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Table 1 Clinical Characteristics of elderly patients with diabetes mellitus

	N	Mean±SEM
Clinical character		
Age (years)	95	72.8±0.5
Male: Female	38 : 57	
Education (years)	77	10.7±0.3
Duration of diabetes mellitus (years)	92	18.4±1.2
Body mass index (kg/m^2)	92	23.2±0.4
Waist/hip ratio	92	0.92±0.0
Systolic blood pressure (mmHg)	95	135.4±1.2
Diastolic blood pressure (mmHg)	95	75.5±0.9
Cardiovascular complication	95	0.16±0.0
Microvascular complication score	74	-0.02±0.1
Fasting blood glucose (mg/dl)	82	164.2±5.1
HbA1c (%)	95	7.9±0.1
Insulin	77	9.3±1.3
Total cholesterol (mg/dl)	95	203.4±3.2
Triglyceride (mg/dl)	95	150.1±12.8
HDL cholesterol (mg/dl)	94	65.0±2.7
Cognitive function		
Mini-mental state examination	80	26.2±0.3
Immediate word-list recall	81	8.2±0.2
Delayed word-list recall	80	6.8±0.3
Immediate paragraph recall	80	7.5±0.3
Delayed paragraph recall	80	5.8±0.3
Stroop test (A)	80	18.8±1.4
Digit symbol substitution test	77	35.8±1.2
MRI		
White matter hyperintensities		
Frontal lobe (ml)	95	1.8±0.2
Parietal lobe (ml)	95	1.0±0.1
Temporal lobe (ml)	95	0.8±0.1
Occipital lobe (ml)	95	0.3±0.1
Thalamus (ml)	95	0.1±0.0
Basal ganglia (ml)	95	0.3±0.0
Total (ml)	95	4.3±0.4
Periventricular hyperintensity	86	9.7±0.31
Evans ratio	95	26.0±0.34
Caudate head index	95	13.5±0.25
inverse Cella media index	95	26.3±0.40
Basal cistern index	95	19.6±0.27

Table 2 Pearson correlation coefficient between cognitive function and other factors

	word-list recall		paragraph recall				WAIS-R
	Immediate	Delayed	Immediate	Delayed	MMSE	Stroop	digit symbol
Age	-0.37	-0.44	-0.16	-0.24	-0.18	0.21	-0.27
Education	0.28	0.34	0.35	0.29	0.21	0.01	0.36
Duration of diabetes mellitus	-0.07	-0.20	-0.08	-0.21	-0.22	0.03	-0.24
Body mass index	0.05	0.10	0.00	0.12	0.23	-0.22	0.10
Systolic blood pressure	-0.04	-0.04	0.00	-0.04	0.01	-0.01	-0.05
Diastolic blood pressure	0.04	0.05	0.16	0.24	0.04	0.01	0.12
Cardiovascular complication	0.06	0.01	-0.08	-0.03	-0.20	0.17	-0.21
Microvascular complication score	-0.13	-0.08	-0.14	-0.07	0.18	-0.06	-0.04
Fasting blood glucose	-0.04	0.04	-0.01	-0.02	-0.12	0.08	-0.10
HbA1c	0.07	0.08	0.07	-0.02	0.07	0.01	-0.07
Insulin	0.12	0.02	-0.08	-0.04	0.05	-0.08	0.01
Total cholesterol	0.07	0.16	0.15	0.28	0.07	-0.10	0.07
Triglyceride	0.04	0.10	0.11	0.17	0.20	0.00	0.08
HDL cholesterol	0.12	0.14	-0.03	0.02	-0.02	-0.11	0.06
Evans ratio	-0.39	-0.19	-0.09	-0.18	-0.03	0.07	-0.36
Caudate head index	-0.35	-0.26	0.00	-0.14	-0.09	0.06	-0.19
inverse Cella media index	-0.41	-0.23	-0.09	-0.27	-0.09	0.04	-0.40
Basal cistern index	-0.12	-0.10	-0.12	-0.10	-0.20	-0.13	-0.21

