ASSESSMENT OF BASILAR ARTERY HEMODYNAMICS IN TYPE 2 DIABETIC PATIENTS WITH NO HISTORY OF CEREBROVASCULAR DISEASE BY USING TRANSCRANIAL DOPPLER ULTRASOUND

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Abstract : We compared intracranial hemodynamics in 121 type 2 diabetic patients who had no history of cerebrovascular disease with findings in 123 matched control subjects. Mean blood flow velocity (MFV) and Fourier pulsatility index were determined by using transcranial Doppler ultrasonography (TCD). MFV in the basilar artery was significantly lower in diabetic than in nondiabetic subjects ($p<0.01$), while Fourier PI of the basilar artery was significantly higher in diabetic than in nondiabetic subjects ($p<0.01$). In multivariate regression analysis, increased Fourier PI and decreased MFV were associated with higher age, female gender, and longer duration of diabetes. Decreased MFV was also associated with microalbuminuria. These findings demonstrated deterioration of basilar artery hemodynamics in patients with type 2 diabetes who have no stroke history. Additionally, repeated TCD may prove to be useful for monitoring cerebrovascular impairments in these patients.

Key words: blood flow velocity, Fourier pulsatility index, diabetes mellitus, transcranial Doppler ultrasonography

INTRODUCTION

Diabetes mellitus is a major risk factor for stroke. Abbott et al.[1] have reported that the occurrence during 12 years of follow-up of stroke was 62.3 per 1000 in subjects with diabetes and 32.7 per 1000 in subjects without diabetes. In the Framingam study[2], diabetes increased the incidence of thrombotic stroke 2.5 times in men and 3.6 times in women. Diabetes mellitus also may be associated with an increased occurrence of lacunar infarction (28 to 43 %)[3-5].

A large variety of cerebral abnormalities can occur in diabetes[6,7] at electrophysiologic, neurochemical, structural, and cognitive levels[6]. These manifestations are considered to result from alterations in cerebral blood flow, glucose transport through the blood-brain barrier, and metabolic regulation[6,7]. To address the first issue, we evaluated intracranial hemodynamics of the basilar artery in stroke-free type 2 diabetic patients and in age- and gender-matched control subjects.

METHODS

Study population

Between September 1992 and August 1996, transcranial Doppler ultrasound (TCD) measurements were performed in 96 patients (male 56, female 40) with type 2 diabetes who

were outpatients at the Oyodo Municipal Hospital. Patients were given a diagnosis of type 2 diabetes mellitus after a 75-g oral glucose tolerance test according to World Health Organization (WHO) criteria, or from a history of treatment with either oral hypoglycemic agents or insulin. The ages of patients ranged from 42 to 78 years (mean, 63.6). Thirty-four patients were treated with oral hypoglycemic agents and 20 were treated with insulin. The following data were obtained from the medical records of each patient: age, gender, history of smoking, history of ischemic heart disease, history of stroke, and signs of senile dementia. Fasting serum concentrations of total cholesterol, triglycerides, blood sugar, and hemoglobin (Hb)A1c were measured within 5 days of transcranial Doppler examination. Total cholesterol and triglyceride levels were measured by cholesterol oxidase-peroxide and glycerol kinase-peroxidase methods, respectively. Serum glucose was measured by a glucose oxidase method. HbA1c was measured by high-performance liquid chromatography. Patients with hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mm Hg) were excluded. The presence or absence of microalbuminuria (albumin/creatinine ratio >15 mg/g·creatinine), peripheral neuropathy, and retinopathy were determined before enrollment in the study. No patients exhibited signs of senile dementia at Mini-Mental State Examination[8] (Table 1).

The nondiabetic group consisted of 130 subjects (male 58, female 72) who had no risk factors for stroke or coronary heart disease (hypertension, diabetes mellitus, hyperlipidemia, or arrhythmia). They were matched for age and gender with the diabetic subjects, ranging in age from 47 to 77 years with a mean of 64.4. Some nondiabetic subjects had diagnoses of gastric ulcer (28 subjects), chronic hepatitis (20), colonic polyp (15), while 67 others were healthy volunteers. Informed consent was obtained from patients in this study.

