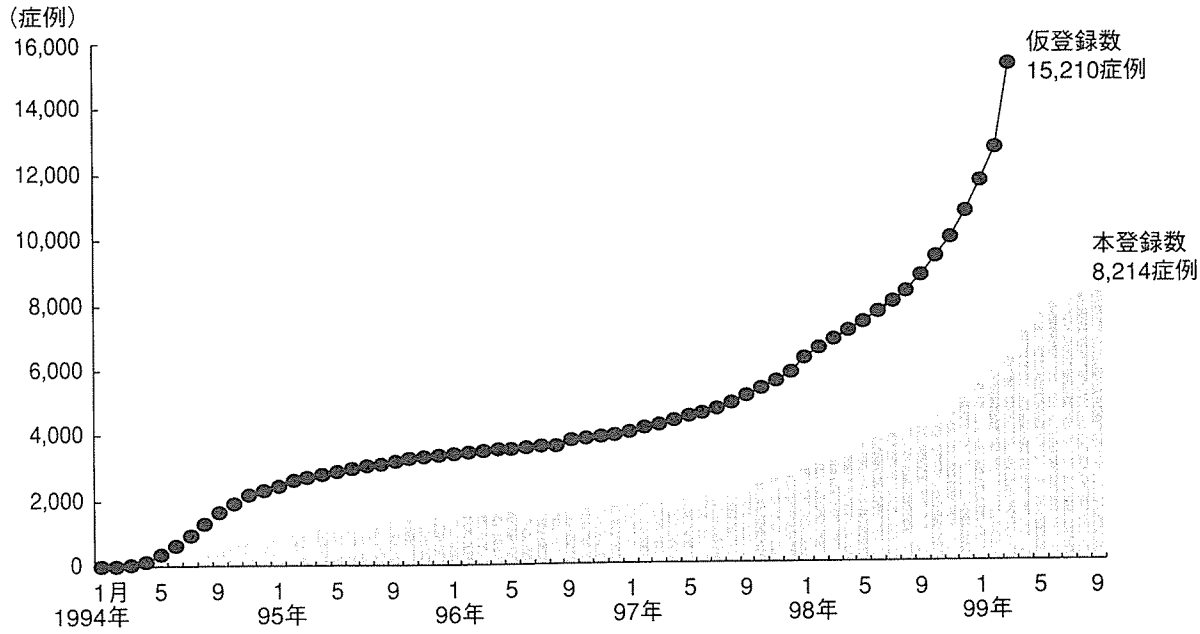
図1　症例登録状況



practical（実践的）試験である。すなわち，MEGA Study で比較されているのは，化学物質としてのプラバスタチンの効果というより，積極的にプラバスタチンを投与する治療戦略と，できるだけそれを控える戦略であるといってよい。この点から MEGA Study と欧米の二重盲検試験の成績を比較することは，きわめて興味深いこととなる。

実　施

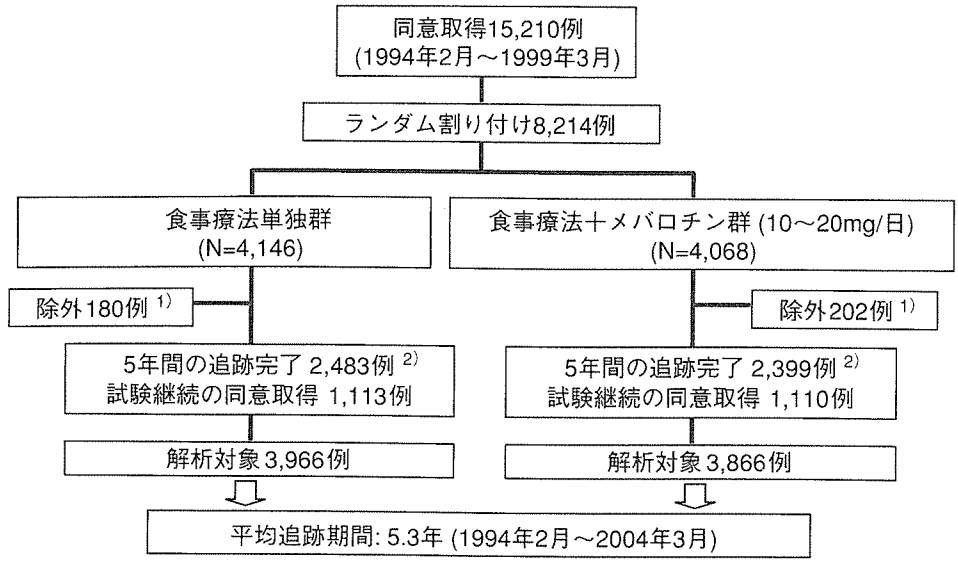
MEGA Study は，1993～94年に厚生省の「薬剤疫学的手法研究事業」として開始され，95年からは三共株式会社が受け継いで実施された（スポンサーが変わる試験というのもめずらしい）。最初の患者登録は94年2月，最後の登録は99年3月，全例がほぼ5年追跡される2004年3月をもって追跡終了とされた。

試験の実施は困難をきわめた。1995～96年まではわが国の臨床試験実施基盤は脆弱であり，図1にみられるように登録も難行した（仮登録の後，2回のコレステロール中央測定結果にもとづいて本登録・割り付けが行なわれる）。データセンターと試験事務局の整備強化，とくに施設へのコーディネータの派遣，（データに直接かかわらないことは一貫しつつの）三共の支援体制の強化，啓蒙書や栄養パンフレット配布・食事会の開催などといった患者に対するインセンティブ向上，新GCP 導入にともなう試験環境の変化などにより，試験途中から登録数は飛躍的に上昇し，当初不可能と思われた目標の登録数が達成された。（なお，試験途中での症例数不足に対する懸念から，追跡5年を迎えた患者に再同意を求め，これに応じた一部患者に対して5年をこえる追跡が行なわれた。主たる解析はこれを含む全観察に対して行なわれている。）

試験の中立性と品質保証を行なうため，本試験では以下のようなシステムを採用した

- スポンサーから独立した試験組織，とくに研究事務局とデータセンターの設置
- 市販後試験では比較的めずらしかったモ

図2　試験フローチャート



1）除外症例の選別については，ランダム割り付け以前の情報にもとづいた適格判定を，データ評価委員会が群分け非開示で実施し，試験終了前までに決定した。
2）5年までの死亡と脱落を除いた数。

