

Effect of renal impairment on cognitive function during a 3-year follow up in elderly patients with type 2 diabetes: Association with microinflammation

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Keywords

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ABSTRACT

Aims/Introduction: We investigated the effect of renal impairment on cognitive function during a 3-year follow up in elderly type 2 diabetic patients, and an association with microinflammation.

Materials and Methods: Four cognitive function tests – Mini-Mental State Examination (MMSE), word recall, Digit Symbol Substitution (DSS) and Stroop Color Word – were carried out in 67 patients. Renal impairment was defined as the presence of albuminuria and a decline in estimated glomerular filtration (eGFR) <60 mL/min/1.73 m². Inflammatory markers, such as highly sensitive C-reactive protein (hs-CRP), tumor necrotizing factor- α (TNF- α), interleukin (IL)-1 β and IL-6, were measured at baseline.

Results: At baseline, cognitive decline was found in patients with renal impairment. The DSS test was independently associated with eGFR decline, whereas MMSE tended to be associated with albuminuria after adjusting for confounding factors. Regarding changes in cognitive function and renal impairment, changes in urinary albumin to creatinine ratios were strongly and independently associated with changes in word recall scores. In patients with persistent eGFR decline, there was a tendency toward a greater decrease in MMSE and DSS scores, whereas in those with newly detected albuminuria, there was a tendency toward a greater decrease in word recall scores. Increased baseline levels of hs-CRP, TNF- α and IL-6 were associated with renal impairment and cognitive function, especially DSS tests, respectively. However, the increased levels were not independent predictors for cognitive decline.

Conclusions: The present study showed a reciprocal relationship between cognitive decline and renal impairment, especially progression of albuminuria. Thus, monitoring treatment using renal biomarkers will be important for preserving both renal and cognitive function.

INTRODUCTION

The complication of renal impairment in diabetic patients might not only bring about serious conditions, such as end-

stage renal failure, but it also causes the onset of cardiovascular events. It is well recognized that impaired cognitive function is likely to be found in diabetic patients as compared with non-diabetic subjects, as previously reported by the Rotterdam study¹ and Hisayama study². An association between renal impairment and cognitive dysfunction has been focused on

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recently^{3–5}, although many mechanisms have been considered for cognitive impairment in diabetic patients⁶. The combined effects of renal impairment and cognitive dysfunction in diabetic patients could synergistically impair their quality of life and cause mortality. Therefore, it is becoming more important than ever to elucidate the mechanisms of an association between renal and cognitive impairment, and prevent the progression of both.

The brain and kidneys are thought to be associated through a variety of mechanisms, and one of them might involve hemodynamic similarities in vascular beds and similarities in the histopathological appearance of small vessels in both organs^{7–9}. Also, it is likely that hyperglycemia and concomitant hypertension in diabetic patients impair microvessels through endothelial dysfunction as a result of microinflammation and oxidative stress, leading to a decreased glomerular filtration rate (GFR) or albuminuria in the kidney⁴, and similarly, they might affect the incidence and progression of cerebral small vessel disease (SVD) in the brain^{10,11}, which could lead to cognitive impairment^{12–14}.

In a 3-year longitudinal observation, we observed that the presence or progression of SVD seen on magnetic resonance imaging was associated with a decline in cognitive function in elderly diabetic patients¹⁴, and, recently, we reported that renal impairment was associated with cognitive dysfunction independently of SVD in a cross-sectional study¹⁵. However, we did not assess how changes in renal impairment affect various aspects of cognitive function in the previous study.

It has also been reported that chronic microinflammation was involved in the pathogenesis of diabetic nephropathy^{16–18}, as well as chronic kidney disease in non-diabetic patients^{19,20} or cognitive impairment in diabetic patients^{21,22} and the general population^{23–25}. However, few studies have considered whether microinflammation is associated with both renal and cognitive impairment. Therefore, in the present 3-year observation, first, we investigated how the presence of and changes in renal impairment were associated with cognitive decline during follow up; and, second, whether microinflammation was a common risk factor for both types of impairment.

MATERIALS AND METHODS

A total of 79 outpatients with type 2 diabetes aged more than 65 years, who were living independently at home without apparent dementia, had the ability to understand this study and freely consent to taking part were recruited for it. A total of 10 patients dropped out during the 3-year follow up. Eight of them were institutionalized or moved, and the remaining two patients died due to lung cancer and cerebral bleeding. In addition, two patients with severe cognitive impairment (Mini-Mental State Examination [MMSE] score <19 points) were excluded at baseline. Therefore, the study was carried out on 67 patients (mean 74.6 ± 5.5 , range 65–89 years) whose known duration of diabetes was 17.0 ± 8.2 years and education years were 9.34 ± 2.25 years. Microvascular complications, such as renal insufficiency (serum creatinine ≥ 2.0 mg/dL), severe

retinopathy, history of stroke, transient cerebral ischemia and atrial fibrillation, were also exclusion criteria.