Measurement of intracranial hemodynamics in the basilar artery

The patients sat in a comfortable chair and leaned forward with the cervical spine flexed to widen the space between the atlas and the skull base. A map of the basilar artery was generated using a transcranial Doppler mapping technique (2-MHz Trans-scan, EME, Germany) through a foramen magnum window. Sample volume was fixed at a diameter of 6 mm. Ultrasonic pulses were directed at the basilar artery at a depth of 70 mm. The map and the sonogram were stored on a computer hard disk for later off-line analysis ; these methods

Table 1. Characterisitics of patients with type 2 diabetes mellitus and control subjects

Items	Controls	Diabetic patients	Statistical sinnificance
No. of cases	130	96	
Gender : male / female	58 / 72	56 / 40	NS
Age (years)	64.4±10.1	63.6±11.0	NS
Duration of diabetes mellitus	—	7.2±7.5	NS
Smoking	62 (50.4%)	120 (50.0%)	NS
Total cholesterol (mg / dl)	186±30	202±48	NS
Triglyceride (mg / dl)	133±42	144±92	NS
Fasting blood sugar (mg / dl)	81±11	168±62	NS
Systolic blood pressure (mm Hg)	128±11	125±10	NS
Diastolic blood pressure (mm Hg)	76±10	76±9	NS

NS ; not significant.

are described in detail in the other paper[9]. All parameters were calculated and stored on the hard disk. Mean blood flow velocity (MFV) was obtained for the waveform envelope. A velocity waveform is a periodic function expressed by an accumulation of simple sine curves :

$$F(t)=MFV+\Sigma Fx \sin(\omega xt+\phi x) \quad (x=1\sim n)$$

where F(t) is a waveform, Fx is the amplitude of eachharmonic, ω is the fundamental angular frequency in radians, and ϕx is the phase angle of each harmonic. Using these definitions, an IBM AT-PC-compatible computer linked to the TCD system calculated automatically the amplitude of each harmonic for each complete cardiac cycle, computing Fourier PI by dividing the amplitude of the first harmonic by the MFV[10]:

$$\text{Fourier PI}=Fx/MFV \quad (x=1).$$

MFV and Fourier PI were calculated foreach five to seven consecutive complete cardiac cycles using the program TRANS-SCAN VER 4.41 (EME, Germany). Mean values were subjected to comparisons.

Statistical analyses

Data were reported as the mean ± standard deviation (SD). The unpaired Student's *t* test was used to compare the diabetic and nondiabetic groups. The relations between MFV or FPI and parameters were evaluated using Person's correlation coefficient and multivariate regression analysis. Statistical analysis was performed using the SPSS package (Release 6.1J, Japan). Differences were considered statistically significant when $p<0.05$.

RESULTS

Hemodynamics in the basilar artery in diabetic patients

MFV in the basilar artery was significantly lower in diabetic patients than in nondiabetic subjects ($p<0.01$). On the other hand, the Fourier PI for the basilar artery was significantly higher in diabetic patients than in nondiabetic subjects ($p<0.01$) (Fig.1).

Difference in basilar artery hemodynamics in diabetic subjects by gender

Gender-related differences were observed in regard to MFV and Fourier PI for the basilar artery in diabetic patients. Basilar artery MFV in female diabetic patients was significantly lower than for males, and Fourier PI for the basilar artery was significantly higher in diabetic females than in males ($p<0.01$, respectively) (Table 2).

Correlation between basilar artery hemodynamics and backgrounds in diabetic patients

Age, the duration of diabetes, and microalbuminuria significantly correlated with MFV and Fourier PI of basilar artery. But HbA1C, fasting blood sugar, and blood pressure did not show a correlation with them (Table 3).

Multivariate analysis for the intracranial hemodynamics

By multivariate regression analysis, MFV showed a significant negative correlation with age, female gender, and the duration of diabetes. On the other hand, Fourier PI showed a significant positive correlation with age, female gender, microalbuminuria, and the duration of diabetes (Table 4).

