

Original Research Article

A Longitudinal SPECT Study of Different Patterns of Regional Cerebral Blood Flow in Alzheimer's Disease with or without Diabetes

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Key Words

Alzheimer's disease · Diabetes mellitus · Regional cerebral blood flow · SPECT

Abstract

Aims: To determine the effect of diabetes mellitus (DM) on regional cerebral blood flow (rCBF) patterns in patients with Alzheimer's disease (AD). **Methods:** We investigated the initial rCBF of 71 AD patients (36 without DM and 35 with DM) and the final rCBF of 23 AD patients (12 without DM and 11 with DM) after an average of 32 months. Single-photon emission computed tomography (SPECT) data were analyzed by statistical brain imaging. **Results:** The initial SPECT showed that AD patients without DM had lower rCBF in the left and right inferior temporal gyri than AD patients with DM. A follow-up SPECT demonstrated that rCBF decreased in more widespread regions, including the parietal, temporal, frontal, and limbic lobes, in AD patients without than with DM. **Conclusion:** This study suggests that functional brain abnormalities in AD differ depending on the DM status at baseline and during follow-up, reflecting neuropathologic differences.

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Introduction

Epidemiologic studies have shown that diabetes mellitus (DM) is associated with an increased risk of Alzheimer's disease (AD) [1]. Although multiple possible mechanisms explaining the association between DM and AD have been proposed, it is known that insulin

resistance and peripheral hyperinsulinemia promote the neurodegeneration that occurs in AD, for example due to β amyloid ($A\beta$) deposits and the increase of tau hyperphosphorylation [2, 3]. Indeed, some investigators have found that DM is associated with hippocampal and whole-brain atrophy [4, 5]. However, it remains unclear whether there are any pathophysiologic differences between AD patients with and without DM. Moreover, it is controversial whether DM also plays a role in the progression of the disease itself [6–10].

In the present study, we first examined the differences in regional cerebral blood flow (rCBF) deficits between AD patients with and without DM on initial single-photon emission computed tomography (SPECT) and then compared rCBF changes between initial and follow-up SPECT in each group. Since rCBF deficits reflect functional brain abnormalities associated with neuronal degeneration, repeated rCBF measurement is considered to be an objective and reliable indicator of disease progression. To the best of our knowledge, this is the first study on the effect of DM on rCBF patterns in AD patients.

Materials and Methods

Subjects

We retrospectively studied 71 AD outpatients with or without type 2 DM (27 men and 44 women, mean age \pm SD 78.7 \pm 5.2 years) attending the Memory Clinic of our hospital. AD patients met the clinical criteria for probable AD established by the National Institute of Neurological and Communicative Disorders Association [11] and had mild-to-moderate AD defined according to a Clinical Dementia Rating score of 1 or 2 [12]. All patients underwent detailed general physical, neurologic, and psychiatric examinations and extensive laboratory tests including brain computed tomography (CT) or magnetic resonance imaging (MRI) to exclude other potential causes of dementia. After the initial evaluation, including SPECT, 66 of the 71 AD patients were given donepezil at a dose of 3 mg once daily for 2 weeks, followed by 5 mg daily thereafter, which was tolerated without serious adverse effects. They were followed up for 24–48 months (mean follow-up time, 28.6 \pm 5.9 months), but we could only obtain both the initial and final SPECT data in 23 AD patients (12 without DM and 11 with DM) because the intervals between cognitive assessment and SPECT in AD patients with and without DM who were lost to follow-up were unfortunately more than 3 months. The severity of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [13]. Progression of dementia was evaluated based on a comparison of the MMSE scores on the initial evaluation and the final evaluation. Subjects were excluded if they had extensive white matter lesions (e.g., low-density lesions on CT or high-intensity lesions on T2-weighted MRI grade 3) using the scale of Fazekas et al. [14] and territorial or cortical infarctions. DM was defined as the use of an oral hypoglycemic drug or a casual (non-fasting) plasma glucose level of ≥ 200 mg/dl according to a report by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [15]. The patients were divided into an AD without DM group ($n = 36$) and an AD with DM group ($n = 35$). The AD with DM group had been diagnosed with type 2 DM, and the duration of DM ranged from a few years to more than 30 years on the initial SPECT. Moreover, 10 of the 35 AD patients with DM had already been receiving medication with oral hypoglycemic agents, including sulfonylureas, biguanides, and α -glucosidase inhibitors at the time of initial SPECT, and 3 of the 11 AD patients with DM with final SPECT were additionally given thiazolidinediones after the initial SPECT. The interval between cognitive assessment and SPECT in all subjects was ≤ 3 months.