Cognitive Function Tests

We selected the following standardized psychological tests for measurement of each function as reported previously¹⁴. MMSE was used to assess orientation, registration, attention, calculation, language and recall with a score range from 0 to 30²⁶. We carried out word recall, a subtest of the Alzheimer's Disease Assessment Scale with a score ranging from 0 to 10, to assess verbal memory²⁷. Complex psychomotor skills were evaluated by the Digit Symbol Substitution (DSS) test, a subtest of the Wechsler Adult Intelligence Scale-Revised with a score ranging from 0 to 93²⁸. We used the modified Stroop Color Word (Stroop) test to assess attention/executive function, in which the seconds to completion are recorded, and the difference between the time required to read the word card and that required to read the dot card is calculated. A wider time difference generally means lower cognitive performance²⁹. All neuropsychological tests were carried out twice in 2006 and 2009 by well-trained psychological testers.

We calculated z-scores (individual test score minus mean test score divided by the standard deviation [SD]) for the neuropsychological tests at baseline and the end of follow up using the mean and SD of the whole population. Cognitive decline was calculated by subtracting the z-scores for word recall (Δ word recall), DSS test (Δ DSS) and Stroop test (Δ Stroop) at baseline from the z-scores at end of follow up. Change in MMSE score (Δ MMSE) was calculated by subtracting baseline scores from the scores at the end of follow up using raw test scores.

Definition of Renal Impairment

Each patient's estimated glomerular filtration rate (eGFR) was calculated from the following three-variable Japanese equation: $GFR (mL/min/1.73 m^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)³⁰. Decline in eGFR was defined as $<60 mL/min/1.73 m^2$. Albuminuria was defined as urinary albumin to creatinine ratios (ACR), which were calculated from two measurements of albumin (mg) and creatinine (g) in spot urine, as follows: normoalbuminuria, <30 mg/g creatinine; microalbuminuria, 30–299 mg/g creatinine; and macroalbuminuria, ≥ 300 mg/g creatinine. Changes in ACR (Δ log ACR) and eGFR (Δ eGFR) were calculated by subtracting baseline from end of follow up after log transformation for ACR.

Evaluation of Patients

Fasting blood samples were separated and analyzed. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and fasting blood glucose were measured using an autoanalyzer and routine enzymatic techniques. Hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan), and HbA1c (%) was estimated as a National Glycohemoglobin Standardization

Program (NGSP) value (%), calculated by the formula $\text{HbA1c (\%)} = \text{HbA1c (Japan Diabetes Society [JDS]) (\%)} \times 1.02 + 0.25^{31}$. Plasma insulin was measured by chemiluminescence enzyme immunoassay. Inflammatory markers were assayed using the quantitative sandwich enzyme technique of the enzyme-linked immunosorbent assay QuantiGlo kit (R&D System, Minneapolis, MN, USA) for tumor necrotizing factor- α (TNF- α) and interleukin-6 (IL-6), and Quantikine kit (R&D System) for interleukin-1 β (IL-1 β). For levels of TNF- α and IL-1 β below the detection limits of the methods used to determine them, the respective detection limits of 0.55 pg/mL ($n = 2$) and 0.125 pg/mL ($n = 16$) were used as measurement values. High-sensitivity C-reactive protein (hs-CRP) was assayed using a monoclonal antibody coated onto polystyrene particles and fixed-timed kinetic nephelometric measurements (BN II; Dade Behring, Marburg, Germany).

Hypertension was defined as prior diagnosis, current treatment with an antihypertensive agent or blood pressure $>140/90$ mmHg when enrolled in the study and during the follow-up period. Dyslipidemia was defined as current treatment with a lipid-lowering drug or LDL cholesterol ≥ 140 mg/dL and/or HDL cholesterol <40 mg/dL and/or triglycerides ≥ 150 mg/dL according to Treatment Guide for Diabetes³².