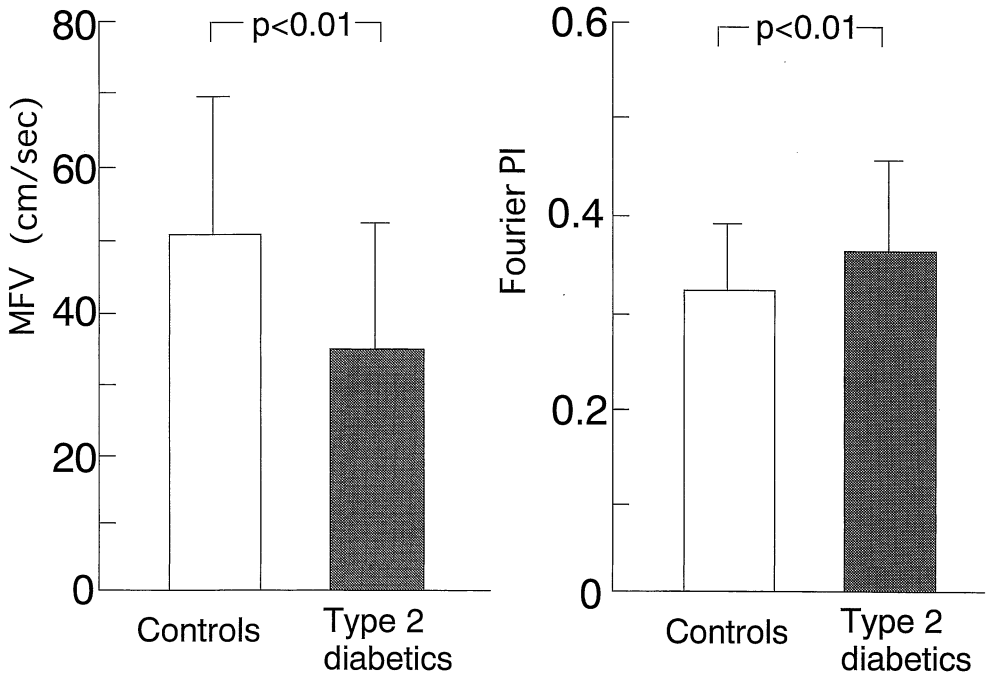

Fig. 1. Intracranial hemodynamics in patients with type 2 diabetes mellitus and control subjects. MFV ; Mean blood flow velocity, Fourier PI ; Fourier pulsatility index.

Table 2. Gender differences in TCD measurements in patients with type 2 diabetics

Variables	Controls			Type 2 diabetics		
	Male	Female	P	Male	Female	P
No. of cases	58	70		56	40	
Age	64.8±10.2	63.7±9.8	NS	63.9±9.1	62.8±11.7	NS
BA-MFV	51.2±17.1	50.9±10.3	NS	38.9±13.1	32.9±8.7	p<0.01
BA-FPI	0.31±0.07	0.33±0.09	NS	0.32±0.07	0.37±0.08	p<0.01

TCD ; transcranial Doppler, BA ; basilar artery, MFV ; mean blood flow velocity, FPI ; Fourier pulsatility index.

DISCUSSION

Diabetic vascular disease is more severe, diffuse, and accelerated than vascular disease in patients without diabetes[11]. A critical deficit in cerebral blood flow may presumably occur in a particular brain region with subsequent sudden focal neurologic dysfunction (i. e. stroke). Such events result from asymptomatic cerebral hypoperfusion progressing during a long or short interval until a critical threshold is passed for clinical expression[12]. The few previous studies concerning cerebral blood flow in diabetic patients with no clinical symptoms or previous history of cerebral nervous system disease have reported diminished CBF values both overall and in individual cerebral regions[13]. A number of autopsy studies have demonstrated particularly marked cerebral atherosclerosis in diabetic patients, especially in the cerebellar arteries and vertebrobasilar system[14]. However, very few reports have described intracranial hemodynamics in these patients[15]. Therefore, the authors studied hemodynamics in the basilar artery in stroke-free type 2 diabetic patients.

Table 3. Correlation between vasilar artery hemodynamics and backgrounds diabetic patients

Items	MFV		Fourier PI	
	r	p	r	p
Age	−0.38	<0.01	0.45	<0.01
Duratiom	−0.41	<0.01	0.38	<0.01
Microalubuminuria	−0.31	<0.05	0.42	<0.01
Fasting blood sugar	−0.28	NS	0.18	NS
HbA1C	−0.11	NS	0.24	NS
Systolic blood pressure	−0.20	NS	0.28	NS
Diastolic blood pressure	−0.10	NS	0.18	NS

MFV ; mean blood flow velocity, PI ; pulsatility index, r ; correlation coeffcient.

Table 4. Multiple regression analysis of MFV and Fourier PI with respect to covariables in diabetic patients

Independent variable	MFV		Fourier PI	
	Partial R	p	Partial R	p
Gender	0.114	<0.01	0.112	<0.01
Age	0.080	NS	0.233	<0.001
Duration	0.134	<0.01	0.249	<0.001
Microalubuminuria	0.043	NS	0.183	<0.01
Model R^2	0.212	<0.01	0.309	<0.001

MFV ; mean blood flow velocity, PI ; pulsatility index,

Basilar artery blood flow velocities in type 2 diabetic patients

In the study using N-isopropyl-^{123}I-p-iodoamphetamine with single-photon emission computed tomography (SPECT), the relative area of the brain showing normal perfusion was significantly reduced in elderly diabetic patients with no history of stroke[16]. Nagamachi et al. have found by using SPECT that average regional cerebral blood flow (CBF) of diabetic patients without CT findings indicative of cerebral infarction was significantly lower than in a nondiabetic group[13]. Decreased CBF might be implicated in pathologic changes in brains of diabetic individuals, as has decreased blood flow to nerve in the pathogenesis of diabetic peripheral neuropathy[17].