Twenty-eight control subjects (12 men and 16 women, age range 56–86 years, mean age \pm SD 77.1 \pm 6.4 years) who had no memory impairment, cognitive disorder, or abnormali-

ties on MRI were assigned to the normal control group. Written informed consent was obtained from all subjects or their closest relative before the study. The study design was approved by the ethics review board of our hospital.

MRI Study

Brain MRI scans (axial T1- and T2-weighted images) at the initial evaluation were obtained from 42 AD patients (22 with DM and 20 without DM) using a 1.5-tesla scanner (Magnetom; Siemens Medical Systems, Erlangen, Germany) with the following parameters: T1-weighted spin echo (TR 450 ms; TE 12 ms; FOV 250 mm, matrix 256 × 256) and T2-weighted fast spin echo (TR 3,540 ms; TE 106 ms; FOV 250 mm, matrix 256 × 256). Qualitative MRI analysis was performed by blinded investigators who assessed periventricular and deep white matter hyperintensities (grades 0, 1, and 2 based on the scale of Fazekas et al. [14]), and lacunar infarctions (defined by low intensity on T1-weighted imaging and high intensity on T2-weighted imaging with a diameter <15 mm) in the deep gray and white matter (infarctions were rated as follows: no, single, and multiple).

SPECT Study

All subjects underwent examination using a triple-head rotating gamma camera (SPECT Picker 3000 XP; Eclipse Systems, Durham, Conn., USA) with a fan beam, permitting a spatial resolution of 6.8 mm full width at half maximum, approximately 15 min after an intravenous bolus injection of 222 MBq of N-isopropyl-p-[¹²³I]-iodoamphetamine. Prior to the injection, the subjects were allowed to rest in a quiet, dimly lit environment for 10 min. SPECT acquisition was undertaken in 24 steps (72 projections), in each of which counts were collected for 40 s. Reconstruction of the images was performed by filters (order 8; cutoff 0.40/cm) with attenuation correction (Chang method 0.09/cm). The matrix size and slice thickness of SPECT images were 128 × 128 and 4.3 mm, respectively.

Three-dimensional stereotactic surface projections created with the Neurological Statistical Image Analysis software developed by Minoshima et al. [16] were employed to evaluate the spatial distribution of abnormal perfusion. Each image set was realigned to the bicommissure stereotactic coordinate system [17]. The differences in individual brain size were eliminated by linear scaling, and regional anatomical differences were minimized by a non-linear warping technique. Each brain was therefore standardized anatomically to match a standard atlas brain while preserving regional perfusion activity. Subsequently, maximum cortical activity was extracted to adjacent predefined surface pixels on a pixel-by-pixel basis using three-dimensional stereotactic surface projections. Data sets were normalized to the mean global activity. To quantify rCBF deficits, the normalized brain activity of each patient was compared with that of 28 normal controls using pixel-by-pixel z-score analysis: (normal mean) – (individual value)/(normal SD). A positive z-score represented a reduced rCBF in the patient in comparison with the normal control mean.

To demonstrate rCBF alterations, 2-sample t test values were calculated on a pixel-by-pixel basis between controls and each group on the initial SPECT, and then converted to z-values by a probability integral transformation. Furthermore, to assess rCBF changes, intra-group differences between the initial and final SPECT data (after about 32 months) were compared: AD with DM group (n = 11) 32.3 ± 6.0 months and AD without DM group (n = 12) 31.5 ± 6.5 months. Next, to measure rCBF reduction, the mean z-score for each patient was calculated by the stereotactic extraction estimation method [18]. Mean z-scores for each gyrus of the frontal, parietal, temporal, occipital, and limbic lobes of the right and left hemispheres were automatically measured (average z-value of the coordinates with a z-value that exceeded 0 – the threshold value). The mean value in each patient was compared with the corresponding mean values of the 28 control subjects on a region-by-region basis, and

Table 1. Characteristics of the whole study group

	AD without DM group (n = 36)	AD with DM group (n = 35)
Age, years	78.3 ± 5.0	79.1 ± 5.5
Gender, men/women	15/21	12/23
Education, years	12.2 ± 2.9	12.3 ± 3.0
Duration of AD, years	2.5 ± 0.7	2.2 ± 1.2
Initial MMSE score	21.7 ± 3.1	21.2 ± 3.8
Final MMSE score	18.7 ± 4.0 [*] , ^{**}	21.1 ± 4.5
Follow-up period, months	27.7 ± 4.1	30.1 ± 8.1
Fasting plasma glucose, mg/dl	97.5 ± 6.9 [#]	152.7 ± 38.6
Hemoglobin A _{1c} , %	5.3 ± 0.4 ^{##}	7.1 ± 1.6
Medication, n of patients		
Donepezil	35	31
DM	0	10
Sulfonylureas		8
Biguanides		2
α-Glucosidase inhibitors		2
Thiazolidinediones		0
Hypertension	7	10
Hyperlipidemia	5	5
Initial blood pressure, mm Hg	139 ± 15/77 ± 8	134 ± 12/76 ± 7

Values are expressed as means ± SD or numbers of patients. * p < 0.05 vs. initial MMSE score. ** p < 0.05 vs. AD with DM group. # p < 0.05 vs. AD with DM group. ## p < 0.05 vs. AD with DM group.

the reduction in rCBF was expressed as a z-score. The method of rCBF measurement was described in detail elsewhere [19].