The present study was approved by the Ethics Committee of Chubu Rosai Hospital. After informed consent was obtained from each of the participants, the study was carried out in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Results were expressed as mean \pm SD. Statistical analysis was carried out using the *t*-test, for comparisons between two groups. Comparisons for factors not forming normal distributions were carried out after log transformation. The chi square test was also carried out, for independence. Comparisons among the groups were carried out using analysis of variance (ANOVA) followed by Bonferroni's *post-hoc* test. Repeated-measures ANOVA was used to examine the interaction between changes in cognitive function and each group. We calculated Pearson's correlation coefficients and partial correlation coefficients adjusted by variables. We carried out multiple linear regression or multiple logistic regression where appropriate, and variables with $P < 0.1$ in univariate analysis were entered for multiple regression analysis. Also, if two variables had collinearity, one of them was not entered. Statistical analyses were carried out using SPSS version 21 software (SPSS, Chicago, IL, USA), and $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinical and Biochemical Characteristics for Presence or Absence of Albuminuria and eGFR Decline at Baseline in Elderly Diabetic Patients

At baseline, 18 patients (27%) were being treated by diet only, 37 (55%) were using oral glucose-lowering medications and 12 (18%) were using insulin. These patients were moderately

well-controlled during the 3 years with an average HbA1c of $7.0 \pm 0.7\%$. The average blood pressure during follow up was $139.2 \pm 12.5/75.4 \pm 7.2$ mmHg, and there were 50 patients with hypertension, of whom 43 (86%) were receiving renin-angiotensin system blockers during follow up. No patients experienced a severe hypoglycemic episode requiring admission, and no patients had a stroke during the follow-up period.

In patients with albuminuria at baseline, higher frequency of RAS blocker use, higher levels of triglycerides, serum creatinine and fasting blood glucose, and lower levels of HDL-C were observed; whereas patients with eGFR decline were older, had lower levels of HDL-C and diastolic blood pressure, and higher levels of serum creatinine (Table 1).

Regarding an association between renal impairment and cognitive functions at baseline, significant differences in MMSE, DSS test and Stroop test scores were found at baseline in patients with albuminuria as compared with normoalbuminuria, and decreased scores for MMSE, word recall and DSS tests were found in patients with a decline in eGFR.

Individual associations of albuminuria and eGFR decline with each cognitive function were examined in multiple logistic regression analysis with age, duration of diabetes, HDL cholesterol, RAS use, log triglycerides, log fasting insulin and fasting blood glucose at baseline as covariables. Only DSS test scores at baseline were independently associated with eGFR decline ($P = 0.015$), while there was a tendency toward an association between MMSE at baseline and albuminuria ($P = 0.065$) after adjustment for the aforementioned covariables.

Association Between Changes in Cognitive Function Scores and Changes in Renal Impairment During Follow-Up

After 3 years, cognitive function scores except those for the Stroop test declined (MMSE 26.1 ± 2.6 at baseline vs 24.0 ± 3.9 at 3 years of follow up, $P < 0.001$; word recall 6.86 ± 1.51 vs 6.46 ± 1.69 , $P = 0.017$; DSS test 33.4 ± 10.2 vs 31.7 ± 12.0 , $P = 0.075$; Stroop test 20.7 ± 13.6 vs 21.5 ± 15.7 , $P = 0.743$).

Factors associated with changes in cognitive function scores during follow up are shown in Table 2. Multivariate analysis showed that independent factors were MMSE scores at baseline for Δ MMSE, Δ log ACR for Δ word recall, age and fasting blood glucose at baseline for Δ DSS test; and Stroop test scores at baseline, average diastolic blood pressure during follow up, and HbA1c at baseline for Δ Stroop test. Regarding associations between changes in renal impairment and cognitive decline, only Δ log ACR was strongly and independently associated with Δ word recall (Figure 1).

At baseline, 13 patients had microalbuminuria and seven patients had macroalbuminuria. During follow up, five patients regressed to normoalbuminuria from microalbuminuria and eight patients progressed to microalbuminuria. After 3 years, 23 patients had albuminuria and in two of them, microalbuminuria had developed into macroalbuminuria. The eGFR had improved in two patients and deteriorated in seven patients.

Table 1 | Clinical and biochemical characteristics for presence and absence of albuminuria and estimated glomerular filtration rate decline at baseline