In the present study, we assessed intracranial hemodynamics in type 2 diabetic patients by using TCD, a noninvasive method for evaluation of cerebral hemodynamics[18]. Several investigators have compared velocities and regional CBF measurements in subjects without known cerebrovascular disease. A significant correlation was found between flow velocities and regional CBF values[19, 20]. Therefore, decreased MVF in the basilar artery observed in the present study could be regarded as reduction of CBF. A decline in MVF of the basilar artery should help to predict the progression of cerebral atherogenesis in diabetic patients.

Pulsatility index for the basilar artery in type 2 diabetic patients

Several pulsatility or resistance indexes have been devised to be independent of vessel-to-transducer angle. The indices are based on empirical observations that velocity waveforms change in parallel with the resistance of vascularbeds change[21]. Pulsatility index introduced by Gosling has been regarded a measure of vascular resistance downstream[21]. Care is needed in interpreting these indexes because abnormalities of cardiac function or impaired elastic properties of the vessels significantly alter values[22]. Fourier PI was introduced by Aaslid and Lindegaard to avoid interaction and distortion by reflected arteries[23]. By

extracting the content in the first harmonic, Fourier PI is intended to minimize distortion caused by the complex configurations of branches of the artery and to display the condition of distal vascular beds more accurately[24, 25]. Sugimori et al. have shown that Gosling PI could not differentiate subjects with essential hypertension complicated by old brain infarcts from a normotensive group, while Fourier PI was significantly higher in the hypertensive group than in the normotensive group[26].

In the present study we used Fourier PI as an index of the downstream vascular resistance. Fourier PI of the basilar artery were significantly higher in diabetic patients than in nondiabetic patients. This result indicates that the downstream vascular resistance of the basilar artery is higher in diabetic patients. Vascular abnormalities and structural damage develop early in human and experimental diabetes[27, 28]; diabetic vascular disease is characterized pathologically by endothelial cell hyperplasia and basement membrane thickening[29]. Thickening of basement membranes of capillaries and atherosclerosis are long-term complications respectively affecting the microvasculature and macrovasculature[30, 31]. Increased Fourier PI would reflect these pathologic changes in diabetic patients. A prospective study of the relationship between prognosis and Fourier PI in diabetic patients is needed to elucidate the clinical significance of Fourier PI.

Gender differences in intracranial hemodynamics in diabetic patients

Relative risk for cerebrovascular complications shows a greater increase beyond that in the general population in diabetic women than in diabetic men[32]. In the study MFV in the basilar artery showed a greater decrease in diabetic women than in diabetic men, and Fourier PI was more increased in diabetic women. Decreased MVF and increased Fourier PI in women with diabetes may help to explain gender-related differences in cerebrovascular complications in diabetic subjects[33]. While we have no obvious explanation for our finding of gender-related differences, epidemiologic evidence supports differences in development of vascular disease between men and women with diabetes[33].

Factors affecting intracranial hemodynamics in diabetic patients

Endothelium, which produces substances such as endothelium-derived relaxing factor, endothelin, and vasoactive prostaglandins, plays a role in regulation in all vascular beds. Since hypertension coexisting with diabetes may act synergistically to injure the endothelium[34], patients with hypertension were excluded from the present study.

In multivariate analysis, MFV showed a significant negative correlation with age, female gender, and duration of diabetes. On the other hand, Fourier PI showed a significant positive correlation with age, female gender, microalbuminuria, and duration of diabetes. Johnson et al.[35] have suggested that decreases in regional CBF may reflect the severity of cerebral diabetic microangiopathy, which presumably is more prevalent in patients with a longer duration of disease. Our results are in accord with Johnson's report assuming that MFV and Fourier PI are correlated with CBF.

No correlation could be observed between MFV or Fourier PI and HbA1c levels. Whether HbA1c levels are related to CBF is controversial[7, 36]. Although increasing fasting blood glucose levels were independently associated with mortality from macrovascular disease[37],

glycemic control during a month-long interval assessed by HbA1c may not affect intracranial hemodynamics in diabetic patients.

In conclusion, the present study indicated that more marked cerebral arteriosclerosis occurs in diabetic patients with no history of stroke than in nondiabetic subjects. TCD measurements could be useful for monitoring early cerebral hemodynamic change in patients with diabetes mellitus.

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