well as other variables including age or glycemic control, were examined by Pearson's correlation analyses. To examine the effects of various factors on log UAE, the following factors were considered as independent variables for multiple regression analysis: log (plasma 5-HIAA concentration); age; duration of diabetes; BMI; A1C; systolic and diastolic blood pressure; plasma total cholesterol, triglyceride, and HDL cholesterol concentrations; and smoking status. All continuous variables are presented as the means ± SD, and $P < 0.05$ was considered statistically significant.

RESULTS

— Clinical characteristics of the 205 men with type 2 diabetes enrolled in this study are as follows: mean age 63.5 ± 11.3 years, duration of diabetes 13.6 ± 11.8 years, BMI 23.0 ± 3.1 kg/m^2, A1C 7.1 ± 1.1%, systolic blood pressure 132 ± 15 mmHg, plasma total cholesterol concentration 4.99 ± 0.86 mmol/l, PWV 1,750 ± 341 cm/s, ABI 1.08 ± 0.17, IMT 0.90 ± 0.22 mm, plaque score 3.8 ± 4.2, and plasma 5-HIAA concentration 7.4 ± 6.6 ng/ml. Positive correlations were found between log (plasma 5-HIAA concentration) and age ($r = 0.358$, $P < 0.0001$), PWV ($r = 0.184$, $P = 0.0243$) (Fig. 1*A*), IMT ($r = 0.397$, $P < 0.0001$) (Fig. 1*C*), plaque score ($r = 0.317$, $P =$

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Abbreviations: 5-HIAA, 5-hydroxyindole-3-acetic acid; 5-HT, 5-hydroxytryptamine, IMT, intima-media thickness; PWV, pulse wave velocity; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

