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High-sensitivity C-reactive protein is associated with hippocampus volume in nondementia patients with type 2 diabetes mellitus

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Abstract

The elevated level of high-sensitivity C-reactive protein (HSCRP) is associated with cognitive dysfunction, for which changes in the hippocampus plausibly play a pivotal role. We tested the hypothesis that an elevated level of HSCRP correlates with hippocampus volume and insulin resistance in nondementia patients with type 2 diabetes mellitus. Subjects included 45 nondementia patients with type 2 diabetes mellitus, who were divided into 2 groups: high-HSCRP group (age, 65 ± 6 years [mean ± SD]; n = 17) and normal-HSCRP group (65 ± 7 years, n = 28). Hippocampus volume has been quantitated with computer-assisted analysis using a magnetic resonance imaging voxel-based specific regional analysis system developed for the study of Alzheimer disease (VSRAD), which yields a *z* score as the end point for assessment of hippocampal volume. The *z* score was higher in the high-HSCRP group than in the normal-HSCRP group ($P < .0001$). The fasting plasma glucose ($P < .05$) and insulin concentrations ($P < .0001$) and the homeostasis model assessment (HOMA) index ($P < .0001$) were higher in the high-HSCRP group than in the normal-HSCRP group. Multiple regression analysis showed that HSCRP levels were independently predicted by *z* score and HOMA index. Our results indicate that the elevated level of HSCRP in Japanese nondementia patients with type 2 diabetes mellitus is characterized by increased hippocampus volume and insulin resistance, and that the *z* score and HOMA index are independent predictors of HSCRP.

1. Introduction

Type 2 diabetes mellitus (DM) increases the risk of stroke [1] and vascular dementia [2]. The pathogenesis of type 2 DM is mainly characterized by insulin resistance [3], which is itself associated with memory impairment [4]. In addition to manifesting subclinical cognition changes, patients with DM were found to have increased risk of the most common form of dementia, Alzheimer disease (AD) [5,6].

High-sensitivity C-reactive protein (HSCRP) is a known sensitive marker of systemic low-grade inflammation [7]; and increased serum concentrations of HSCRP have been associated with poor memory [8], poor global cognitive performance [9], as well as vascular dementia [10].

Given that the hippocampus plays a pivotal role in specific aspects of memory and learning, declining cognitive performance in association with obesity might plausibly be linked to changes in hippocampus volume [11,12]. Among community-living healthy older people, the hippocampal volume normally declines with age [13,14]. The changes are nonetheless important because preclinical cognitive impairments correlate with smaller hippocampal size [15,16]. Recently, hippocampus volume has been quantitated with computer-assisted analysis using a magnetic resonance imaging (MRI) voxel-based specific regional analysis system developed for the study of AD (VSRAD), which yields a *z* score as an indicator of the extent of hippocampal volume [17].

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In this study, we hypothesized that increased level of HSCRP is associated with hippocampus volume and insulin resistance in type 2 DM patients. To test our hypothesis, we compared the presence of hippocampus volume in addition to the metabolic profiles of nondemented Japanese patients with diagnosis of type 2 DM, who were stratified into groups with normal or high HSCRP scores, so as to identify the independent predictors of HSCRP.

2. Subjects and methods

We screened 91 subjects seen in the Department of Endocrinology of Oita Red Cross Hospital between the period of December 2008 and August 2009 for the treatment of type 2 DM detected on medical examination. Of these, 45 patients (26 men and 19 women), with ages ranging from 51 to 74 years (mean SD age of 65 ± 7 years), fulfilled the inclusion criteria and were enrolled in the present study. The inclusion criteria were as follows:

1. Organic heart disease was not present as determined by treadmill exercise electrocardiography. We excluded the subjects who exhibited abnormal ST-T wave changes by treadmill exercise electrocardiography.
2. Absence of causes of secondary hypertension (ie, primary aldosteronism, renovascular hypertension, hyperthyroidism, and pheochromocytoma).
3. No history of chronic diseases, such as renal failure, pulmonary disease, liver dysfunction, arteriosclerotic obliterans, sleep apnea syndrome, and symptomatic cerebrovascular disease, was noted.
4. Patients were not currently receiving treatment with insulin therapy.
5. Mini-Mental State Examination (MMSE) score less than or equal to 24 (indicative of cognitive dysfunction)

Of the 91 screened patients, 46 were excluded from further evaluation because of the violation of the inclusion criteria. The excluded subjected included 16 patients under treatment with insulin, 6 with angina pectoris, 5 with renal failure, 4 with sleep apnea syndrome, 3 with symptomatic cerebrovascular disease, 3 with secondary hypertension (1 primary aldosteronism, 1 renovascular hypertension, 1 hyperthyroidism), 2 with arteriosclerotic obliterans, 2 with MMSE score less than or equal to 24 (1 patient with score of 23 and 1 patient with score of 22), 2 with inflammatory diseases (2 with rheumatoid arthritis), 2 with liver dysfunction, and 1 with lung disease. Therefore, only 45 patients were selected for the study.