Statistical Analysis

Values were expressed as means ± SD. Statistical analysis was performed using Student's t test, χ^2 test, Mann-Whitney U test, and Wilcoxon signed-rank test. A comparison of mean z-scores for cerebral subregions between the two groups was performed by one-way ANOVA and post hoc t tests with Bonferroni's corrections. A p value < 0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics of the two groups are summarized in tables 1 and 2. There were no significant differences between the AD without DM group and the AD with DM group with regard to age, gender, education, duration of symptoms, initial MMSE score, follow-up duration, use of an acetylcholinesterase inhibitor (donepezil), or blood pressure on medical examination. Moreover, age did not significantly differ between patients and controls. The average initial and final MMSE scores were 21.7 ± 3.0 and 19.6 ± 3.5 in the AD without DM group who were lost for the final SPECT, and 20.8 ± 3.6 and 20.3 ± 3.5 in the AD with DM group who were lost for the final SPECT, respectively. By definition, although fasting plasma glucose and hemoglobin A_{1c} levels were normal in the AD without DM group, they were higher in the AD with DM group. MMSE scores at the final evaluation were significantly lower compared with the initial evaluation in the AD without DM group, but not in the AD

Table 2. Characteristics of the patients presenting at the final follow-up

	AD without DM group (n = 12)	AD with DM group (n = 11)
Age, years	78.9 ± 4.6	77.9 ± 6.3
Gender, men/women	6/6	5/6
Education, years	12.3 ± 3.3	11.8 ± 2.9
Duration of AD, years	2.4 ± 0.9	2.0 ± 0.8
Initial MMSE score	22.5 ± 2.8	22.3 ± 3.8
Final MMSE score	17.4 ± 4.6*, **	21.7 ± 5.1
Initial fasting plasma glucose, mg/dl	97.7 ± 7.0 [#]	138.0 ± 26.0
Final fasting plasma glucose, mg/dl	107 ± 22 ^{##}	132 ± 23
Initial hemoglobin A _{1c} , %	4.8 ± 0.3 ^{###}	7.0 ± 1.8
Final hemoglobin A _{1c} , %		6.5 ± 0.9
Duration of DM		
≤3 years		7
3–10 years		0
10–20 years		4
>20 years		0
Duration of anti-DM medication		
≤3 years		6
3–10 years		1
>10 years		3
Type of DM medication during follow-up		5
Sulfonylureas		1
Biguanides		2
α-Glucosidase inhibitors		1
Thiazolidinediones		3
Initial blood pressure score	136 ± 17/76 ± 8	136 ± 17/76 ± 7
Final blood pressure score	127 ± 11/76 ± 9	138 ± 16/75 ± 8
Medication, n of patients		
Hypertension	2	5
Calcium channel blockers	2	4
Angiotensin-converting enzyme inhibitors	0	1
Angiotensin-2 receptor blockers	0	0
Hyperlipidemia	2	4
Statins	1	3

Values are expressed as means ± SD or numbers of patients.

* p < 0.05 vs. initial MMSE score. ** p < 0.05 vs. AD with DM group. # p < 0.05 vs. AD with DM group. ## p < 0.05 vs. AD with DM group. ### p < 0.05 vs. AD with DM group.

with DM group. As illustrated by table 2, the final hemoglobin A_{1c} levels were lower than the initial levels, but the difference was only significant in the AD without DM group.

In table 3, qualitative MRI parameters are compared. There were no significant differences between the 20 AD patients without DM and the 22 AD patients with DM in terms of periventricular ($\chi^2 = 1.43$, d.f. = 2) and deep white matter hyperintensity lesions ($\chi^2 = 0.05$, d.f. = 2) or lacunar infarctions ($\chi^2 = 3.35$, d.f. = 2). Sixteen patients without DM and 13 patients with DM in whom only brain CT was performed had no abnormal high- or low-density lesions in their parenchyma.