〔Nakamura H, MEGA Study Group：AHA, 2005〕

ニタ派遣とコーディネータ派遣
- 試験結果を途中でモニタし，中止やプロトコル変更を勧告する独立モニタリング委員会の設置
- 米国CDC（Centers for Disease Control）認証によるコレステロール値（総コレステロールとHDL）の中央測定
- 厳正な中央割り付け
- 濃密なデータマネジメント
- 患者適格性判定のための評価委員会（27回開催）
- 盲検化でのイベント評価委員会（6回開催と持ち回り判定）
- 消息不明例に対する住民基本台帳閲覧による転居先・生死確認

最後の住民基本台帳閲覧を除けば，いずれも今日では大規模臨床試験の常道ではあるが，当時これらを大規模に採用した点でMEGA Studyは画期的であった。ちなみに，濃密なデータマネジメントの結果，調査票などの資料総量は45トンの規模となった。また徹底した追跡により，（同意撤回による追跡終了を追跡完了と換算すれば）追跡不能例はわずか102例の1.3%であった。

結　果

MEGA Studyのサブグループ解析および追加解析は現在進行中であり，種々の学会や雑誌で公開され議論されることになろう。ここでは総括医師・中村治雄先生により2005年11月16日AHA（American Heart Association）プレナリーセッションで発表された主解析結果の提示を行なう。

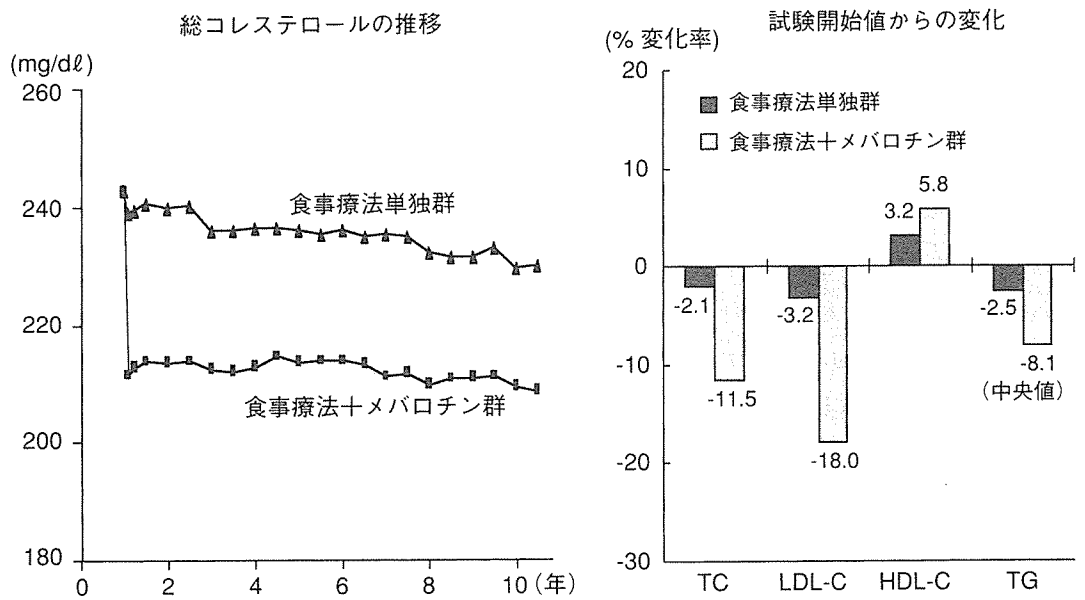
図2が症例のフロー図である。除外のおもな理由は，登録後の不適格判定（もちろん盲検下）であった。表1は患者背景を示す。これだけの大規模試験となると，単純なランダム化でも（厳正に行なわれれば）背景要因は

表1　患者背景

	食事療法単独群 (N=3,966)	食事療法十メバロチン群 (N=3,866)
平均年齢	58.4	58.2
女性 (%)	2,718 (68.5)	2,638 (68.2)
BMI (kg/m^2)	23.8	23.9
SBP／DBP (mmHg)	132.4／78.8	132.0／78.4
高血圧 (%)	1,664 (42.0)	1,613 (41.7)
糖尿病 (%)	828 (20.9)	804 (20.8)
喫煙 (%)	791 (19.9)	823 (21.3)
男性	620 (15.6)	660 (17.1)
女性	171 (4.3)	163 (4.2)

〔Nakamura H, MEGA Study Group：AHA, 2005〕

図3　脂質値の変化



〔Nakamura H, MEGA Study Group：AHA, 2005〕

均等に分布することがよくわかる。(症例数が大きいので，意味がない差でも一定の確率で統計的には有意となる。背景要因の群間差を検定することがよく行なわれるが，無意味であり，主要雑誌ではいさめられる。) 欧米のこれまでの一次あるいは二次予防試験と大きく異なることは，

・女性の割合が大きい
・糖尿病，高血圧の合併割合が大きい
・HDL-C が相対的に高い

ことであろう。前2点は日常診療の反映と解釈できる。

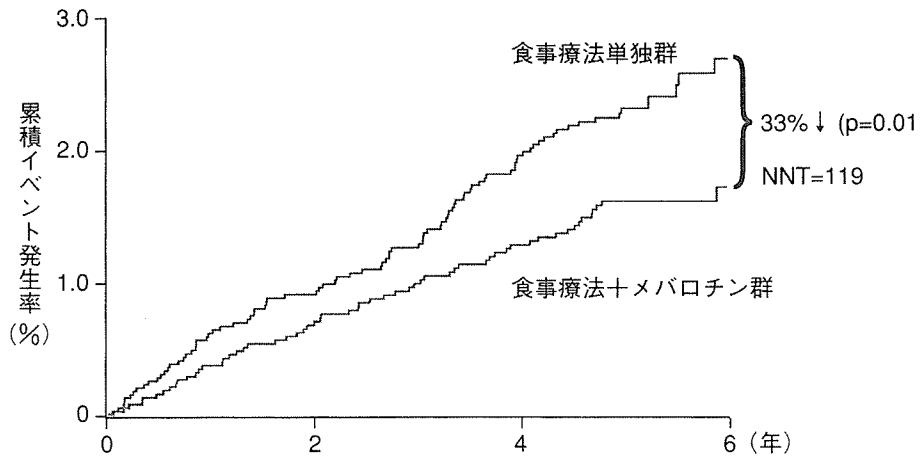
図3はコレステロール値の低下を示す。対照群でも低下がみられるのは，抗高コレステロール薬の投与など対照群にも適切な医療が行なわれていることの反映である。プラバス