	Total	Albuminuria		eGFR (mL/min/m ²)	
		(-)	(+)	eGFR ≥60	eGFR <60
<i>n</i> (male/female)	67 (28/39)	47 (17/30)	20 (11/9)	47 (19/28)	20 (9/11)
Age (years)	74.6 ± 5.5	73.9 ± 5.5	76.1 ± 5.3	73.4 ± 4.8	77.3 ± 6.2**
Duration of diabetes (years)	17.0 ± 8.2	16.6 ± 8.4	18.2 ± 7.8	15.8 ± 7.5	19.9 ± 9.1 [#]
Body mass index (kg/m ²)	22.9 ± 3.3	22.6 ± 3.5	23.5 ± 2.9	22.7 ± 3.3	23.2 ± 3.5
Smoking (non/current)	54/13	40/7	14/6	36/11	18/2
Serum creatinine (mg/dL)	0.79 ± 0.23	0.74 ± 0.20	0.92 ± 0.24***	0.70 ± 0.12	1.02 ± 0.25
Systolic BP (mmHg)	139.2 ± 17.9	137.9 ± 19.0	142.5 ± 14.8	137.8 ± 17.2	142.7 ± 19.3
Diastolic BP (mmHg)	77.2 ± 7.9	77.5 ± 7.7	76.5 ± 8.5	78.5 ± 7.8	74.0 ± 7.3*
RAS blockers use (+/-)	40/27 (59.7%)	24/23 (51.1%)	16/4 (80.0%)*	25/22 (53.2%)	15/5 (75.0%) [#]
T-cholesterol (mg/dL)	206.2 ± 29.6	207.1 ± 29.0	204.0 ± 31.5	203.4 ± 30.2	212.8 ± 27.6
HDL cholesterol (mg/dL)	53.5 ± 15.3	57.1 ± 15.6	45.1 ± 10.9***	56.1 ± 15.8	47.5 ± 12.4*
Triglycerides (mg/dL)	127.0 ± 88.2	107.3 ± 55.4	173.3 ± 127.9***	115.3 ± 60.0	154.5 ± 131.0
LDL cholesterol (mg/dL)	124.3 ± 24.0	125.4 ± 25.4	121.8 ± 20.6	122.4 ± 25.7	129.0 ± 19.4
Statin use (+/-)	29/38 (43.3%)	18/29 (38.3%)	11/9 (55.0%)	19/28 (40.4%)	10/10 (50.0%)
Fasting blood glucose (mg/dL)	137.2 ± 30.0	132.0 ± 29.0	149.7 ± 29.3*	136.5 ± 30.3	139.1 ± 30.0
Fasting insulin (μU/mL)	7.64 ± 5.40	6.69 ± 3.62	9.88 ± 7.88 [#]	7.59 ± 6.00	7.75 ± 3.75
HbA1c (%)	7.08 ± 0.83	6.97 ± 0.78	7.34 ± 0.91	7.09 ± 0.81	7.07 ± 0.90
hs-CRP (mg/L)	0.85 ± 1.26	0.51 ± 0.58	1.64 ± 1.93*	0.48 ± 0.56	1.73 ± 1.89
TNF-α (pg/mL)	2.47 ± 1.02	2.21 ± 0.79	3.07 ± 1.25***	2.13 ± 0.68	3.27 ± 1.22
IL-1β (pg/mL)	0.34 ± 0.23	0.31 ± 0.20	0.42 ± 0.29 [#]	0.34 ± 0.26	0.33 ± 0.18
IL-6 (pg/mL)	1.60 ± 1.56	1.16 ± 0.95	2.61 ± 2.17****	1.24 ± 0.85	2.44 ± 2.36*
MMSE	26.1 ± 2.6	26.7 ± 2.4	24.7 ± 2.7***	26.6 ± 2.5	25.0 ± 2.7*
Word recall (z-score)	0.12 ± 0.94	0.20 ± 1.01	-0.05 ± 0.74	0.28 ± 0.93	-0.25 ± 0.86*
DSS test (z-score)	0.08 ± 0.92	0.25 ± 0.88	-0.34 ± 0.91*	0.34 ± 0.90	-0.57 ± 0.60****
Stroop test (z-score)	0.03 ± 0.92	-0.24 ± 0.77	0.47 ± 1.14***	-0.13 ± 0.76	0.21 ± 1.21

Values are expressed as mean ± standard deviation. [#]*P* < 0.1, **P* < 0.05, ***P* < 0.01, ****P* < 0.005, *****P* < 0.001 different from albuminuria (-) or estimated glomerular filtration rate (eGFR) ≥60. Statistical analyses were carried out using the unpaired *t*-test for comparison of two means, and the chi square test for independence. Triglycerides, fasting insulin, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are log transformed and comparison of the two means is carried out. BP, blood pressure; DSS, Digit Symbol Substitution; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; T-cholesterol, total cholesterol.

We divided patients into three groups: no renal impairment, newly detected renal impairment and persistent renal impairment during follow-up, and patients with improved renal impairment were assigned to the no renal impairment group. MMSE and DSS test scores showed a tendency to deteriorate to a greater extent in patients with persistent decline in eGFR than in those with new decline or without decline in eGFR. In contrast, decreases in word recall scores tended to be greater in patients with newly detected albuminuria than in the other groups (Figure 2). However, no such interaction among groups with regard to cognitive function was observed for the Stroop test (data not shown).

