

# Association of Vascular Risk Factors With Hippocampal Atrophy and Cognitive Impairment

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Vascular risk factors including type 2 diabetes and hypertension play an important role on brain structural changes and cognitive impairment. However, it remains unclear whether risk factors increase the risk of cognitive decline through ischemic vascular change or degenerative neuropathology. We investigated the relationship between vascular or degenerative change of the brain, vascular risk factors and cognitive impairment. Seven-hundred and eighty-four volunteers took medical examination including brain imaging and neuropsychological tests for general intelligence, frontal lobe function, visuospatial function and affective function. Hippocampal volume and asymptomatic ischemic lesions were assessed on magnetic resonance imaging. Type 2 diabetes was associated with lower scores on frontal and visuospatial function tests and hippocampal atrophy which was related to decline of frontal and visuospatial function. However, type 2 diabetes did not contribute to ischemic vascular pathology. Hypertension was associated with ischemic white matter changes in addition to hippocampal atrophy, but the direct association with cognitive impairment is not significant. Thus, type 2 diabetes may cause reduction of fronto-parietal executive function through degenerative neuropathology, independent of ischemic vascular pathology.

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Key words: hippocampal atrophy, cognitive impairment, type 2 diabetes, hypertension, deep and subcortical white matter hyperintensity

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## INTRODUCTION

It is reported that aging and lifestyle-related disease are independently associated with increased risk of cognitive impairment [1, 2]. This association is important because therapeutic intervention in treatable diseases can prevent the development of dementia. A prospective study has shown that elderly diabetic patients were at a greater risk for developing dementia than non-diabetic subjects [3]. We have reported that patients with type 2 diabetes showed reduced volume of the hippocampus and the degree of atrophy was associated with decreased score of general cognitive function test (i.e. Mini-Mental State Examination (MMSE)) [4]. Hypertension has been reported to be a risk of dementia [2, 5]. Hypertension alters the structure of cerebral blood vessels and disrupts intricate vasoregulatory mechanisms that assure an adequate blood supply to the brain. These alterations threaten the cerebral blood supply and increase the susceptibility of the brain to ischemic injury as well as Alzheimer's disease (AD) [6]. Thus, both type 2 diabetes and hypertension could cause brain damage through large or small vasculopathy or/and neurodegenerative process. However, it is unclear how each vascular risk factor affects the pathophysiology of cognitive decline associated with lifestyle-related diseases.

Neuroimaging studies demonstrate the impact of vascular risk factors on brain structures [7]. Both infarct and white matter hyperintensity, as well as brain atrophy, appear to contribute to cognitive impairment [8]. Although type 2 diabetes and hypertension might be associated with both atrophy and cerebrovascular disease, it is not clear whether atrophy or cerebrovascular lesions form the link between life-style diseases and cognitive impairment.

This study aimed to clarify whether vascular risk

factors including type 2 diabetes and hypertension affect brain structural changes and cognitive impairment, and whether asymptomatic ischemic lesions also contribute to cognitive impairment in volunteers free from neuropsychiatric diseases.

## MATERIALS AND METHODS

### *Subjects*

Seven-hundred and eighty-four elderly volunteers (440 males and 344 females, mean age 61.9 years, range 32-90 years). They voluntarily participated in a medical examination of the brain at the Health Science Center in Shimane. The inclusion criteria were as follows: no history of neurological or psychiatric disorders including stroke and dementia, no abnormalities on neurological examination, and the provision of informed consent to participate in this study. The participants underwent medical check, laboratory test, neuropsychological test, and magnetic resonance imaging (MRI). The study design was approved by the institutional ethics committee of Shimane University Hospital.

### *Clinical background*

Clinical information included age, sex, history of type 2 diabetes (defined as a fasting blood glucose level  $\geq 126$  mg/dL, HbA1c  $\geq 6.5\%$ , or a history of treatment for diabetes), history of hypertension (defined by the use of an antihypertensive agent, systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg), and history of dyslipidemia (defined as a low-density lipoprotein cholesterol level  $\geq 140$  mg/dL, triglyceride level  $\geq 150$  mg/dL, high-density lipoprotein cholesterol level  $< 40$  mg/dL, or a history of treatment with lipid-lowering medication). A smoker was defined as any subject whose smoking index exceeded 200. Regular alcohol consumption was defined as more than 58 g of alcohol consumed per day.