All subjects gave their written informed consent to participate in the study; and the study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

2.1. Patients and methods

The clinical characteristics of the patients in the high-HSCRP group and normal-HSCRP group are summarized in Table 1. Eleven of the 17 patients in the high-HSCRP group and 16 of the 28 patients in the normal-HSCRP group met the criteria for essential hypertension. All of these patients were being treated with calcium channel antagonists, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers with diuretics. *Dyslipidemia* was defined as fasting triglycerides levels of at least 200 mg/dL or high-density lipoprotein cholesterol (HDL-C) concentration less than 45 mg/dL for women and less than 35 mg/dL for men [18].

2.2. Definition of hypertension

Hypertension was defined by measurement of arterial blood pressure (BP) as the average of 3 measurements obtained with a mercury-column sphygmomanometer after 10 minutes of physical resting by the patients. *Essential*

Table 1
Clinical characteristics of studied patients

	Normal-HSCRP group	High-HSCRP group	*P* value
Age (y)	65 ± 7	65 ± 6	NS
Sex (men/women)	16/12	10/7	NS
HSCRP (mg/L)	1.6 ± 1.0	6.6 ± 1.6	<.0001
Duration of diabetes (y)	10.8 ± 4.1	11.5 ± 4.9	NS
Hypertension (%)	64	65	NS
Duration of hypertension	5.8 ± 3.2	6.2 ± 4.3	NS
Dyslipidemia (%)	39	41	NS
Smoking habits (%)	25	29	NS
Drug use (%)			
Sulfonylurea	36	35	NS
α-Glucosidase inhibitors	29	29	NS
Pioglitazone	25	24	NS
Statin	32	35	NS
Calcium channel antagonists	39	41	NS
ACE inhibitors	25	24	NS
Angiotensin receptor blocker	36	41	NS
BMI (kg/m^2)	24.6 ± 2.1	26.5 ± 1.8	.0014
Waist circumferences (cm)	84.6 ± 8.9	91.5 ± 9.8	.0194
Systolic BP (mm Hg)	130 ± 10	134 ± 8	NS
Diastolic BP (mm Hg)	78 ± 8	79 ± 7	NS
Heart rate (beat/min)	68 ± 6	70 ± 7	NS
Total cholesterol (mg/dL)	199 ± 29	209 ± 34	NS
Triglyceride (mg/dL)	124 ± 36	155 ± 28	.0028
HDL-C (mg/dL)	49 ± 9	42 ± 8	.0099
LDL-C (mg/dl)	126 ± 33	137 ± 27	NS
FPG (mg/dL)	138 ± 22	152 ± 29	.0112
F-IRI (μU/mL)	6.2 ± 1.5	8.7 ± 2.1	<.0001
HOMA index	2.1 ± 0.6	3.3 ± 0.9	<.0001
Hemoglobin A_{1c} (%)	7.5 ± 1.1	7.6 ± 0.9	NS
Uric acid (mg/dL)	6.0 ± 1.3	7.0 ± 1.1	.0235
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	NS

Data are presented as means ± SD. ACE indicates angiotensin-converting enzyme; NS, not significant.

hypertension was defined as diastolic BP of at least 90 mm Hg, systolic BP of at least 140 mm Hg, or self-reported use of antihypertensive medication [19].

2.3. Laboratory methods

Blood was extracted from the antecubital vein with the patient in the recumbent position at 7:00 AM after an overnight fast. All patients underwent routine laboratory tests, including assays for serum electrolytes, serum total cholesterol, serum triglycerides, serum HDL-C, serum low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), and fasting immunoreactive insulin (F-IRI). The LDL-C concentration in serum was determined by the Friedewald formula [20] based on the concentrations of total cholesterol, triglycerides, and HDL-C. Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index, as follows: (fasting plasma insulin [in microunits per milliliter] × FPG [in millimoles per liter])/22.5 [21]. High-sensitivity assays for CRP were performed according to previously described methods (Dade Behring, Tokyo, Japan) [22]. Based on the level of HSCRP, the subjects were divided into 2 groups: HSCRP greater than 3.0 to 10.0 mg/L (high-HSCRP group) and HSCRP less than or equal to 3.0 mg/L (low-HSCRP group) [7]. Patients who exhibited high HSCRP levels (ie, >10.0 mg/L) were excluded from this study [23].