Figure 1a and b presents the relative decrease in rCBF in the AD without DM group and in the AD with DM group compared with normal controls on the initial SPECT, respectively. Both groups showed significant decreases in rCBF in the parietotemporal lobes, posterior

Table 3. Qualitative MRI analysis results

	AD without DM group (n = 20)	AD with DM group (n = 22)
<i>White matter lesions</i>		
Periventricular hyperintensity lesions		
0	11	16
1	6	4
2	3	2
Deep white matter hyperintensity lesions		
0	13	15
1	5	5
2	2	2
<i>Lacunar infarctions</i>		
No	12	14
Single	4	7
multiple	4	1

cingulate and cinguloparietal transitional areas, and frontal association cortices, and these decreases are considered characteristic features of AD. Figure 1c compares three-dimensional views of decreased rCBF between AD patients with and without DM. Statistical mapping demonstrated that regions with decreased rCBF included the left and right inferior temporal gyri in the AD without DM group compared with the AD with DM group. However, the AD with DM group had no significantly decreased rCBF areas compared with the AD without DM group.

Figure 2a and b presents rCBF changes between initial and final SPECT in both groups. In the AD without DM group rCBF was decreased in the temporoparietal and cingulate gyri of the right and left hemispheres. In contrast, in the AD with DM group rCBF was decreased in small and scattered regions of the right and left hemispheres, including the anterior cingulate region. Both groups showed improvement in rCBF levels in some regions of the frontal and medial occipital lobes, and in the cerebellum.

Mean z-scores for the cerebral subregions on the initial and final SPECT were compared in the two groups (table 4). On the initial SPECT, z-scores for the left inferior temporal gyrus were significantly higher in the AD without DM group than in the AD with DM group. In comparison with the initial SPECT, the final SPECT showed significantly higher z-scores in widespread regions, including the frontal, parietal, temporal, and limbic lobes of the AD without DM group, and in the right anterior cingulate region of the AD with DM group. Neither group had significantly lower z-scores in any regions on the final SPECT compared with the initial SPECT.

Discussion

We found that the AD without DM group had greater rCBF deficits at the initial evaluation in the left and right inferior temporal gyri than the AD with DM group, even though both had comparable MMSE scores and duration of symptoms. According to the study of Delacourte et al. [20], neurofibrillary degeneration with paired helical filament tau was systematically present and patients at the first stage of AD had large amounts of paired helical filament tau in the temporal cortex. Considering such findings, the higher hypoperfusion in

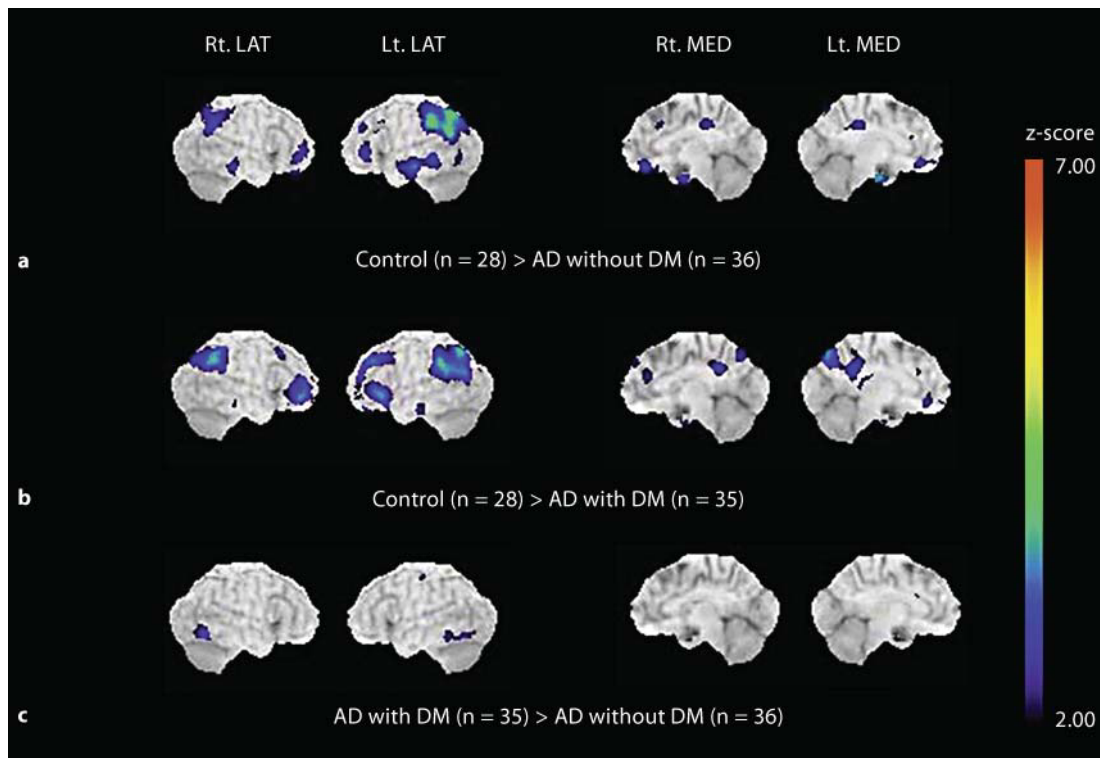


Fig. 1. Statistical maps showing the relative decrease in rCBF in the AD without DM group and AD with DM group.