### *Neuropsychological test*

All participants were assessed using a neuropsychological test battery that included the MMSE for general cognitive function including orientation, registration, attention, recall, and language, the Frontal Assessment Battery (FAB) for frontal lobe func-

tion [9], the Kohs' block test [10] for visuospatial function, the Self-rating Depression Scale (SDS) [11], and the Apathy Scale (AS) [12].

### *Neuroimaging study*

MRI examinations were performed, using a 1.5-Tesla MRI (Symphony Ultra Gradient, Siemens). The entire head of each patient was scanned using T2-weighted images (T2WI; TR = 4500 ms, TE = 86 ms) and FLAIR images (TR = 8000 ms, TE = 92 ms) in the transverse plane with a slice thickness of 7 mm. In addition, T1-weighted images (T1WI) of the entire brain were measured for the voxel-based morphometry (VBM) (192 sagittal slices, repetition time = 2170 ms, echo time = 3.93 ms, inversion time = 1100 ms, flip angle =  $15^\circ$ , matrix size =  $256 \times 256$ , field of view =  $256 \times 256$  mm<sup>2</sup>, isotropic spatial resolution = 1 mm).

The volume of hippocampus was quantified with an Statistical Parametric Mapping (SPM)2-based VBM analysis procedure [13]. The software for the measurement is distributed under the name as voxel-based specific regional analysis system of Alzheimer's disease (VSRAD). VSRAD automatically calculated Z value, which reflects the severity of gray matter loss in the hippocampal region of an individual subject by comparing it with the original normal database template. The index of hippocampal region atrophy was defined as a mean value of a positive Z score in a region of interest at bilateral hippocampal regions. We defined hippocampal atrophy ranged from grades 1 to 3; grade 1 for Z value between 0.0 and 1.0, grade 2 for Z value between 1.0 and 2.0, and grade 3 for Z value more than 2.0. In a clinical setting, grade 1 means no atrophy, grade 2 is interpreted as slight atrophy, grade 3 is indicative of significant atrophy.

We evaluated silent brain infarction (SBI), periventricular hyperintensity (PVH), deep and subcortical white matter hyperintensity (DSWMH) as asymptomatic ischemic lesions. SBI was defined as a focally hyperintense lesion  $> 3$  mm and  $< 15$  mm in diameter on T2WI, corresponding to a hypointense lesion on T1WI. PVH and DSWMH were evaluated separately, because PVH is found adjacent to the ventricles, whereas DSWMH is found away from them. PVH was graded using a scale from 0

to 4 [14], and we defined grades 3 and 4 as positive PVH. DSWMHs were graded using a scale from 0 to 3 according to the Fazekas' grading scale [15], and we defined grades 2 and 3 as positive DSWMH.

### Statistical analysis

A general linear model was used for the analysis of influence of vascular risk factors and MRI changes on cognitive impairment and relationship between vascular risk factors and MRI changes. Because age and sex have potentially influences on all biological measures including vascular risk factors, cognitive impairment, and MRI changes, we entered age and sex as covariates for all analyses. A level of  $p < .05$  was accepted as statistically significant. Statistical analysis was performed with the SPSS software package (version 22, IBM Co.).

## RESULTS

Clinical backgrounds of the participants are shown in Table 1, which includes vascular risk factors, neuropsychological test scores and MRI data. Vascular risk factors are overlapping. We studied the influence of vascular risk factors on cognitive impairment using a generalized linear model with type 2 diabetes, hypertension, dyslipidemia, smoking and alcohol habit as explanatory variables, and age and sex as covariates (Table 2). Type 2 diabetes was significantly associated with lower scores on FAB (Wald chi-square = 12.4,  $p < .001$ ) and Kohs' block test (Wald chi-square = 8.36,  $p < .01$ ), but MMSE, SDS and AS scores were not affected by type 2 diabetes. On the other hand, hypertension and dyslipidemia did not affect any neuropsychological test scores. Even after smoking and alcohol

Table 1. Clinical background

Vascular risk factors	
Type 2 diabetes	10.7%
Hypertension	54.4%
Dyslipidemia	47.1%
Smoking	38.5%
Alcohol habit	16.3%
Neuropsychological test score (mean $\pm$ SD)	
Mini-mental state examination	28.0 $\pm$ 2.1
Frontal assessment battery	16.0 $\pm$ 1.8
Kohs' block test	100.8 $\pm$ 19.0
Self-rating depression scale	34.5 $\pm$ 7.6
Apathy scale	10.9 $\pm$ 5.5
MRI findings	
Hippocampal atrophy (grade 1 / 2 / 3)	56.3% / 34.6% / 9.2%
Silent brain infarction (positive rate)	20.4%
Periventricular hyperintensity (grade $\geq$ 3)	5.2%
DSWMH (grade $\geq$ 2)	13.1%