2.4. Cognitive performance

Cognitive function was measured using the MMSE [24]. The MMSE is a 23-item global cognitive function test that includes questions on orientation in time and place, attention, language, memory, and visual construction. The test was originally designed as a screening instrument for cognitive impairment and dementia, and is widely used in both clinical practice and scientific studies. The score ranges from 0 to 30, and the cutoff of 27 suggests mild cognition impairment.

2.5. Brain MRI

All brain MRI studies were performed on a 1.5-T system. Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence at 11.4/4.4/1 (repetition time/echo time/excitation) produced a gapless series of contiguous, thin sagittal sections with the following parameters: flip angle, 15°; acquisition matrix, 256 × 256; field of view, 31.5 cm; section thickness, 1.23 mm.

2.6. Voxel-based MRI analysis

The automated method of voxel-based morphometry (VBM) [25] objectively maps loss of gray matter on a voxel-by-voxel basis after an anatomical normalization procedure analogous to that used in functional neuroimaging. The advantage of VBM over analyses based on a region of interest is that VBM produces an unbiased result from exploration of the whole brain. The acquired MRI were reformatted to gapless 2-mm–thick transaxial images. Images were analyzed using Statistical Parametric Mapping (SPM2) (Wellcome Department of Imaging Neuroscience, London, United Kingdom) running on MATLAB (The Math Works, Sherborn, MA). The SPM2 analysis demonstrated significant declines of gray matter concentrations of patients only in the bilateral parahippocampal areas [17]. The VBM method has been further developed for automated diagnosis of very early AD, which came to be designed as the VSRAD [17].

The acquired brain MRIs were resampled to gapless thin-slice transaxial images. Images were analyzed using statistical parametric mapping program, such that each image volume was coregistered to the standard template MRIs in the common coordinate system of MNI T1 MRIs template [25,26].

Three-dimensional images were used so as to correct for differences in brain size and shape and facilitate intersubject averaging. In the first anatomical standardization, only the affine transformation was used. The normalized MRIs were then segmented into gray matter, white matter, cerebrospinal fluid, and other compartments using a modified version of clustering algorithm, the maximum likelihood "mixture model" algorithm. The segmentation procedure involved calculation for each voxel a Bayesian probability of belonging to each tissue class based on a priori MRI information with a nonuniformity correction. The segmented gray matter images were then subjected to an affine and nonlinear anatomical standardization using a template of a priori gray matter. The anatomically standardized gray matter images were smoothed with an isotropic Gaussian kernel 12 mm in full width at half maximum to exploit the partial volume effects so as to create a spectrum of gray matter intensities. The gray matter intensities are equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensities can therefore be taken as equivalent to gray matter concentration [25]. VSRAD running on Windows XP compares the gray matter image of an individual patient to the mean and SD of gray matter images of the 41 healthy subjects using voxel-by-voxel z score analysis after voxel normalization to global mean intensities in the same manner as we implemented in the easy z score imaging system (eZIS). Each group of aged-matched healthy subjects was selected for each group of patients in this study. The control subjects did not have DM, showed no clinical evidence of cognitive deficits or neurologic disease, and were not taking short- or long-term drug therapy at the time of the imaging examinations. They had no abnormal findings on MR images, disregarding age-related atrophy and white matter change on T2-weighted images. Each gray matter image of the patients was compared with the mean and SD of gray matter images of the 41 healthy subjects using voxel-by-voxel z score analysis after voxel normalization to global mean intensities; z score = (control mean − individual value)/(control SD) [17]. These z score maps were displayed by overlay on tomographic sections. VSRAD can automa-

tically analyze 3-dimensional T1-weighted MRI data as a series of segmentation, anatomical standardization, and smoothing using SPM2 without a Matlab program and yields a *z* score analysis of the bilateral temporal areas.