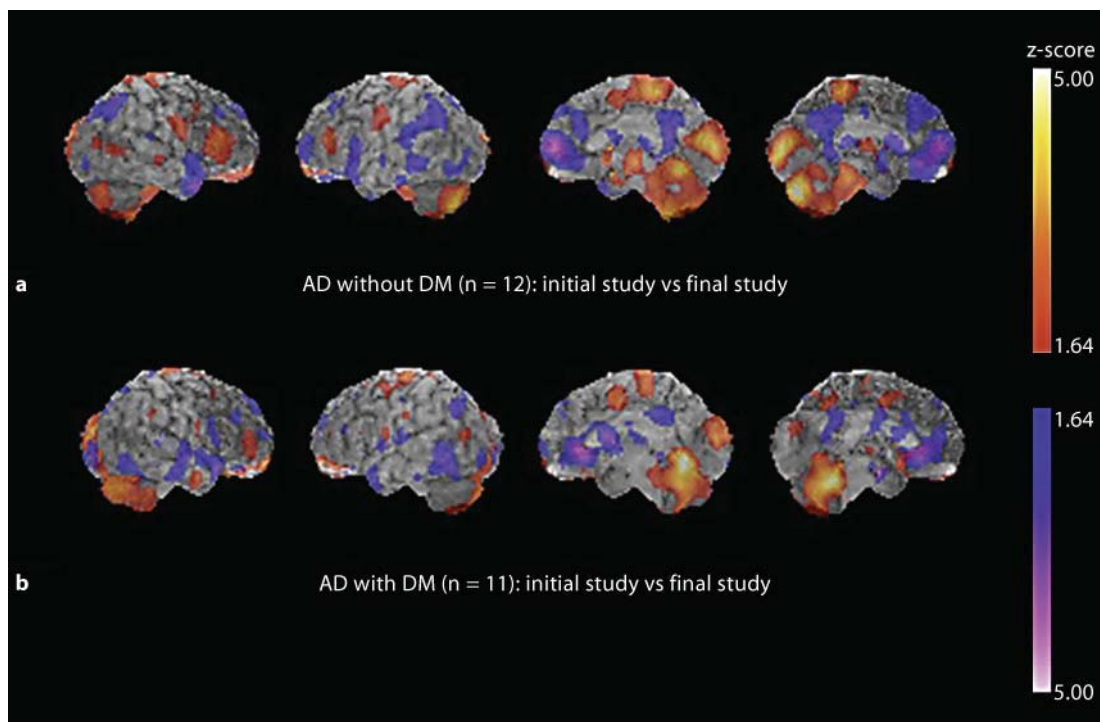


Fig. 2. Statistical maps showing the relative changes on repeated SPECT in the AD without DM group and AD with DM group. The red scale indicates the relative rCBF increase, and the blue scale the relative rCBF decrease.

Table 4. Results of z-scores for each cerebral subregion on initial and final SPECT