Table 3 Canonical correlation between cognitive function and WMHs

Canonical correlation coefficient; 0.65			P=0.004
Immediate word-list recall	0.22	WMHs of frontal lobe	-0.03
Delayed word-list recall	0.32	WMHs of parietal lobe	-0.21
Immediate paragraph recall	0.07	WMHs of temporal lobe	-0.23
Delayed paragraph recall	0.17	WMHs of occipital lobe	0.19
MMSE	0.39	Thalamus	-0.21
Stroop test (A)	-0.25	Basal ganglia	-0.10
Digit symbol substitution test	0.48	Total WMHs	-0.22
		Periventricular hyperintensity	-0.32

Each value represents correlation of canonical valuables.

Table 4 Canonical correlation between cognitive function and clinical indices

Canonical correlation coefficient; 0.78			p=0.881
Immediate word-list recall	0.25	Age	0.16
Delayed word-list recall	0.11	Education	-0.09
Immediate paragraph recall	-0.08	Duration of diabetes mellitus	-0.13
Delayed paragraph recall	0.16	Body mass index	-0.14
MMSE	-0.46	Waist/hip ratio	0.06
Stroop test (A)	0.47	Systolic blood pressure	0.14
Digit symbol substitution test	0.07	Diastolic blood pressure	0.23
		Cardiovascular complication	-0.20
		Microvascular complication	0.07
		Fasting blood glucose	0.28
		HbA1c	0.05
		Insulin	0.51
		Total-cholesterol	0.09
		Triglyceride	-0.02
		HDL-cholesterol	0.00

Each value represents correlation of canonical valuables.

Table 5 Canonical correlation between WMHs and clinical indices

Canonical correlation coefficient; 0.87			p=0.500
WMHs of frontal lobe	0.28	Age	0.39
WMHs of parietal lobe	0.19	Education	0.02
WMHs of temporal lobe	0.37	Duration of diabetes mellitus	0.16
WMHs of occipital lobe	-0.01	Body mass index	-0.07
Thalamus	0.67	Waist/hip ratio	-0.12
Basal ganglia	0.12	Systolic blood pressure	0.26
Total WMHs	0.39	Diastolic blood pressure	0.14
Periventricular hyperintensity	0.31	Cardiovascular complication	-0.29
		Microvascular complication	-0.15
		Fasting blood glucose	-0.12
		HbA1c	0.10
		Insulin	-0.09
		Total-cholesterol	-0.17
		Triglyceride	-0.08
		HDL-cholesterol	-0.02

Each value represents correlation of canonical valuables.

Table 6 Canonical correlation between cognitive function and subcortical brain atrophy

Canonical correlation coefficient; 0.61			p=0.010
Immediate word-list recall	-0.50	Evans ratio	0.52
Delayed word-list recall	-0.38	Caudate head index	0.50
Immediate paragraph recall	-0.17	inverse Cella media index	0.55
Delayed paragraph recall	-0.33	Basal cistern index	0.20
MMSE	-0.19		
Stroop test (A)	0.30		
Digit symbol substitution test	-0.43		

Each value represents correlation of canonical valuables.

Table 7 Canonical correlation between subcortical brain atrophy and clinical indices

Canonical correlation coefficient; 0.65			p=0.999
Evans ratio	0.50	Age	0.33
Caudate head index	0.23	Education	-0.27
inverse Cella media index	0.60	Duration of diabetes mellitus	0.26
Basal cistern index	-0.17	Body mass index	0.16
		Waist/hip ratio	0.05
		Systolic blood pressure	0.11
		Diastolic blood pressure	-0.04
		Cardiovascular complication	0.23
		Microvascular complication	0.16
		Fasting blood glucose	0.05
		HbA1c	0.05
		Insulin	0.13
		Total-cholesterol	-0.04
		Triglyceride	0.10
		HDL-cholesterol	-0.11

Each value represents correlation of canonical valuables.