We also investigated an association between cognitive function and the presence of albuminuria or eGFR decline, assigning participants to four groups categorized by the presence or absence of albuminuria or eGFR. Although the group with both types of renal impairment had significantly poorer cognitive scores in MMSE, DSS and Stroop tests at

baseline as compared with the group without either, no significant differences in changes in individual cognitive functions during follow up among the four groups were observed (data not shown).

Association Between Levels of Inflammatory Markers at Baseline and Renal Impairment

Significantly higher levels of hs-CRP, TNF-α and IL-6 were observed in patients with albuminuria and eGFR decline (Table 1). Log IL-6, log IL-1β, log TNF-α and log hs-CRP were associated with albuminuria (*P* = 0.004, *P* = 0.024, *P* = 0.064, *P* = 0.088, respectively), whereas log hs-CRP and log TNF-α were independently associated with eGFR decline (*P* = 0.014, *P* = 0.011, respectively) after adjusting for variables as aforementioned. In addition, levels of TNF-α at baseline were significantly lower in patients without albuminuria (2.24 ± 0.79 pg/mL, *P* < 0.05) and eGFR decline (2.10 ± 0.71 pg/mL, *P* < 0.001) than in those with persistent albuminuria

Table 2 | Factors associated with changes in cognitive function scores during follow up

	Univariate analysis		Multivariate analysis	
	Correlation coefficient	P-value	Standardized β coefficient (SE)	P-value
Δ MMSE			$r^2 = 0.306, P = 0.001$	
Age	-0.309	0.011	-0.209 (0.078)	0.092
DBP at baseline	0.261	0.033	0.176 (0.052)	0.127
eGFR at baseline	0.260	0.034	0.130 (0.029)	0.306
Log IL-6 at baseline	-0.254	0.040	-0.139 (1.406)	0.200
MMSE at baseline	-0.235	0.056	-0.367 (0.153)	0.002
HDL-C at baseline	0.205	0.096	0.145 (0.026)	0.209
Δ Word recall (z-score)			$r^2 = 0.297, P < 0.001$	
Δ Log ACR	-0.476	0.000	-0.427 (0.208)	0.000
Word recall at baseline	-0.292	0.016	-0.204 (0.102)	0.084
Education years	-0.207	0.093	0.110 (0.392)	0.323
Log TG at baseline	0.230	0.061	-0.045 (0.042)	0.698
Δ DSS test (z-score)			$r^2 = 0.229, P = 0.009$	
Age	-0.305	0.014	-0.261 (0.013)	0.041
DBP at baseline	0.296	0.016	0.242 (0.009)	0.051
Average DBP during follow up	0.244	0.051	Not applied	
FBG at baseline	-0.214	0.084	-0.272 (0.002)	0.026
Education years	0.207	0.093	-0.137 (0.030)	0.253
Log IL-6 at baseline	-0.212	0.093	-0.053 (0.236)	0.682
Δ Stroop test (z-score)			$r^2 = 0.628, P < 0.001$	
Stroop score at baseline	-0.570	0.000	-0.632 (0.097)	0.000
Average DBP during follow up	0.402	0.001	0.252 (0.019)	0.021
HbA1c at baseline	-0.318	0.009	-0.175 (0.133)	0.046
Smoking	-0.250	0.043	-0.128 (0.272)	0.134
Average SBP during follow up	0.219	0.077	-0.046 (0.011)	0.658
DBP at baseline	0.208	0.094	Not applied	

No smoking was 0, smoking was 1. Δ , change; ACR, albumin to creatinine ratio; DBP, diastolic blood pressure; DSS, Digit Symbol Substitution; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SE, standard error; TG, triglycerides.

(3.11 ± 1.34 pg/mL) and eGFR decline (3.29 ± 1.28 pg/mL) during follow up, and the baseline levels in patients with newly diagnosed albuminuria (2.53 ± 1.04 pg/mL) and new eGFR decline (2.57 ± 0.54 pg/mL) were between those in patients with normal renal function and persistent renal impairment, although the differences were not significant. Hs-CRP and IL-6 levels also showed a similar tendency (data not shown).

In the group with both albuminuria and eGFR decline, levels of hs-CRP, TNF- α and IL-6 at baseline were significantly higher (2.87 ± 2.10 mg/L, 3.84 ± 1.29 pg/mL, 3.44 ± 2.69 pg/mL, respectively) as compared with the group without either type of renal impairment (0.49 ± 0.62 mg/L, 2.08 ± 0.72 pg/mL, 1.09 ± 0.73 pg/mL, respectively).