		AD without DM group		AD with DM group	
		baseline	month 32	baseline	month 32
<i>Frontal lobe</i>					
Superior frontal gyrus	L	1.03 ± 0.37	1.11 ± 0.34	0.93 ± 0.41	1.02 ± 0.58
	R	0.93 ± 0.40	0.99 ± 0.43	0.93 ± 0.47	1.05 ± 0.62
Middle frontal gyrus	L	1.06 ± 0.34	1.25 ± 0.50	1.01 ± 0.44	1.05 ± 0.75
	R	1.10 ± 0.47	1.12 ± 0.55	0.96 ± 0.41	0.97 ± 0.51
Inferior frontal gyrus	L	1.06 ± 0.44	1.32 ± 0.78	1.19 ± 0.47	1.26 ± 0.80
	R	0.86 ± 0.47	0.91 ± 0.38	0.79 ± 0.32	0.87 ± 0.32
Medial frontal gyrus	L	1.02 ± 0.36	1.18 ± 0.36	0.95 ± 0.42	1.09 ± 0.54
	R	0.96 ± 0.32	1.19 ± 0.53*	1.03 ± 0.47	1.11 ± 0.65
Orbital gyrus	L	0.83 ± 1.02	1.47 ± 1.02	0.94 ± 0.81	1.02 ± 0.97
	R	1.45 ± 1.27	1.22 ± 0.76	0.70 ± 0.68	0.95 ± 1.10
Rectal gyrus	L	0.98 ± 0.73	1.22 ± 0.74	0.89 ± 0.35	0.83 ± 0.66
	R	0.80 ± 0.45	1.20 ± 0.61	0.73 ± 0.42	0.73 ± 0.56
Paracentral lobule	L	0.40 ± 0.48	0.71 ± 0.61*	0.57 ± 0.42	0.61 ± 0.31
	R	0.46 ± 0.34	0.51 ± 0.43	0.45 ± 0.36	0.59 ± 0.21
Precentral gyrus	L	0.81 ± 0.27	0.89 ± 0.35	0.70 ± 0.17	0.76 ± 0.32
	R	0.73 ± 0.23	0.78 ± 0.29	0.62 ± 0.27	0.67 ± 0.27
Subcallosal gyrus	L	0.99 ± 0.60	0.99 ± 0.41	0.77 ± 0.48	0.69 ± 0.38
	R	0.52 ± 0.31	0.68 ± 0.42	0.61 ± 0.59	0.68 ± 0.34
<i>Parietal lobe</i>					
Superior parietal lobule	L	1.12 ± 0.49	1.34 ± 0.75	1.05 ± 0.22	1.02 ± 0.27
	R	0.89 ± 0.50	1.07 ± 0.63	0.93 ± 0.12	1.01 ± 0.75
Inferior parietal lobule	L	1.35 ± 0.76	1.72 ± 0.90*	1.33 ± 0.83	1.32 ± 0.84
	R	1.02 ± 0.59	1.43 ± 0.96*	1.08 ± 0.70	1.29 ± 0.86
Angular gyrus	L	1.20 ± 0.56	1.76 ± 1.09*	1.35 ± 0.76	1.33 ± 0.97
		0.74 ± 0.88	1.44 ± 1.24*	1.22 ± 1.06	1.38 ± 1.19
Postcentral gyrus	L	0.95 ± 0.51	0.88 ± 0.48	0.76 ± 0.37	0.79 ± 0.31
	R	0.83 ± 0.33	0.78 ± 0.59	0.72 ± 0.27	0.83 ± 0.37
Precuneus	L	0.83 ± 0.40	1.15 ± 0.67	1.15 ± 0.66	1.14 ± 0.55
	R	0.70 ± 0.51	0.95 ± 0.69	0.95 ± 0.47	1.12 ± 0.54
Supramarginal gyrus	L	1.36 ± 0.78	1.90 ± 1.15	1.58 ± 0.94	1.44 ± 1.21
	R	0.89 ± 0.68	1.29 ± 1.12*	1.37 ± 0.92	1.28 ± 1.14
<i>Temporal lobe</i>					
Superior temporal gyrus	L	1.08 ± 0.38	1.34 ± 0.54	0.91 ± 0.17	1.04 ± 0.52
	R	0.91 ± 0.52	1.33 ± 0.70*	0.80 ± 0.38	0.95 ± 0.38
Middle temporal gyrus	L	1.13 ± 0.39	1.47 ± 0.73*	1.00 ± 0.41	1.16 ± 0.52
	R	0.92 ± 0.78	1.24 ± 0.98*	0.86 ± 0.22	0.95 ± 0.35
Inferior temporal gyrus	L	1.37 ± 0.81 [#]	1.45 ± 1.05	0.95 ± 0.26	1.21 ± 0.51
	R	1.12 ± 0.73	1.25 ± 0.80	0.91 ± 0.29	1.13 ± 0.49
Transverse temporal gyrus	L	0.39 ± 0.59	0.54 ± 0.73	0.49 ± 0.45	0.56 ± 0.66
	R	0.39 ± 0.45	0.40 ± 0.48	0.29 ± 0.47	0.40 ± 0.55
<i>Occipital lobe</i>					
Superior occipital gyrus	L	1.05 ± 0.96	1.17 ± 0.97	0.80 ± 0.46	0.60 ± 0.40
	R	0.91 ± 0.96	1.06 ± 1.08	0.85 ± 0.81	0.82 ± 1.02
Middle occipital gyrus	L	1.17 ± 0.87	1.49 ± 1.15	0.81 ± 0.33	0.93 ± 0.47
	R	1.08 ± 0.84	1.25 ± 1.10	0.66 ± 0.46	0.91 ± 0.74
Inferior occipital gyrus	L	0.60 ± 0.50	0.84 ± 0.68	0.51 ± 0.46	0.50 ± 0.45
	R	0.85 ± 0.68	0.83 ± 0.92	0.65 ± 0.53	0.70 ± 0.75
Cuneus	L	0.89 ± 0.63	0.76 ± 0.48	0.75 ± 0.34	0.76 ± 0.43
	R	0.72 ± 0.60	0.70 ± 0.42	0.68 ± 0.37	0.65 ± 0.60
Fusiform gyrus	L	1.53 ± 0.84	1.46 ± 0.98	0.80 ± 0.38	1.19 ± 0.56
	R	1.07 ± 0.62	1.28 ± 0.74	0.71 ± 0.26	1.01 ± 0.48
Lingual gyrus	L	0.62 ± 0.75	0.38 ± 0.32	0.54 ± 0.43	0.67 ± 0.50
	R	0.58 ± 0.55	0.44 ± 0.59	0.50 ± 0.70	0.42 ± 0.45