This program registered the SPM {*t*} results for significant decline of gray matter concentrations in patients determined by group comparison in the first group as a specific region of interest. Using the average value of positive *z* scores in the specific region of interest in a *z* score map as the threshold, receiver operating characteristic (ROC) curves were determined using the ROCKIT 0.9β and the PlotROC programs developed by Metz et al [27]. The programs calculate the area under the ROC curves (Az), accuracy, sensitivity, and specificity. Accuracy was determined as the value at the point where the sensitivity is the same as the specificity on the ROC curve. Hirata et al [17] demonstrated the automated voxel-based analysis using a *z* score value in the bilateral medial temporal areas including the entorhinal cortex after anatomical standardization of gray matter images. The programs calculate the area under the ROC curves; and accuracy were 0.949 (95% confidence interval, 0.880-0.982) and 87.8%, respectively. Details of the procedures have been described previously [28].

2.7. Statistical analysis

Data were presented as mean ± SD. Differences between the 2 groups were analyzed by the unpaired Student *t* test, χ^2 test, or Fisher exact probability test.

A *P* value of < .05 was considered statistically significant. Simple (Spearman rank) correlation coefficients between HSCRP and various parameters were calculated. Stepwise multiple regression analyses were calculated. We evaluated the association between the levels of HSCRP and other factors, including the *z* score, body mass index (BMI), triglyceride levels, HDL-C levels, uric acid levels, FPG concentrations, plasma insulin concentrations, and HOMA index values. In our multivariate analysis, F values of at least 4 were considered significant.

3. Results

As shown in Table 1, the mean ages of the type 2 DM patients in the high- and normal-HSCRP groups were similar; and there were no significant differences between the groups with respect to sex, duration of diabetes, duration of hypertension, smoking habits, or administered medications. The BMI and waist circumferences were higher in the high-HSCRP group than in the normal-HSCRP group.

The resting heart rate and systolic and diastolic BPs were not significantly different between the 2 groups.

With regard to lipid metabolism, FPG and insulin concentrations and HOMA index values were higher in the high-HSCRP group than in the normal-HSCRP group. However, there was no significant difference in hemoglobin A_{1c} between the 2 groups. The concentration of serum triglyceride was higher, whereas that of serum HDL-C was lower, in the high-HSCRP group than in the normal-HSCRP group. Serum total cholesterol level was not significantly different between the groups. The concentration of uric acid was higher in the high-HSCRP group than in the normal-HSCRP group. Parameters for the assessment of renal function, including serum creatinine concentration, were similar between the 2 groups.

Fig. 1 shows the cognitive performance based on the MMSE score, which was not significantly different between

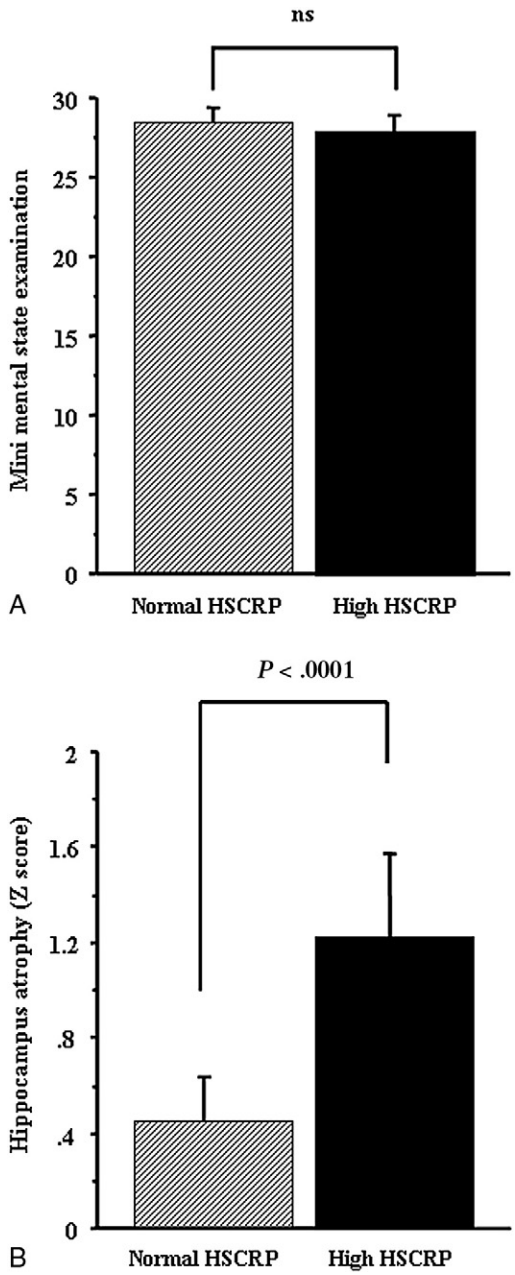

Fig. 1. A, Comparison of MMSE between type 2 DM patients with normal HSCRP and with high HSCRP. B, Comparison of hippocampus volume (*z* score) between type 2 DM patients with normal HSCRP and with high HSCRP. Data are presented as mean ± SD.