表2　一次評価項目

	件数 (/1000人・年) 食事療法単独群 (N=3,966)	食事療法十メバロチン群 (N=3,866)	ハザード比	p値
冠動脈疾患 (%)	101 (5.0)	66 (3.3)	0.67	0.01
心筋梗塞 (%)	33 (1.6)	17 (0.9)	0.52	0.03
致死性	3	2	—	—
非致死性	30	16	—	—
心臓死/突然死 (%)	10 (0.5)	5 (0.3)	0.51	0.21
狭心症 (%)	57 (2.8)	46 (2.3)	0.83	0.35
CABG/PTCA (%)	66 (3.2)	39 (2.0)	0.60	0.01

〔Nakamura H, MEGA Study Group：AHA, 2005〕

図4　一次評価項目：冠動脈疾患（CHD）



対象症例数	0	1y	2y	3y	4y	5y	6y	7y	8y	9y
食事療法単独群	3966	3758	3648	3529	3430	2476	830	442	349	223
食事療法十メバロチン群	3866	3642	3490	3385	3307	2434	859	454	376	249

〔Nakamura H, MEGA Study Group：AHA, 2005〕

タチン群のLDL-C低下は欧米の結果と比べ若干小さい（表5参照）。表2・図4に示したように，プライマリエンドポイントの発生抑制効果はハザード比にして33%減少（p=0.01）。5年追跡までに限定した場合には30%減少（p=0.03）であった。セカンダリーエンドポイントに対する結果は表3のとおりで，脳卒中の抑制効果は全体では有意でなかったものの，5年追跡に限定するとハザード比にして35%抑制（p=0.03）であった。このギャップを解釈するための追加解析が進行中である。

がん以外の有害事象の発生については表4に示した。懸念された肝機能異常，CK上昇において群間差はなく，横紋筋融解は発生しなかった。がん発症は試験群・対照群それぞれ108件，116件であり，差はなかった。

図5には主要なサブグループ解析結果を，

表3　二次評価項目

	例数 (/1000人・年) 食事療法単独群 (N=3,966)	食事療法十メバロチン投与群 (N=3,866)	ハザード比	P値
脳卒中 (%)	62 (3.0)	50 (2.5)	0.83	0.33
脳梗塞	46	34	—	—
頭蓋内出血	14	16	—	—
判別不明	2	0	—	—
冠動脈疾患十脳梗塞 (%)	144 (7.1)	98 (5.0)	0.70	0.005
脳梗塞十一過性脳虚血発作 (%)	53 (2.6)	40 (2.0)	0.78	0.23
全心血管系疾患 (%)	172 (8.5)	125 (6.4)	0.74	0.01
総死亡 (%)	79 (3.8)	55 (2.7)	0.72	0.055
心血管系	18	11	0.63	—
非心血管系	61	44	0.74	—

〔Nakamura H, MEGA Study Group：AHA, 2005〕

表4　有害事象および臨床検査値異常

	例数(%) 食事療法単独群 (N=3,966)	食事療法十メバロチン群 (N=3,866)
重篤有害事象	395 (10.0)	404 (10.5)
ALT＞100 IU	107 (2.8)	104 (2.8)
CK＞500 IU	98 (2.6)	111 (3.1)
横紋筋融解症	0	0

〔Nakamura H, MEGA Study Group：AHA, 2005〕

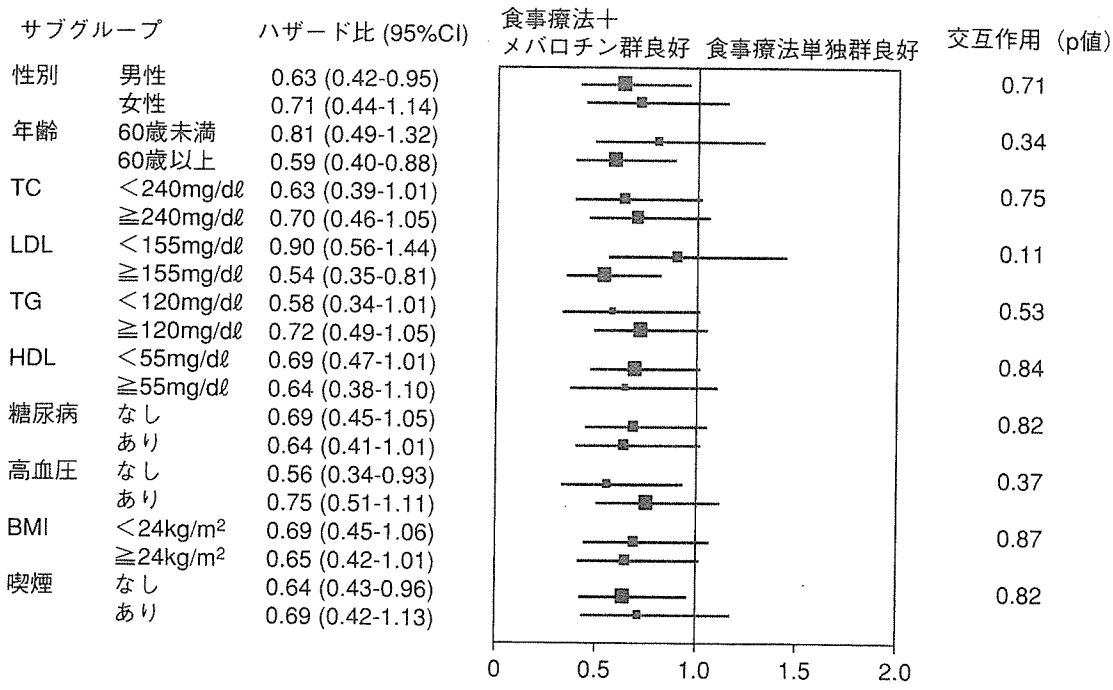
表5には欧米のこれまでの一次予防試験成績との比較を挙げた。投与と強い交互作用がみられる背景要因は存在しない。また，前述のようにLDL-C低下の効果は強くないものの，CHDイベント発生においては欧米と同様の結果が得られたことが特徴といえる。

まとめれば，本試験の対象である軽・中度の高コレステロール血症の日本人患者に対してプラバスタチン10～20mg投与はCHD発生予防の観点から有効であり，安全性も高い。欧米の成績と比べればLDL-Cの低下は小さいものの，相対リスク（ハザード比）では同等の効果が検証された。