Table 4 (continued)

		AD without DM group		AD with DM group	
		baseline	month 32	baseline	month 32
<i>Limbic lobe</i>					
Thalamus	L	0.25 ± 0.27	0.24 ± 0.38	0.26 ± 0.18	0.32 ± 0.30
	R	0.25 ± 0.31	0.29 ± 0.34	0.28 ± 0.26	0.37 ± 0.54
Cingulate gyrus	L	0.84 ± 0.35	1.16 ± 0.23*	0.85 ± 0.33	1.06 ± 0.26
	R	0.83 ± 0.31	1.00 ± 0.23*	0.80 ± 0.36	1.01 ± 0.24
Parahippocampal gyrus	L	1.22 ± 0.42	1.14 ± 0.64	0.77 ± 0.54	0.92 ± 0.50
	R	0.66 ± 0.31	0.91 ± 0.44	0.71 ± 0.36	0.81 ± 0.54
Anterior cingulate gyrus	L	0.96 ± 0.43	1.27 ± 0.58*	0.96 ± 0.31	1.22 ± 0.62
	R	0.83 ± 0.42	1.13 ± 0.49	0.87 ± 0.34	1.16 ± 0.46*
Posterior cingulate gyrus	L	0.84 ± 0.50	1.12 ± 0.42	1.00 ± 0.54	1.07 ± 0.57
	R	0.69 ± 0.52	0.87 ± 0.37	0.74 ± 0.47	0.95 ± 0.56
Uncus	L	1.50 ± 0.67	1.54 ± 1.06	0.86 ± 0.47	1.08 ± 0.66
	R	0.98 ± 0.42	0.82 ± 0.49	0.82 ± 0.39	1.03 ± 0.60

* p < 0.05 vs. baseline score. # p < 0.05 vs. AD with DM at baseline.

the left and right inferior temporal gyri may reflect more severe neuronal degeneration by AD pathology. Moreover, compared with the initial SPECT, in the follow-up SPECT, rCBF in the AD without DM group was significantly reduced in widespread regions, including the parietal, temporal, frontal, and limbic lobes, whereas it was significantly reduced only in the anterior cingulate region in the AD with DM group. Our results suggest that functional brain abnormalities of AD differ depending on DM status at baseline and during follow-up.

Some investigators have examined the relation of DM with the neuropathologic features of AD, including neuritic plaques and neurofibrillary tangles, but the results were inconclusive [21–25]. One study only found an association (with the ε4 allele) in a subgroup of individuals with DM [21], whereas others failed to demonstrate an association between DM and the histopathologic features of AD [22–24]. Beeri et al. [25] found that DM was associated with less AD neuropathology. However, Launer [26] reported that, compared with non-DM individuals, those with DM have structural brain changes that reflect neuronal degeneration as well as vascular damage, and it is likely that DM leads to microstructural changes not observed on MRI. Therefore, we assume that microvascular abnormalities may more strongly affect the pattern of rCBF deficits in the AD with DM group than in the AD without DM group, although our MRI study demonstrated that the involvement of the damaged white matter and the number of lacunar infarctions were not significantly different in the two groups. In a recent study, Sonnen et al. [27] observed two patterns of cerebral damage in patients with dementia according to DM status. In non-DM individuals, dementia was associated with a greater Aβ burden, whereas in DM individuals, dementia was associated with more microvascular infarctions. A recent clinical cohort study revealed that cognitive decline during follow-up was faster in AD alone than in AD combined with cerebrovascular disease [28]. In the present study, the AD with DM group had less rCBF deficits in the inferior temporal gyrus on the initial SPECT and we consider that they had slower cognitive decline than the AD without DM group during the follow-up time, even though the MMSE scores and duration of disease were comparable on the initial SPECT, because they may have had brain damage, including microvascular or metabolic abnormalities intrinsic to DM, but with less AD neuropathology than the AD without DM group.