Correlation Between Levels of Inflammatory Markers at Baseline and Cognitive Function at Baseline, After 3-year Follow-Up and Changes in Them

Significant correlations between inflammatory markers, such as hs-CRP, TNF- α and IL-6, and cognitive function indicators, such as MMSE, DSS and Stroop tests, were mainly observed at

baseline and after 3 years, but not for changes in them during follow up. However, such significant associations found at baseline and after 3 years disappeared after adjustment for the variables shown in Table 3, and tendencies toward correlation were only found between hs-CRP and TNF- α levels at baseline, and DSS tests at baseline, and between TNF- α and IL-6 levels at baseline and Δ Stroop test.

DISCUSSION

Cross-sectional and longitudinal studies on an association between renal and cognitive impairment have recently been carried out in diabetic patients^{4,14,33,34}, as well as the general population^{3,5,35}. Although it is widely accepted that chronic kidney disease is a potent risk factor for cognitive impairment, the details remain controversial³⁶. In many studies, the estimation of cognitive function was carried out using MMSE, a simple, global test for screening. In the present study, a decline in MMSE was also partially associated with renal impairment. Regarding specific cognitive domains, it is generally agreed that frontal lobe functions, such as psychomotor speed, executive

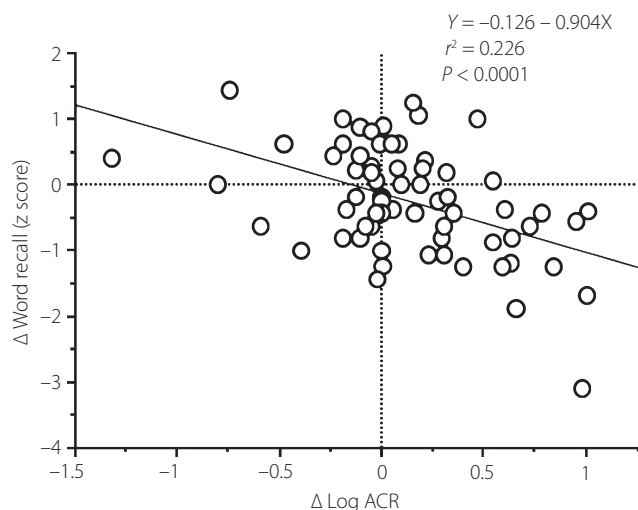


Figure 1 | Correlation between changes in log albumin to creatinine ratios ($\Delta\log$ ACR) and changes in word recall ($\Delta\text{word recall}$) during follow up. $\Delta\log$ ACR was calculated by subtracting baseline from the end of follow up after log transformation for ACR. $\Delta\text{Word recall}$ was calculated by subtracting the z-scores for word recall at baseline from the z-scores at the end of follow up.

function and attention, are impaired in patients with renal impairment^{4,12,13,37}, and impairment of memory has also been reported^{4,5}. Our recent¹⁵ and the present study cross-sectionally observed an association between renal impairment and DSS and Stroop tests, which reflect frontal lobe function.

Regarding an association between types of renal impairment and cognitive impairment, albuminuria and eGFR decline, respectively, have been reported to be associated with cognitive dysfunction. A recent meta-analysis by Etgen *et al.*³⁶ showed that significant cognitive decline was observed in subjects with eGFR decline in both cross-sectional and longitudinal studies, although they mentioned that there was insufficient data available for a separate analysis on albuminuria. However, it has also been reported that albuminuria is more associated with cognitive decline than eGFR decline, and that albuminuria was associated with decreased verbal memory performance and impaired processing speed and executive function⁴. In the present study, although impaired cognitive functions, except word recall, were significantly related to albuminuria at baseline, significance disappeared after adjusting for confounding factors, and there was only a tendency toward an association for MMSE. In contrast, a significant decline in DSS tests was observed in patients with eGFR decline at baseline, even after adjustment. In addition, poorer scores for MMSE, DSS, and Stroop tests were found in patients with both albuminuria and eGFR decline as compared with those without either. In the Reasons for Geographic and Racial Differences in Stroke (REGARD) study, albuminuria and low eGFR were complementary, but not additive, even though they were indepen-

dently associated with incident cognitive impairment⁵. Which type of renal impairment is more associated with cognitive dysfunction remains controversial, because it is likely that many factors, such as the selected subjects and their age³⁸, selected cognitive domains, and classification bias regarding renal impairment will affect the results. In this regard, further studies will be required for clarification.