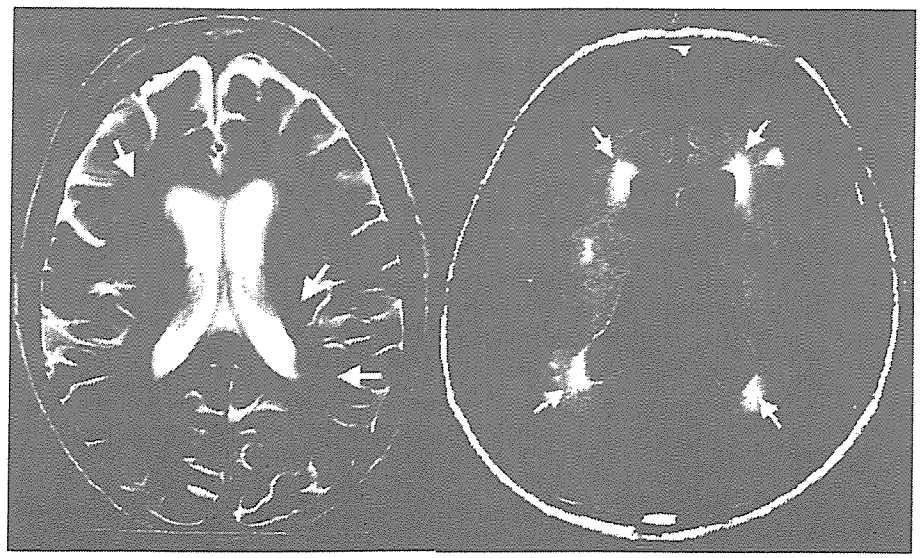

Figure 1 An example of subcortical (left) and periventricular (right) white matter hyperintensities on brain MR imaging.

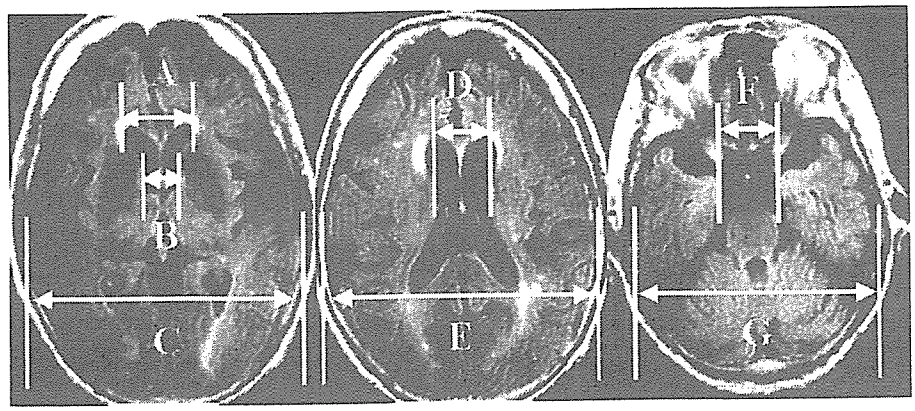

Figure 2 Measured portions on MR imaging. A, the maximum distance between the tips of the anterior horns; B the width between the bilateral heads of the caudate nuclei; C, the maximum transverse inner diameter of the cranial space at the same MR section (left); D, the maximum width of the cella mediae; E, the maximum transverse inner diameter at the same section (center); F, the internal width between the bilateral temporal lobe at the level of basal cistern; G, the maximum transverse inner diameter at the same level (right). Evans ratio= A/C, Caudate Head Index=B/C, inverse Cella Media Index= D/E, Basal Cistern Index= F/G.