今後の解析

女性に限定した解析，脳卒中（梗塞）に対する解析，高血圧合併例・糖尿病合併例に対するサブグループ解析などが進行中である。また対照群をコホートとみなした疫学的なリスク因子の解析も貴重な情報を与えると期待される。コレステロール低下以外のスタチンのプレオトロピック効果以外に，脱落や併用薬（とくに対照群におけるスタチン投与）の影響を考慮した解析も解釈を補うために実施中である。今後はこれらの解析結果の吟味・

図5　サブグループ解析: 冠動脈疾患の低下効果



〔Nakamura H, MEGA Study Group：AHA, 2005〕

表5　スタチンを用いた一次予防試験における脂質値の変化とCHDリスク

試験名	mg/dℓ (%変化) LDL-C 前値	LDL-C 試験期間	HDL-C 前値	HDL-C 試験期間	CHD相対リスク低下（RRR）	CHDRRR/LDL低下
WOSCOPS*	192	142 (-26)	44	46 (+5)	-31	1.2
AFCAPS/TexCAPS	150	115 (-25)	36	39 (+6)	-37	1.5
ALLHAT-LLT†	146	105 (-28)	48	49 (+2)	-9	0.3
ASCOT-LLA†	133	87 (-35)	51	50 (0)	-36	1.1
CARDS	118	71 (-40)	54	55 (1)	-37	0.9
MEGA	157	128 (-18)	58	60 (+6)	-33	1.8

WOSCOPS, N Engl J Med 1995 ; 333 : 1301-1307　AFCAPS/TexCAPS, JAMA 1998 ; 279 : 1615-1662　ALLHAT-LLT, JAMA 2002 ; 288 : 2998-3007　ASCOT-LLA, Lancet 2003 ; 361 : 1149-1158　CARDS, Lancet 2004 ; 364 : 685-696

＊ 試験期間中のLDL値およびHDL値は試験前値からの%変化で算出した。

† LDL 値およびHDL値のmmol/ℓ からmg/dℓ への変換には38.7を乗じた。

〔Nakamura H, MEGA Study Group：AHA, 2005〕

解釈そしてわが国の医療環境下での医療経済評価を通じ，高コレステロール血症治療ガイドラインへの反映がなされることは確実である。規模のみではなく，この意味でもMEGA Studyはメガな影響をもつ試験であった。

付　記

本稿は，総括医師・中村治雄先生により2005年11月16日 AHA プレナリーセッション

で発表された主解析結果にもとづいて，試験のデータセンター長を務めた大橋がまとめたものである。正式な論文は投稿中であり，引用の場合にはそちらを参照されたい。

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RESEARCH ARTICLE

Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT)

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Abstract

Background Type 2 diabetes is associated with cognitive dysfunction and increases the risk of dementia in the elderly. The aim of this study was to explore, by means of magnetic resonance (MR) imaging, possible relationships among clinical profiles of diabetes, cognitive function, white matter hyperintensities (WMHs) and subcortical brain atrophy.

Methods Data were obtained from 95 nondemented type 2 diabetic participants aged 65 years or over, enrolled in an intervention trial for Japanese elderly diabetic patients. Cognitive function was measured with neuropsychiatric tests, including mini-mental state examination (MMSE), verbal memory, digit symbol substitution and Stroop tests. Hyperintensity was classified into periventricular, deep white matter, thalamic and basal ganglia. Four ventricle-to-brain ratios were used to measure subcortical atrophy. To identify clinical features of diabetes, indices of glycemic control, lipid metabolism, blood pressure and complications were examined. Canonical correlation analysis and regression analysis were used to assess correlation.

Results Scores for digit symbol substitution and MMSE negatively correlated with WMHs in the parietal lobe and hyperintensities in the thalamus, respectively. Lower scores for memory and digit symbol substitution showed positive association with enlarged subcortical atrophy adjacent to lateral ventricles. There was no association between clinical pictures of diabetic patients with cognitive dysfunction and of those with morphological changes in the brain.

Conclusions Impaired cognitive domains of the speed of mental processes and memory were associated with WMHs and subcortical atrophy. Degenerative changes in the cerebral small vessels may constitute predictive factors for the rate of cognitive dysfunction in elderly diabetic patients.

Keywords type 2 diabetes mellitus; elderly; cognitive dysfunction; periventricular hyperintensity; white matter hyperintensities; subcortical atrophy

Introduction

Type 2 diabetes is an age-related disease with a prevalence in Japan estimated at more than 5% of the population [1]. For elderly diabetic patients, the

purpose of treatment is not only to control plasma glucose levels, but also to prevent diabetic complications. Prospective intervention studies have provided evidence that intensive glycemic control effectively slows the onset and progression of diabetic vascular complications associated with type 2 diabetes [2]. However, these epidemiological investigations did not consider the various aspects of the prevention of cognitive decline in elderly diabetic patients.

The influence of diabetes on brain function has been of interest for more than 80 years [3,4]. Subjects with type 2 diabetes initially manifest deficits in abstraction, problem solving, memory and the completion of tasks involving speed and complex perceptual-motor responses. Recently, several epidemiological studies have shown that diabetes increases the risk for the most common forms of dementia, Alzheimer's disease and vascular dementia [5–9]. Hence, the most critical issue is to identify the factors responsible for diabetic cognitive impairment that lead to severe cognitive decline in the elderly.

Diabetes-related brain disorders have been considered multifactorial and attributed to genetic predisposition, nutritional factors, cerebrovascular disorders and the neurotoxic effects of hypoglycemia and hyperglycemia [10]. The so-called Rotterdam study, which is one of the largest population-based cohort studies, demonstrated conclusively that diabetic subjects with cerebrovascular diseases and with insulin treatment are more prone to dementia [5]. Recent biological findings have supported the view that several risk factors could be linked to diabetes and cognitive dysfunction in the elderly [10,11]. However, clinical pictures of elderly diabetes are various and elderly diabetic patients may have coincident neuropsychiatric disorders, thus making it difficult to identify the factors specifically responsible for cognitive decline.