Regarding the progression of renal impairment and cognitive decline, the large-scale ONTARGET/TRANSCEND studies³⁵ reported that the presence and degree of albuminuria, and the progression to albuminuria were associated with worsened cognitive function. In addition, in the recent subanalysis of the ACCORD trial, it was reported that persistent albuminuria and progressive albuminuria were associated with a decline in cognitive function in relatively young individuals with diabetes and unimpaired eGFR³⁹. Another longitudinal study also reported that cognitive function was declining in a subject group with renal impairment during the follow-up period, though there was no association between renal and cognitive impairments at baseline¹³. In the present study, a decline in verbal memory was strongly associated with the degree of change in albuminuria rather than status of albuminuria at baseline, suggesting that progressive changes in albuminuria could accelerate cognitive decline. Accordingly, supreme treatment for preventing the incidence and progression of albuminuria at the early stage will be required in order to avoid not only end-stage renal disease, but also dementia.

In contrast, an association between changes in eGFR and cognitive function was not found in the present study, and only a tendency toward decreasing scores in MMSE and DSS tests was seen in patients with persistent eGFR decline. However, patients with persistent eGFR decline were older as compared with patients without it. As we previously reported that cognitive decline was more developed in older patients in the same subject group¹⁴, it is likely that age had a strong impact on declining cognitive function.

Many studies have suggested that cerebral SVD is related to renal impairment^{10,11} and cognitive dysfunction^{12,13,40}. Our previous results¹⁴ also were in line with the findings of these studies. As the brain and kidney might be considered as end organs having similar low-resistance vascular beds and endothelial structures, which are affected by inflammation and oxidative stress, impaired endothelial function in the brain could lead to SVD or neurodegeneration through damage to the blood-brain barrier⁴¹, whereas endothelial dysfunction in the kidney might contribute to impaired glomerular filtration and secondary protein leakage^{4,7-9}. Therefore, the findings of the recent studies³⁹ and the present study suggest that endothelial dysfunction is a common factor for renal and cognitive impairment, as albuminuria is a measure for endothelial pathology.

Microinflammation is also thought to be one of the potent factors for such impairment, and inflammatory markers have been reported to be associated with cerebral SVD⁴²⁻⁴⁴, cognitive impairment^{21-25,44} and renal disease¹⁶⁻²⁰. The rise in