Association of diastolic blood pressure and lower HbA1c with frontal brain atrophy in elderly diabetics

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To the Editor: There is growing evidence that diabetes increases the risk of dementia for the elderly, and several studies have reported an association between diabetes and brain atrophy.[1-4] Moreover, hippocampal and amygdalar atrophy in diabetes have recently been shown to be associated with insulin resistance.[4] As the hippocampus is a key structure for memory formation, the degree of brain atrophy of the hippocampus may partially account for neuropsychological deficits in the memory of diabetic patients. Besides a weakened declarative memory, diabetes is often associated with impairment of cognitive speed and attention, which are frontal lobe-related brain functions.[5] However, it remains to be established whether morphometric changes occur in the frontal brain. This report concerns a preliminary study to investigate whether frontal brain atrophy (FBA) increases in elderly diabetics, and to explore the factors leading to the development of FBA.

The enrolment for this study comprised 67 patients with type 2 diabetes (aged 60-84) treated at Kobe University Hospital and 48 healthy individuals (aged 60-86) who underwent a medical examination at the Division of Health Consultation of the Minato Health Facilities, Kobe. Diabetes was diagnosed based on information from clinical charts regarding the medical history of diabetes, blood examination results, and the presence of diabetic complications. Patients suffering from alcohol abuse, hepatic diseases, dementia, and subjects with neurological deficits due to a previous stroke were excluded.[6] After an overnight fast, serum concentrations of blood glucose (FBG), HbA1c, total-cholesterol, triglyceride, and HDL-cholesterol were determined. All CT examinations were conducted with a third-generation scanner. FBA was identified with the aid of a planimeter applied to the CT section as described elsewhere.[7] Briefly, we manually outlined the frontal intracranial area (A) and pericerebral frontal area (B) after which FBA was calculated as a percentage expressed as (B)/(A). Statview ver. 5.0 was used for analysis of the data. Based on the hypotheses formulated in advance, 0.05 was selected as the level of significance.

Clinical features of control and diabetic subjects shown in Table 1 indicate that there were no differences in age, gender or serum levels of total-cholesterol,

triglyceride, and HDL-cholesterol. Serum concentrations of FBG and HbA1c, body mass index, and systolic/diastolic blood pressure, on the other hand, were significantly higher in diabetic patients. Five subjects had shown evidence of hypoglycemia during the preceding six months.[8] The FBA of diabetic patients was 16.8±0.5% and that of control subjects was 15.0±0.8%, for a significant difference after adjustment for age (ANCOVA: p=0.018). The association between clinical variables and FBA in diabetic subjects was tested by regression analysis, showing that FBA increased according to age (standardized β= 0.21, p= 0.01). After adjustment for age, men (β= 0.22, p= 0.07) and subjects with elevated diastolic blood pressure (β= 0.37, p= 0.009) were likely to have higher FBA, whereas HbA1c correlated negatively with FBA (β= -0.26, p= 0.05). The other indices of diabetes did not show any significant association with FBA. Multiple regression analysis, however, showed that age (β= 0.46, p= 0.002), diastolic blood pressure (β= 0.38, p= 0.002), and HbA1c (β= -0.23, p= 0.04) were significantly associated with FBA. Addition of other variables to the multiple regression analysis did not yield any significant correlation. Control subjects were subjected to a similar analysis, but except for age, no significant correlation was observed (data not shown).

Our study thus provides evidence that FBA increases in elderly diabetics and that age, diastolic blood pressure and lower HbA1c are independent risk factors. The finding of an association of higher blood pressure with brain atrophy agrees with previous results.[2] Our second finding that serum levels of HbA1c are negatively associated with FBA was unexpected. To the best of our knowledge, there have been no reports to date linking brain atrophy and HbA1c in elderly diabetics.[9] The elderly diabetics in our study had a longer history of diabetes with a higher prevalence of several diabetic vascular complications than did subjects of other studies.[1-2] It appears likely that strict blood glucose control combined with the limited cerebrovascular reserve capacity in elderly diabetics causes the disruption of cerebral glucose and energy metabolism homeostasis, resulting in subsequent neuronal degeneration. Because even a modest increase in the brain atrophy rate may lead to later cognitive impairment,[7,10] our observation suggests the importance of careful management of elderly diabetics considering brain atrophy. The