To address these controversies regarding cognitive decline in elderly diabetic patients, we conducted a large-scaled prospective study of the Japanese Elderly Diabetes Intervention Trial (J-EDIT). J-EDIT was a prospective intervention study designed to investigate and identify the clinical characteristics of nondemented diabetic elderly. In the report presented here, we have analyzed the baseline measures of cognitive dysfunction in nondemented elderly with type 2 diabetes. The aim of this study was to explore possible associations among diabetic cognitive dysfunction, brain morphological changes detected on magnetic resonance (MR) imaging, and diabetic clinical features. To analyze brain MR images, we focused on white matter hyperintensities (WMHs) and subcortical brain atrophy because subcortical structural changes have been associated with cognitive impairment in demented and nondemented elderly subjects [12,13]. We classified hyperintensities into periventricular, deep white matter, thalamic and basal ganglia. The research questions were: (1) What diabetic indices are associated with cognitive dysfunction? (2) Which WMHs influence specific cognitive domains of elderly diabetic patients? (3) Do brain structural changes on MR imaging correlate with clinical measurements of diabetes? To address these questions, we adopted the canonical correlation analysis and regression analysis.

Materials and methods

Participants

J-EDIT started in 2001 as a prospective intervention study of Japanese elderly with diabetes mellitus to prevent the several diabetic complications. The study involved 1173 diabetic subjects from 42 institutes and hospitals in Japan who were 65 years or older (mean age was 71.8 ± 4.6) and whose serum HbA_{1c} levels were ≧7.0%. Written informed consent was obtained from all patients. From these subjects enrolled in the J-EDIT, we selected 95 subjects with type 2 diabetes [14], who were treated at Kobe University Hospital, Nagoya University Hospital, Chiaki Hospital, Aoki Memorial Hospital, Nagoya Kyoritsu Hospital and Tokyo Metropolitan Geriatric Hospital. The diabetic participants who had difficulties in communicating, or showed signs of speech disturbance, deafness, severe disturbance of visual acuity, dementia and serious deterioration of the activities of daily life were excluded from this study. Clinical diagnosis of dementia was established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [15]. Subjects with chronic renal failure (serum creatinine >1.5 mg/dL), serious heart failure or symptomatic cerebral infarctions were also excluded from this study.

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and information of diabetes mellitus, blood examinations and complications were obtained from clinical charts [14]. Blood samples were obtained by vein puncture after overnight fasting to assess serum levels of glucose, HbA_{1c}, total cholesterol, triglyceride and HDL cholesterol. Serum insulin concentrations were measured in patients who were not receiving insulin therapy. Diabetic vascular complications were assessed for the coexistence of nephropathy, retinopathy, neuropathy and coronary diseases. Retinopathy was assessed fundoscopically through the dilated pupils by experienced ophthalmologists. The degree of retinopathy was classified into five categories; 0 (no retinopathy), 1 (intraretinal hemorrhages and hard exudates), 2 (soft exudates), 3 (intraretinal microvascular abnormalities, venous caliber abnormalities and venous beading), 4 (neovascularization of the disc or elsewhere in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and retinal detachment). Nephropathy was assessed in terms of the mean urinary albumin-to-creatinine ratio (ACR) and rated as 1 (no nephropathy: ACR <30 μg/mg), 2 (microalbuminuria: 30 ≦ ACR < 300 μg/mg), or 3

(persistent proteinuria: ACR ≧ 300 μg/mg or urinary protein ≧30 mg/dL). Diabetic neuropathy was classified as 1 (no neuropathy), 2 (loss of Achilles tendon reflex without neuropathic symptoms including paresthesia), or 3 (neuropathic symptoms). Coronary artery diseases were considered to be present when diabetic patients had at least one of the following: a history of myocardial infarction characterized by a typical clinical picture (chest pain, chest oppression, dyspnea, typical changes on ECG accompanied by pathological Q waves and/or localized ST variations), and typical enzymatic changes. Cardiovascular complications were classified into two categories, that is, presence or absence of coronary artery diseases.

Clinical diagnosis of hypoglycemia was based on the modified Whipple triad: symptoms and/or signs consistent with a low glucose concentration, low plasma glucose concentrations (<60 mg/dL), and relief of symptoms associated with the restoration of plasma glucose level [16]. Subjects with at least one hypoglycemic episode during the recent 12 months were considered to have hypoglycemia.

Procedures for analysis of the brain MR imaging: For every diabetic subject, a series of axial standard T1-weighted (repetition time [TR], 400 ms; echo time [TE], 12 ms), T2-weighted (TR, 3000 ms; TE, 90 ms; a 256 × 512 matrix) and fluid-attenuated inversion-recovery (FLAIR) (TR, 7500 ms; TE 110 ms; inversion time, 2200 ms; a 256 × 512 matrix) MR sequences of the brain were performed using 1.5 T MR units (Gyroscan NT-Intera and Gyroscan ASC-NT, both Philips, Eindhoven, The Netherlands; SIGUMA MR/I, General Electric, Milwaukee, WI). Scans in parallel with the anterior commissura–posterior commissura line were performed from the vertex to the foramen magnum with 7-mm thick slices and an interslice gap of 1.4 mm.

We analyzed WMHs and subcortical brain atrophy on MR images. WMHs appeared as hyperintense on T2-weighted images, but did not leave a clear hypointense hole on T1-weighted images (Figure 1(a)). FLAIR was used to obtain a clearer picture of the various WMHs [17], which were classified into subcortical WMHs and periventricular hyperintensity (PVH) (Figure 1(b)). WMHs were considered periventricular if the largest diameter was adjacent to the ventricular lining; otherwise, they were considered subcortical. PVH was rated semiquantitatively as 0 (none), 1 (pencil thin lining: <3 mm from the edge of ventricles), 2 (smooth halo: 3–10 mm), 3 (extending cap or thick lining: 10–25 mm), 4 (large confluent: >25 mm) for three separate regions; adjacent to frontal horns (frontal caps), adjacent to the wall of the lateral ventricles (bands), and adjacent to the occipital horns (occipital caps). The overall degree of PVH was calculated by adding up the scores for the three separate compartments (range 0–24) [18,19]. The number and size of subcortical WMHs were counted in the frontal, parietal, occipital and temporal lobes, as were the number and size of hyperintensities in the basal ganglia and thalamus. The size of subcortical WMHs was classified, according to the largest diameter, that is, small (1–3 mm), medium (3–10 mm), or large (>10 mm) [17]. To calculate the volume of subcortical hyperintensities, they were assumed to be spherical with a fixed diameter of 2, 6 and 12 mm for each of the three respective categories.

Linear analysis of subcortical brain atrophy, Evans ratio (ER), inverse cella media index (iCMI), caudate head index (CHI), and basal cistern index (BCI) were all calculated [20–23]. The following were measured with slide calipers: the maximum distance between the tips of the anterior horns (A), the width between the bilateral heads of the caudate nuclei (B), the maximum transverse inner diameter of the intracranial space (C), the maximum width of the cella mediae (D) and the maximum transverse inner diameter (E). Finally, the internal width between the bilateral temporal lobe (F) and the maximum transverse inner diameter (G) were calculated. The CHI, iCMI, ER and BCI were calculated with the following respective formulae: CHI = B/C, iCMI = D/E, ER = A/C and BCI = F/G, respectively (Figure 2).