the 2 groups (high-HSCRP group, 27.8 ± 1.4; normal-HSCRP group, 28.2 ± 1.1; P = not significant; Fig. 1A). However, hippocampus volume (z score) was higher in the high-HSCRP group than in the normal-HSCRP group (1.221 ± 0.352 vs 0.479 ± 0.228, $P < .0001$, Fig. 1B).

Table 2 depicts the correlation between the HSCRP level and age, BMI, and other variables in both groups. The HSCRP levels were positively correlated with the BMI values, triglyceride, FPG, fasting plasma insulin concentration, uric acid levels, HOMA index values, and z score. The HSCRP levels were negatively correlated with the HDL-C.

Multiple regression analysis was performed using the stepwise procedure (Table 3). The level of HSCRP was independently predicted by z score (F value = 8.124) and HOMA index (F value = 8.292).

Table 2
Correlations between HSCRP and various parameters

Parameters	Univariate analysis	
	R	P value
Age	0.109	.4750
Duration of DM	0.162	.2867
BMI	0.387	.0086
Waist circumferences	0.425	.0036
Systolic BP	0.161	.2950
Diastolic BP	0.196	.2018
Heart rate	0.171	.2666
Total cholesterol	0.240	.1127
Triglyceride	0.435	.0029
HDL-C	-0.399	.0066
LDL-C	0.246	.1028
Uric acid	0.348	.0191
FPG	0.359	.0155
F-IRI	0.617	<.0001
HOMA index	0.685	<.0001
Hemoglobin A_{1c}	0.082	.5903
Creatinine	0.168	.2702
MMSE	-0.259	.0861
Hippocampus atrophy (z score)	0.671	<.0001

Table 3
Stepwise regression analysis between HSCRP and other parameters

Independent variable	Regression coefficient	Standard error	Standard regression coefficient	F value
To HSCRP intercept	−1.446			
Hippocampus volume (z score)	2.364	0.829	0.403	8.124
HOMA index	1.263	0.439	0.407	8.292

4. Discussion

In the present study, type 2 DM patients with elevated HSCRP manifested hippocampus volume as evaluated by the z score. Among the metabolic parameters that we investigated, fasting plasma concentrations of glucose and insulin and the HOMA index were higher in patients with high HSCRP than in those with normal HSCRP. In addition, multiple regression analysis revealed that the levels of HSCRP could be independently predicted by the HOMA index values and z score in Japanese nondementia patients with type 2 DM.

Recent studies have demonstrated a close relationship between elevated CRP and insulin resistance [29,30]. Yudkin et al [29] reported that low but relatively elevated CRP in healthy subjects is related to insulin resistance when assessed by BMI, HOMA index, BP, HDL-C, and triglyceride, and that increased proinflammatory cytokines, interleukin-6 and tumor necrosis factor–α (TNF-α), play an important role in the low level of chronic inflammatory state. Subsequently, by analyzing the nondiabetic population of the Insulin Resistance Atherosclerosis Study [31], Festa et al [30] also reported that the level of CRP correlated with BMI, insulin sensitivity (assessed by intravenous glucose tolerance test), and fasting plasma levels of insulin and proinsulin. They suggested that CRP is not only a predictor of cardiovascular events but also an independent predictor of insulin sensitivity. In the present study, consistently, the level of HSCRP correlated with BMI, HDL-C, fasting plasma insulin concentration, and HOMA index. Being different from those 2 prior studies [29,30], our study enrolled type 2 DM patients who did not receive insulin treatment.