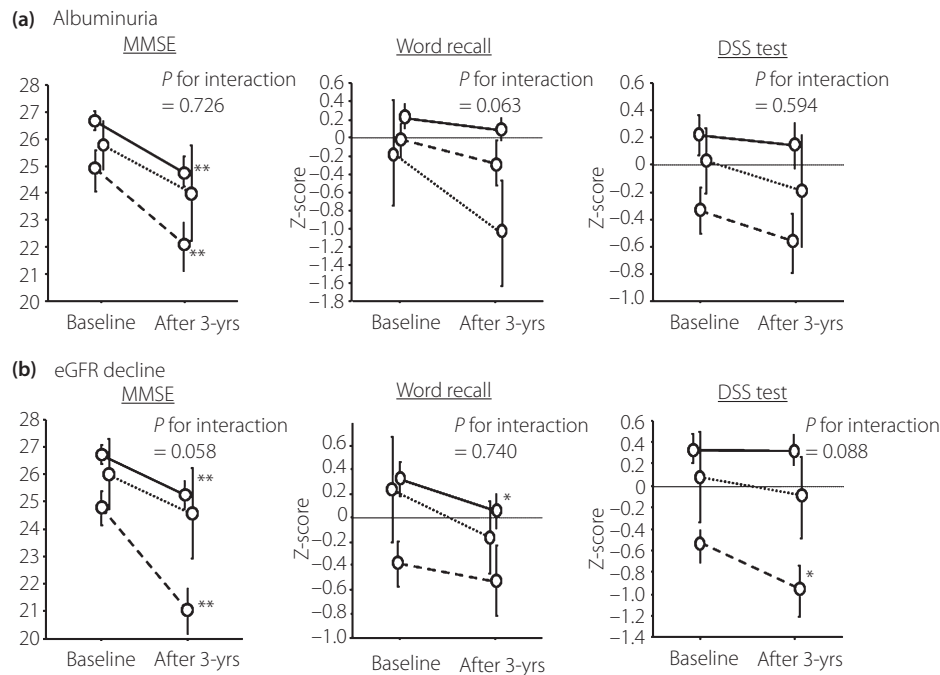


Figure 2 | Association between changes in renal impairment and changes in Mini-Mental State Examination (MMSE), word recall and Digit Symbol Substitution (DSS) test scores during follow up. Data are expressed as mean \pm standard error at baseline and after the 3-year (3-yrs) follow up. Broken line: presence of albuminuria ($n = 15$) or estimated glomerular filtration rate (eGFR) decline <60 mL/min/1.73 m² ($n = 18$); dotted line: newly detected albuminuria ($n = 8$) or eGFR decline ($n = 7$); solid line: absence of albuminuria ($n = 44$) or eGFR decline ($n = 42$). * $P < 0.05$, ** $P < 0.01$ compared with baseline by paired t -test. For MMSE, (a) albuminuria main effect of time $P = 0.025$, main effect of group $P < 0.001$, time \times group interaction $P = 0.726$; (b) eGFR decline, main effect of time $P < 0.001$, main effect of group $P < 0.001$, time \times group interaction $P = 0.058$. For word recall, (a) albuminuria, main effect of time $P = 0.057$, main effect of group $P < 0.005$, time \times group interaction $P = 0.063$; (b) eGFR decline main effect of time $P = 0.042$, main effect of group $P = 0.041$, time \times group interaction $P = 0.740$. For DSS test, (a) albuminuria main effect of time $P = 0.093$, main effect of group $P = 0.052$, time \times group interaction $P = 0.594$; (b) eGFR decline main effect of time $P < 0.001$, main effect of group $P = 0.038$, time \times group interaction $P = 0.088$, P -values show the results of repeated-measures ANOVA.

Table 3 | Correlation between levels of inflammatory markers at baseline and cognitive function at baseline, after 3-year follow up, and the change in it

	MMSE			Word recall (z-score)			DSS test (z-score)			Stroop test (z-score)		
	Base	After	Δ	Base	After	Δ	Base	After	Δ	Base	After	Δ
Log hs-CRP	-0.272* (-0.198)	-0.278* (-0.071)	-0.103 (-0.036)	-0.226# (-0.150)	-0.131 (-0.014)	0.091 (0.146)	-0.376*** (-0.239#)	-0.365*** (-0.211)	-0.075 (0.000)	0.311* (0.131)	0.267* (0.122)	0.000 (0.041)
Log TNF- α	-0.249* (-0.009)	-0.372*** (-0.052)	-0.221# (-0.032)	-0.249* (-0.023)	-0.327** (-0.064)	-0.135 (-0.149)	-0.489*** (-0.240#)	-0.439*** (-0.067)	-0.035 (0.202)	0.200 (-0.122)	0.260* (-0.113)	0.074 (0.247#)
Log IL-1 β	-0.258* (-0.196)	-0.165 (-0.055)	-0.007 (0.127)	-0.121 (-0.018)	-0.126 (-0.071)	-0.022 (-0.022)	-0.164 (-0.015)	-0.162 (0.007)	-0.036 (0.062)	0.141 (0.139)	-0.059 (-0.102)	-0.149 (-0.109)
Log IL-6	-0.246* (-0.038)	-0.400*** (-0.194)	-0.254* (-0.141)	-0.185 (-0.029)	-0.136 (-0.130)	0.036 (-0.041)	-0.370*** (-0.199)	-0.431*** (-0.166)	-0.212# (-0.025)	0.252* (0.017)	0.321** (0.226)	0.087 (0.244#)

Values are correlation coefficients and values in parenthesis are partial correlation coefficient adjusted by age, sex, years of education, duration of diabetes, statin and renin-angiotensin system use, systolic blood pressure, diastolic blood pressure, glycated hemoglobin (HbA1c), current smoking, the presence of dyslipidemia, log ACR and estimated glomerular filtration rate. # $P < 0.1$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.001$. DSS, Digit Symbol Substitution; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MMSE, Mini-Mental State Examination; TNF- α , tumor necrosis factor- α .

hs-CRP, TNF- α and IL-6 levels observed in patients with renal impairment in the present study was consistent with previous research results. Similarly, levels of inflammatory markers at

baseline were associated with MMSE and DSS tests at baseline and after 3 years, whereas they were not associated with changes during follow up. Also, IL-6 levels at baseline were

correlated with changes in MMSE and DSS tests, in accordance with the findings of previous studies²². However, such significant correlations disappeared after adjusting for confounders, including renal markers. Thus, it still remains unclear whether inflammatory markers are an independent predictor for cognitive decline, and further large-scale studies are expected to clarify this.

There were several limitations to the present study. It was a small-scale hospital-based study, and cognitive impairment as a result of vascular dementia was indistinguishable from that as a result of Alzheimer's disease, and the effect of this cannot be ignored.

In conclusion, the present study showed a reciprocal relationship between cognitive decline and renal impairment, especially the progression of albuminuria. Thus, early and effective treatment that prevents the development of renal impairment will be important for preserving both renal and cognitive function. Monitoring treatment using renal biomarkers is expected to maintain a good quality of life for elderly diabetic patients.

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