Two raters who had no knowledge of the clinical data analyzed the brain MR imaging. To test the interrater reliability, the result of the two raters was subjected to correlation analysis for comparison in a random sample of 15 subjects. The analysis showed a strong correlation ($r = 0.85–0.89$, $P < 0.0001$), which suggested that the method of measurement used for this study was reliable.

Measurement of cognitive function

We used neuropsychiatric test batteries to examine the cognitive function of each of the subjects by assessing the speed of cognitive processes, as well as the extent of verbal memory, and global cognitive function. Two tests were used to assess the speed of mental processes: Stroop B (naming the color of the character that was printed in a color other than the one signified by the characters) and the digit symbol substitution test of the Wechsler Adult Intelligence Scale-Revised [24,25]. Verbal memory was assessed with the immediate and delayed word-list recall from the logical memory subtest of the Alzheimer's Disease Assessment Scale and of the paragraph from

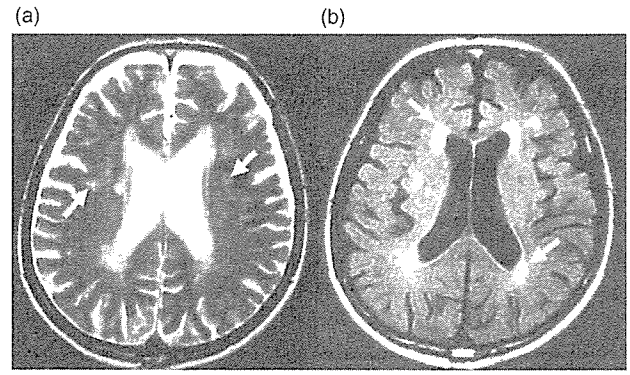

Figure 1. An example of subcortical (a) and periventricular (b) white matter hyperintensities on brain MR imaging

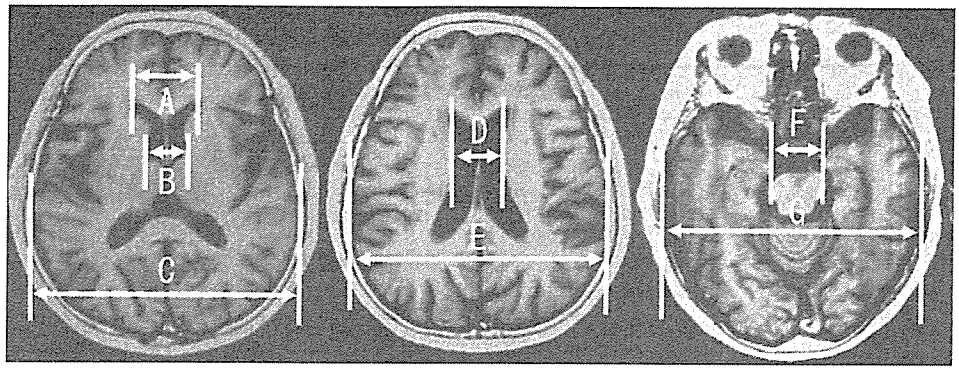

Figure 2. Measured portions on MR imaging. A, the maximum distance between the tips of the anterior horns; B, the width between the bilateral heads of the caudate nuclei; C, the maximum transverse inner diameter of the cranial space at the same MR section (left); D, the maximum width of the cella mediae; 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

the neuropsychological tests of the National Center of Neurology and Psychiatry, Japan [26,27]. Finally, MMSE was used to measure global cognitive function [28].

Statistical analysis

To explore the association among cognitive profiles, clinical variables of diabetes, and morphological changes in MR imaging, we used canonical correlation analysis and regression analysis [29]. There were four sets of variables: seven cognitive tests, sixteen clinical variables of diabetes, eight brain WMH regions and four indices of brain atrophy. Since multiple test corrections would wipe out virtually any test significance, and variables within the same class often show a high degree of correlation, thus rendering the correlations redundant, we adopted the canonical correlation analysis to identify the direct relationship between two sets of variables. The fundamental principle behind canonical correlation analysis is the creation of a number of canonical solutions, each consisting of a linear combination of one set of variables, which has the form:

$$U_i = a_1(predictor_1) + a_2(predictor_2) + \cdots + a_m(predictor_m)$$

and a linear combination of the other set of variables, which has the form:

$$V_i = b_1(criterion_1) + b_2(criterion_2) + \cdots + b_n(criterion_n)$$

The purpose is to determine the coefficients (a's and b's) that maximize the correlation between canonical variates U_i and V_i. The first canonical correlation is the highest possible correlation between any linear combination of the variables in the predictor set and any linear combination of the variables in the criterion set.

A way of interpreting the canonical solutions is to look at the correlations between the canonical variates and the variables in each set. These correlations are called structure coefficients. The logic here is that variables that are highly correlated with a canonical variate have more in common with it and they should be considered more important when deriving a meaningful interpretation of the related canonical variates. As a substantial value of structure coefficients, an absolute value equal to or greater than 0.3 is often used [30,31].

For adjustment of confounders such as age and education, the correlation between cognitive function and MRI findings detected by the canonical correlations analysis was reanalyzed with multiple linear regression analysis. Statistical significance was defined as $p < 0.05$.

Results

Clinical characteristics of the 95 elderly diabetic patients are shown in Table 1. The mean age of the patients and duration of diabetes mellitus were 72.8 ± 0.5 years and 18.4 ± 1.2 years, respectively. Average HbA_{1c} was $7.9 \pm 0.1\%$, while other indices, such as blood pressure, serum cholesterol level and body mass index, were within reasonable limits. Eighteen diabetic subjects were receiving insulin therapy and 21 patients had hypoglycemic episodes. Because the number of patients in this study with insulin treatment or with hypoglycemic episodes was small, we could not analyze the effect of insulin therapy or hypoglycemia on cognitive dysfunction.