Although the specific mechanism that links the HSCRP level and insulin resistance remains to be elucidated, several mechanisms could explain our observations. Arner [32] has suggested that the flux of lipids from the visceral fat depot to liver might account for hepatic insulin resistance. In a canine model, development of insulin resistance occurred concomitantly with visceral adiposity when animals were fed a diet of normal caloric intake, but modestly increased fat content [33]. Another possible mechanism is the contribution of adipocyte-associated bioactive substance such as TNF-α, adiponectin, and resistin. The TNF-α level is essentially dependent on HSCRP [34] and inversely correlated with insulin sensitivity in obese type 2 DM patients [35]. In contrast, adiponectin decreases as HSCRP increases [36], such that hypoadiponectinemia in patients with increased HSCRP is closely related to insulin resistance and hyperinsulinemia [37]. Gene and protein expression of the polypeptide resistin, which is originally defined as a factor linking obesity and insulin resistance, is increased in abdominal fat [38]. Plasma resistin levels have been reported to be markedly elevated in obese mice and to be decreased by insulin sensitizers, such as thiazolidinediones [39].

There are several reports on the relationship between HSCRP and poor memory [8] and poor global cognitive performance [9]. Teunissen et al [8] reported that CRP levels are significantly associated with performance in the Word Learning Test of a healthy population over the 6-year follow-up period. Prospective study on nondemented elderly people described that CRP levels are associated with cognitive decline as evaluated by MMSE among well-functioning African American and white population [9]. However, in these reports, cognitive performance was evaluated with

MMSE; they did not measure hippocampal atrophy. Furthermore, in the present study, hippocampus volume was evaluated by a computer-assisted analysis using VSRAD, an automated MRI-based analysis. Cognitive performance in our study was assessed with the use of MMSE [24]. Recently, hippocampus volume has been evaluated by VSRAD, which yields a *z* score as an indicator index of the extent of hippocampal volume [17]. In our subjects, MMSE score was not significantly different between the 2 groups; but the *z* score for hippocampal volume was higher in the high-HSCRP group than in the normal-HSCRP group.

Although the specific mechanism that links the HSCRP level and hippocampus volume remains to be elucidated, several mechanisms could explain our observations. First, CRP may contribute to atherosclerotic processes [40] and can increase the expression of adhesion molecules such as vascular cell adhesion molecules and intercellular adhesion molecules in vascular endothelial cells [40,41], including endothelial cells in human brain [42]. Second, among the possible causal mechanisms, the insulin receptor is expressed in discrete neuronal population in the central nervous system, including the hippocampus [43], where it is proposed to participate in cognitive function [44]. Insulin improves cognition even in nondiabetic humans and in experimental animals in a variety of paradigms [45]. In addition, the acquisition of a spatial learning task, namely, the Morris mater maze, increases insulin receptor expression and signaling in brain [46]. Physiologically relevant increases in plasma insulin levels also stimulate the translation of the insulin-sensitive glucose transporter GLUT4 to the plasma membrane in the rat hippocampus [47]. These data support the hypothesis that activation of insulin receptor signaling cascades in brain improves cognitive/behavior performance. Furthermore, insulin resistance is a potentially modifiable risk factor for cognitive decline and dementia [48].

Taken together, it is possible that interactions between the HSCRP, hippocampus atrophy, and insulin resistance interact and reinforce each other through mechanisms that may be associated with endothelial dysfunction.

This is the first reported that he nondementia with type 2 DM patients in the high-HSCRP group had hippocampus volume was evaluated by *z* score and insulin resistance than those in the normal-HSCRP group.

There are several limitations to this study. First, the present study had a relatively small study population and was cross-sectional in design. In this respect, that is HSCRP, hippocampus atrophy and insulin resistance without direct mechanism to link them together. And a prospective protocol makes more sentences. Second, a previous study has revealed the relationship between type 2 DM and cognitive impairment [48]. This implies that further clinical investigations are needed to examine the relationship between type 2 DM and dementia. Third, 65% of our high-HSCRP group and 64% of our normal-HSCRP group, respectively, had been diagnosed earlier with essential hypertension; and all of these patients were being treated with antihypertensive drugs before enrolment. In this regard, several antihypertensive drug classes have been reported to improve insulin sensitivity [49,50]; and these medications may have influenced the results. Finally, it is uncertain if *z* score can be directly translated into a measure of hippocampus volume without explicit anatomical segmentation of the MR images in the present study. Consequently, further clinical investigations are needed to determine the relationship between HSCRP, metabolic parameters, and hippocampus volume in type 2 DM.

In conclusion, our findings suggest that higher levels of HSCRP are associated with hippocampus volume and insulin resistance. Hippocampus volume and insulin resistance were independent predictors of HSCRP in a small cohort of Japanese nondementia patients with type 2 DM. In the future, large cohort studies including other populations may be beneficial for elucidating these relationships.

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