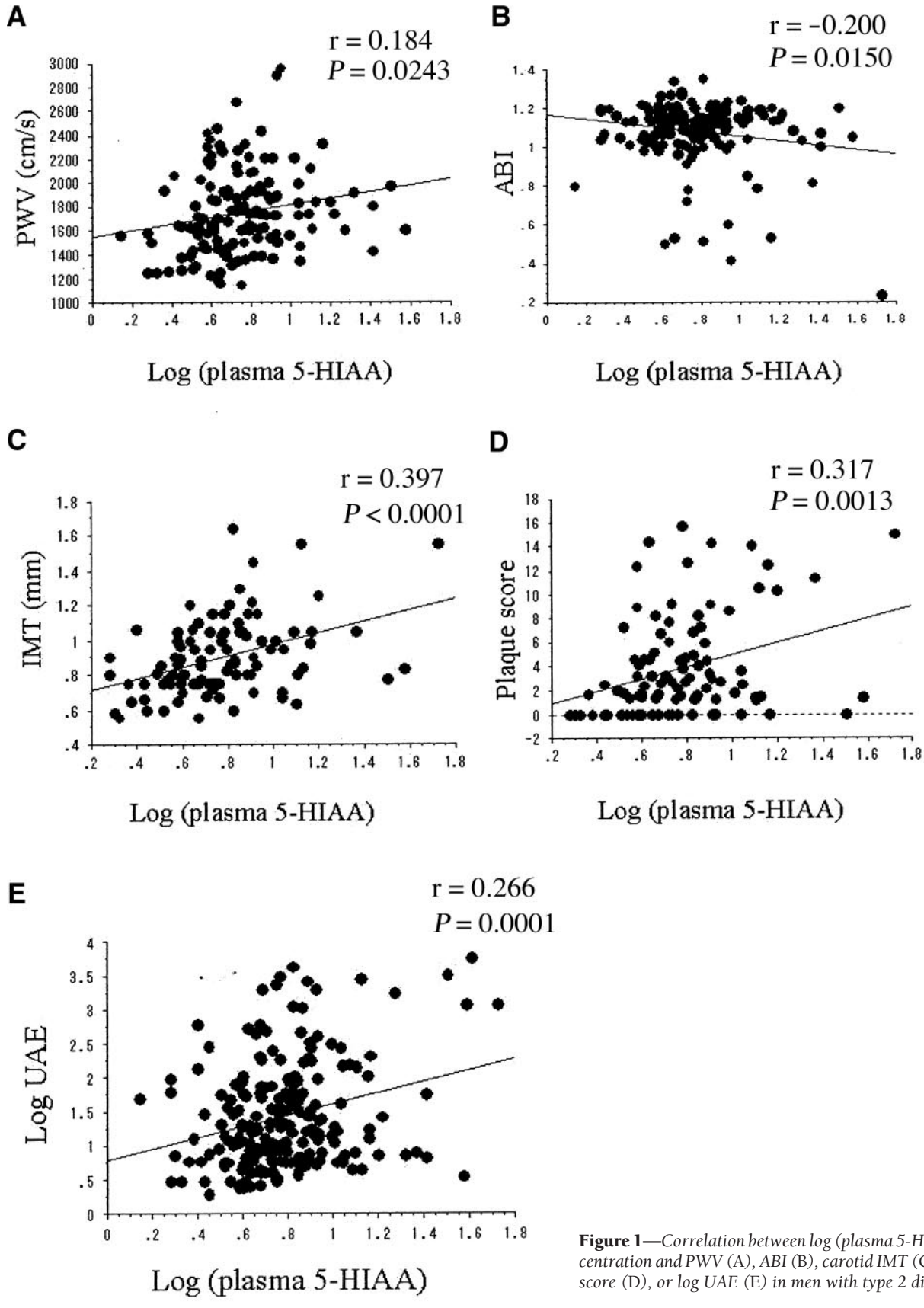

Figure 1—*Correlation between log (plasma 5-HIAA) concentration and PWV* (A)*, ABI* (B)*, carotid IMT* (C)*, plaque score* (D)*, or log UAE* (E) *in men with type 2 diabetes.*

0.0013) (Fig. 1*D*), or log UAE ($r = 0.266$, $P = 0.0001$) (Fig. 1*E*). An inverse correlation was found between log (plasma 5-HIAA concentration) and ABI ($r = -0.200$, $P = 0.0150$) (Fig. 1*B*). Multiple regression analysis demonstrated that log (plasma 5-HIAA concentration) ($\beta = 0.214$, $P = 0.0049$), duration of diabetes ($\beta = 0.196$, $P = 0.0169$), A1C ($\beta = 0.202$, $P = 0.0115$), and systolic blood pressure ($\beta = 0.306$, $P = 0.0120$) were independent determinants of log UAE.

CONCLUSIONS — In the present study, we found positive correlations between log (plasma 5-HIAA concentration) and log UAE, PWV, IMT, or plaque score and an inverse correlation between log (plasma 5-HIAA concentration) and ABI. Log (plasma 5-HIAA concentration) also correlated inversely with glomerular filtration rate (data not shown); via the 5-HT_{2A} receptor, 5-HT induces the contraction, migration, and proliferation of vascular smooth muscle cell, followed by various intracellular signal transduction mechanisms (9–11). Watanabe et al. (12–14) demonstrated that 5-HT exerts a synergistic interaction with oxidized LDL, hydrogen peroxide, angiotensin II, endothelin-1, or monocyte chemoattractant protein-1 in inducing vascular smooth muscle cell proliferation. These findings indicate that 5-HT contributes to deterioration of peripheral blood flow. Kasho et al. (15) demonstrated that 5-HT increased the production of type 4 collagen by cultured human mesangial cells through 5-HT_{2A} receptor, which was mediated by activation of protein kinase C and subsequent increase in transforming growth factor-β activity. Currently, sarpogrelate hydrochloride, a potent 5-HT_{2A} receptor antagonist that inhibits 5-HT-induced vasoconstriction and platelet aggregation (16), is used clinically as antiplatelet drugs for prevention of thrombosis in atherosclerotic disease. Takahashi et al. (17) reported that sarpogrelate hydrochloride reduced the degree of UAE, indicating the potential usefulness of this agent for the protection of development and progression of diabetic nephropathy. Takahashi et al. (17) demonstrated that urinary 5-HIAA in diabetic patients was higher than that in normal subjects. Moreover, the vasoconstrictor response to 5-HT has been reported to be increased due to 5-HT receptor hypersensitivity in diabetic patients (2). To our knowledge, this is the first study that has examined the relationship between plasma 5-HIAA concentration and degree of UAE in men with type 2 diabetes. However, the cross-sectional nature of our study does not permit determination of causality. Large prospective trials and intervention studies are needed to better assess the effects of 5-HT on diabetic nephropathy and atherosclerosis in men with type 2 diabetes.

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