Canonical correlation analysis indicated a strong association of cognitive function with WMHs ($p = 0.004$) (Table 2). The canonical valuable of WMHs was contributed with the digit symbol substitution test, MMSE, immediate/delayed word-list recall, and Stroop tests (correlation of canonical variables: 0.76, 0.65, 0.33, 0.47, −0.41, respectively), and the canonical valuable of cognitive function was contributed with PVH and WMHs in the parietal, temporal and occipital lobes, total WMHs, and hyperintensities in the thalamus (correlation of canonical variables: −0.45, −0.33, −0.31, 0.33, −0.34, −0.39, respectively), but not with WMHs in frontal lobe. In other words, digit symbol substitution test, MMSE and immediate/delayed word-list recall had a negative

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
Retinopathy	88	0.70 ± 0.1
Nephropathy	87	0.59 ± 0.1
Neuropathy	87	0.66 ± 0.1
Fasting blood glucose (mg/dL)	82	164.2 ± 5.1
HbA_{1c} (%)	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 (B)	80	40.2 ± 1.6
Digit symbol substitution test	77	35.8 ± 1.2
MRI	–	–
White matter hyperintensities (WMHs)	–	–
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. Canonical correlation between cognitive function and WMHs

Canonical correlation coefficient; 0.64			$P = 0.004$
Immediate word-list recall	0.33	WMHs of frontal lobe	−0.07
Delayed word-list recall	0.47	WMHs of parietal lobe	−0.33
Immediate paragraph recall	0.14	WMHs of temporal lobe	−0.31
Delayed paragraph recall	0.29	WMHs of occipital lobe	0.33
MMSE	0.65	Thalamus	−0.39
Stroop test (B)	−0.41	Basal ganglia	−0.23
Digit symbol substitution test	0.76	Total WMHs	−0.34
–	–	Periventricular hyperintensity	−0.45

Each value represents correlation of canonical valuables.

correlation with PVH and with WMHs in the parietal and temporal lobes, total WMHs and hyperintensities in the thalamus and positive correlation with WMHs in the occipital lobe. These results suggest that diabetic patients

Table 3. Canonical correlation between cognitive function and subcortical brain atrophy

Canonical correlation coefficient; 0.61			$p = 0.004$
Immediate word-list recall	−0.79	Evans ratio	0.83
Delayed word-list recall	−0.61	Caudate head index	0.79
Immediate paragraph recall	−0.28	Inverse cella media index	0.92
Delayed paragraph recall	−0.55	Basal cistern index	0.35
MMSE	−0.32	–	–
Stroop test (B)	0.30	–	–
Digit symbol substitution test	−0.71	–	–

Each value represents correlation of canonical valuables.

with more predominant WMHs except in the frontal lobe were more deficient in terms of speed of mental processes and in verbal memory.

The relationship between cognitive function and clinical indices was analyzed. No correlation could be established between cognitive function and clinical indices of diabetes, including glycemic control, lipid metabolism, blood pressure and complications of diabetes mellitus (data not shown). There was no correlation between WMHs and diabetic clinical pictures including diabetic control and complications (data not shown).

Table 3 shows a clear correlation of diabetic cognitive dysfunction with subcortical brain atrophy indices ($p = 0.004$). Lower scores for word-list recall and digit symbol substitution test, as well as delayed paragraph recall were positively associated with enlarged ER, CHI and iCMI. Canonical correlation did not detect a significant association between brain atrophy and diabetic clinical indices (data not shown).

The results were reanalyzed with regression analysis to adjust for age, education and systolic blood pressure, because these factors were generally considered to have effects on the cognitive function and/or brain structural changes on MR images [32,33]. The variables that strongly contributed to the canonical variates between cognitive functions and MRI findings were selected as the criterion variables of the regression analysis. In these analyses, digit symbol substitution test was associated with WMHs of parietal lobe, and MMSE was correlated with hyperintensities in the thalamus after adjustment for age, education and systolic blood pressure (Table 4). Table 5 shows the significant relationship between immediate word-list recall and CHI and the association between digit symbol substitution test and inverse cella media index.

Discussion

The study presented here represents the first investigation analyzing the possible associations between cognitive dysfunction and clinical features, with simultaneous evaluation of brain morphological changes detected on MR images in nondemented elderly with type 2 diabetes. It was found that WMHs and subcortical brain atrophy

Table 4. Multivariate regression analysis for subcortical WMHs with adjustment for age, education and blood pressure

Digit symbol substitution test	*P*-value	95% CI
WMHs of frontal lobe	0.13	−0.0004–0.0033
WMHs of parietal lobe	<0.05	−0.0057–0.0002
WMHs of temporal lobe	0.99	−0.0039–0.0038
WMHs of occipital lobe	0.56	−0.0048–0.0087
Thalamus	0.34	−0.0187–0.0065
Basal ganglia	0.31	−0.0092–0.0030
Periventricular hyperintensity	0.54	−1.34–0.70
MMSE	*P*-value	95% CI
WMHs of frontal lobe	0.85	−0.0004–0.0005
WMHs of parietal lobe	0.10	−0.0012–0.0001
WMHs of temporal lobe	0.47	−0.0006–0.0012
WMHs of occipital lobe	0.18	−0.0005–0.0027
Thalamus	<0.05	−0.0062–0.0002
Basal ganglia	0.57	−0.0018–0.0010
Periventricular hyperintensity	0.93	−0.23–0.25

Each variable is adjusted for age, education, and systolic blood pressure.
CI: confidence intervals

Table 5. Multivariate regression analysis for subcortical atrophy with adjustment for age, education, and blood pressure

Immediate word-list recall	*P-value*	95% CI
Evans ratio	0.50	−0.24–0.12
Caudate head index	<0.05	−0.33–0.02
Inverse cella media index	0.28	−0.22–0.07
Basal cistern index	0.77	−0.14–0.11
Digit symbol substitution test	*P*-value	95% CI
Evans ratio	0.87	−1.15–1.35
Caudate head index	1.00	−1.07–1.08
Inverse cella media index	<0.05	−2.07–0.08
Basal cistern index	0.13	−1.54–0.20

Each variable is adjusted for age, education, and systolic blood pressure
CI: confidence intervals.

strongly correlate with several domains of diabetic cognitive impairment, such as impaired speed of cognitive processes and memory. Our study also indicates that the various and separate subcortical hyperintensities in the parietal lobes and in the thalamus, but not in the frontal lobe, are associated with diabetic cognitive impairment. However, we could not detect the diabetic factors responsible for cognitive dysfunction, nor for the morphological changes on MR images, in spite of our thorough investigation of the various diabetic indices, including diabetic control, complications and comorbidities. These findings were established with the canonical correlation analysis used for our study.