Several studies have examined the effect of DM on the rate of cognitive decline [6–10]. However, the results are controversial; some found faster [6] or slower [7, 8] cognitive decline in AD patients with DM, or even no effects of DM on the rate of cognitive decline [9, 10]. Although the Rotterdam study reported the effects of antidiabetic medication on the pathogenesis of clinical AD [29], the Sacramento Area Latino Study on Aging (SALSA) illustrated that antidiabetic drugs appear to be useful for alleviating cognitive decline among individuals with DM, especially for those with a longer duration of disease [30]. A recent study in a large autopsy cohort demonstrated that the combination of insulin with other DM medication is associated with less AD neuropathology [31]. In this study, about 36% of the subjects had DM for >10 years, and in about 64% of the subjects DM was diagnosed within the last 3 years. Because >60% of patients were relatively newly diagnosed, we cannot discount the possibility that the AD with DM group in our study is not representative of the entire DM population and thus carries a survival advantage which may be associated with a less aggressive cognitive decline. Insulin-sensitizing agents, such as rosiglitazone and pioglitazone (agonists of PPAR γ), have been shown to inhibit inflammatory gene expression, alter A β homeostasis, and exhibit neuroprotective effects. Recent clinical trials have found that agonists of PPAR γ improve cognition and memory in AD patients [32]. In the present study, PPAR γ agonists might have affected rCBF changes because 3 of the 11 AD patients with DM during the follow-up period were given thiazolidinediones after the initial SPECT. In addition, antihypertensive drugs and statins, which were more frequently administered in DM patients than in non-DM subjects, may offer some therapeutic relief for AD patients. Recent studies have found evidence that some antihypertensive medications, including calcium channel blockers [33], angiotensin-converting enzyme inhibitors [34], angiotensin-2 receptor blockers [35] and statins [36], prevent the incidence of AD, reduce cognitive decline, and are associated with less severe AD pathology. These findings explain the slower rate of cognitive and functional decline in patients with DM. However, it is unlikely that antihypertensive medications and statins had any effects in the present study, because the blood pressure data in both groups were good at the initial and final evaluation, and hypertensive medication did not significantly differ between the initial and final evaluation.

Our study has some limitations. First, follow-up SPECT was only obtained in one third of the patients (12 patients without DM and 11 patients with DM), which raises the possibility that patients with dramatic deterioration of dementia were lost to follow-up SPECT. However, patients included in the follow-up SPECT are possibly representative of the entire population, since their clinical and demographic characteristics were comparable to those of the entire cohort. Despite the relatively small study cohort, there were clear differences in rCBF decline between patients with and without DM. Second, this study lacked non-demented DM subjects as a control group. We believe that the comparison of rCBF in the AD with DM group with the non-demented DM subjects was necessary in order to closely investigate rCBF patterns in the AD with DM group, because rCBF patterns may differ between non-demented DM patients and normal controls. Third, although our AD diagnosis was not neuropathologically confirmed, neuroimaging studies were used as part of the diagnostic process. In particular, rCBF reductions in the parietotemporal association cortex on SPECT are recognized as a diagnostic pattern for AD, and SPECT provides a higher specificity for other types of dementia than clinical criteria [37]. As our patients presented characteristic features of rCBF patterns in AD on baseline SPECT, we feel confident that all cases in the present series of AD did indeed have AD. Fourth, it remains uncertain whether MMSE is the more appropriate instrument for assessing cognitive decline in AD. Although disease severity was measured using MMSE in this study, a single measurement may be an imperfect index of the rate of change in symptoms over an extended period. Be that as it may, a recent study revealed that the validity of measurements of the rate of change in MMSE was reliable

when observations were separated by 3 years or more [38]. As we followed up our patients for 24–48 months, the rate of cognitive decline is likely to be a reliable parameter for assessing the cognitive decline in AD. Fifth, although the present analysis assumes a constant rate of decline, the rate of decline in neuropsychologic function can be quite variable. MMSE scores may plateau, especially in the very early stages of AD. Since our patients had mild-to-moderate stages defined by a mean MMSE score of approximately 21 at the initial evaluation, most patients may have a relatively steady course of cognitive decline. Furthermore, almost all patients in this study were treated with donepezil, which may slow the clinical progression of AD. Therefore, the rate of cognitive decline in our patients may be different from that in patients who never used cholinesterase inhibitors. Thus, the effect of medication on clinical progression should be taken into consideration, since the majority of patients examined in this study have been treated with a cholinesterase inhibitor.

Conclusion

In the initial SPECT, a lower rCBF in the left and right inferior temporal gyri was observed in the AD without DM group than in the AD with DM group. A follow-up SPECT showed that, in the AD without DM group, rCBF decreased in more widespread regions, including the parietal, temporal, frontal, and limbic lobes, than in the AD with DM group. Functional brain abnormalities in AD may differ depending on the DM status at baseline and during follow-up, reflecting neuropathologic differences.

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Disclosure Statement

The authors have no conflicts of interest.

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