Previous studies have investigated the relationship between WMHs and cognitive decline in nondemented and demented elderly [18,34–38]. Cognitive test scores in older adults were found to be worse in the presence of severe WMHs, even after adjustments for age, gender and education [18]. PVH is more likely than subcortical WMHs to be associated with speed of cognitive processes and memory [18,34,35]. The white matter of the subcortical structure can be divided into the area just beneath the neocortex and the area surrounding the ventricles. The periventricular region contains many long association fibers that connect the cerebral cortex with subcortical nuclei such as those found in the striatum and in more distant cortical areas. On the other hand, the subcortical region close to the neocortex features a high density of short looped U-fibers connecting adjacent cortical areas [39]. Periventricular WMHs damage the long-tract white matter pathways connecting many cortical areas, which might explain their effects on multiple domains of cognition.

Impaired cognitive function in elderly diabetic patients was correlated with subcortical WMHs in the parietal lobe as well as hyperintensities in the thalamus in this study. The thalamus is recognized to be associated with cognitive functions such as learning, memory and executive function [32,40]. The parietal lobe constitutes association areas that are the sites of cortical integration for all behavior such as vision, body awareness and spatial orientation and for abstract and complex cognitive functions. Recent neuroradiological studies have demonstrated reduced regional cerebral blood flow and metabolism in Alzheimer's disease especially in the parieto-temporal cortical areas and correlated with the distribution of Alzheimer's pathological features, while the primary sensorimotor and visual cortical areas were relatively preserved [41,42]. Symptoms of early stage Alzheimer's disease originate from the impaired temporal and parietal lobe functions. Incidental onset of Alzheimer's disease in elderly diabetic patients can be expected to exacerbate the functional loss and clinical symptoms related to temporal and parietal lobes, as also observed in the case of diabetic cognitive dysfunction.

The pathophysiological origins of WMHs are still unclear, with vascular and nonvascular contributions likely to be causative factors. Subcortical WMHs on T2-weighted MR imaging correlate with several pathological changes such as myelin pallor, dilatation of the perivascular space, myelin or axonal loss, scattered cystic infarcts and angionecrosis. Periventricular hyperintensities on MR scans are associated with partial breakdown of the ependymal cell lining and subependymal gliosis in addition to the pathological changes of subcortical WMHs [43,44]. Although characteristic pathological features of the diabetic brain have yet not been identified, vascular compromise is common in the elderly and is accompanied by damage to white matter pathways [12,45]. Age and hypertension have been the most consistent predictors of WMHs [32,33,46,47], while some other studies have indicated that diabetes increases the risk of WMHs [13,36,48]. The increased WMHs in elderly diabetic patients, presumably accompanied by as yet unidentified clinical variables, may account, at least in part, for diabetic cognitive dysfunction.

To reduce the rate of dementia in elderly diabetic patients, it is crucial to identify the factors responsible for the progression toward severe cognitive decline. Degenerative changes in cerebral small vessels may affect diabetic cognitive dysfunction, while it seems likely that it is also influenced by diabetic metabolic abnormalities and complications with or without unidentified genetic susceptibility. However, the results of our study do not

support the notion of any relationship between cognitive dysfunction and diabetic clinical characteristics. Whether variations in glucose homeostasis influence cognitive function remains controversial [49–51], although it has been found that the cognitive function of diabetic and nondiabetic subjects fluctuates in accordance with the serum glucose levels [50,51]. At the same time, increased insulin resistance is associated with atrophy of medial temporal lobe structures in elderly diabetic patients [52]. For these reasons, new surrogate markers that reflect chronic hyperglycemia in the diabetic brain are needed. Hyperglycemia causes oxidative stress via the polyol pathway, enhances advanced glycation end products (AGE), and increases lipid peroxidation and imbalances in the generation of reactive oxygen species and their scavengers [53,54]. N^{ε}-Carboxymethyllysine (CML), the most prominent AGE product, is crucially involved in the development of diabetic microangiopathy [55], and the level of CML expression is high in the blood vessels and brain of diabetic patients, but low in aging controls [56]. Oxidative stress has also been implicated in the pathophysiology of Alzheimer's disease and hypoxic brain insults [57–59]. Progression of diabetic retinopathy strongly correlates with the total sum of blood glucose control, and may constitute a predictor for cerebral small vessel disease [60,61].

Certain limitations of our study need to be considered. The first limitation is that this analysis was a cross-sectional study. The second is the possibility that participants with some other cognitive dysfunction could be involved in this study. The mean MMSE score of our diabetic patients was 26.2 ± 0.3, which means that most of the subjects did not attain the full MMSE score. In particular, we could not completely exclude the patients with mild cognitive impairment. The third limitation is the method for measuring brain atrophy. We used linear measurements to evaluate subcortical atrophy adjacent to the lateral ventricles, and this procedure is outdated and less accurate than the recently developed volumetric analysis of MR images [62]. However, volumetric MR analyses of a number of diabetic patients from different institutes and hospitals could not be performed. Finally, we did not estimate the effects of treatment *per se* for diabetes, hypertension and lipid abnormalities on diabetic cognitive domains. The Rotterdam study has suggested that the use of oral medication and insulin treatment for diabetes increases the association with dementia, while MR imaging has demonstrated that hypertension is associated with cognitive dysfunction and WMHs [63,64]. Recent prospective intervention studies have indicated that appropriate blood pressure control delays the progression of cognitive decline [65]. Furthermore, there are indications that impaired cholesterol transport may play a pathophysiological role in Alzheimer's disease and that HMG-CoA reductase inhibitors (statin) may have a protective effect on cognitive dysfunction in the elderly [66–68]. Most of the diabetic subjects enrolled in this study were successfully treated for their blood pressure and lipid abnormalities, which could diminish the impact of hypertension and lipid abnormalities on diabetic cognitive impairment and brain structural changes. The effects of these limitations of our study will be analyzed in the prospective intervention J-EDIT study.

In summary, WMHs and subcortical brain atrophy observed on MRI scans of elderly diabetic patients without symptomatic brain infarctions were found to be associated with impaired speed of mental processes and memory, while WMHs are thought to be responsible for degenerative changes of cerebral small vessels and to be implicated in the pathogenesis of cognitive impairment. These findings suggest that hyperintensities in the parietal lobe and thalamus and subcortical atrophy, in particular, constitute predictors of the rate of cognitive dysfunction in elderly diabetic patients and may underlie procession toward severe cognitive impairment. Our prospective J-EDIT study should help to determine the factors that can prevent cognitive dysfunction in elderly diabetic patients.

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