DSWMH = deep and subcortical white matter hyperintensity

Table 2. The effects of vascular risk factors on cognitive function test scores

	MMSE		FAB		Kohs' block test		SDS		AS	
	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI
Type 2 diabetes	.76	-7.11~.27	12.4**	-1.27~-1.36	8.36*	-10.9~-2.1	1.29	2.83~.75	.28	-1.64~.94
Hypertension	1.27	-.48~.13	.01	-.26~.28	.35	-3.49~1.87	2.66	.19~2.0	2.68	.13~1.44
Dyslipidemia	.37	-.21~.40	.12	-.32~.22	.65	-1.57~3.77	.24	-.82~1.36	.10	-.39~1.18

All data are controlled for age and sex \*  $p < .01$ , \*\*  $p < .001$

MMSE = mini-mental state examination, FAB = frontal assessment battery, SDS = self-rating depression scale, AS = apathy scale, CI = confidence interval

Table 3. The influence of vascular risk factors on brain structural changes

	HA (grade 1 vs. grade 3)		SBI		PVH		DSWMH	
	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI
Type 2 diabetes	6.69**	.23~1.66	.41	-.37~.74	.12	-1.26~.88	.06	-.58~.75
Hypertension	5.35*	.10~1.17	3.80	-.002~.72	9.06**	.48~1.93	12.8†	.38~1.29
Dyslipidemia	1.00	-.78~.25	.18	-.44~.26	.05	-.72~.57	.48	-.58~.28

All data are controlled for age \*  $p < .05$ , \*\*  $p < .01$ , †  $p < .001$

HA = hippocampal atrophy, SBI = silent brain infarction, PVH = periventricular hyperintensity, DSWMH = deep and subcortical white matter hyperintensity, CI = confidence interval

Table 4. The relationship between brain structural changes and cognitive function test scores

	MMSE		FAB		Kohs' block test		SDS		AS	
	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI	Wald chi-square	95% CI
HA (grade 1 vs. grade 3)	3.46	-.03~1.01	43.5**	-1.94~-1.05	22.3**	-15.5~-6.40	.02	-1.78~2.02	.70	-.82~2.03
SBI	5.67*	.10~1.04	.84	-.59~.21	9.20**	-10.6~-2.28	1.35	-2.75~.70	.00	-1.3~1.29
PVH	.95	-1.56~.52	.06	-.92~.72	.01	-9.13~8.44	3.40	-.21~7.03	.66	-1.60~3.87
DSWMH	.30	-.69~.50	.98	-.24~.72	.23	-6.33~3.85	4.26*	-4.34~.11	1.89	-2.69~.47

All data are controlled for age \*  $p < .05$ , \*\*  $p < .01$

MMSE = mini-mental state examination, FAB = frontal assessment battery, SDS = self-rating depression scale, AS = apathy scale, HA = hippocampal atrophy, SBI = silent brain infarction, PVH = periventricular hyperintensity, DSWMH = deep and subcortical white matter hyperintensity, CI = confidence interval

habit were included in the model, the results were not changed (data not shown).

The relationship between vascular risk factors and brain structural changes was analyzed with binomial regression analysis including age and sex as covariates (Table 3). We found that type 2 diabetes and hypertension had significant contributions to hippocampal atrophy when groups 1 and 3 for hippocampus were compared (Wald chi-square = 6.69,  $p < .01$  for diabetes, and Wald chi-square = 5.35,  $p < .05$  for hypertension). Dyslipidemia did not affect the prevalence of hippocampal atrophy. Furthermore, we studied the relationship between asymptomatic ischemic lesions including SBI, PVH, and DSWMH and vascular risk factors. Hypertension had significant influences on asymptomatic ischemic lesions (Wald chi-square = 9.06,  $p < .01$  for PVH, and Wald chi-square = 12.8,  $p < .001$  for DSWMH, and Wald chi-square = 3.80,  $p = 0.051$  for SBI). This indicates that hypertension affects both hippocampal atrophy and asymptomatic ischemic lesions, whereas type 2 diabetes contributes exclusively to hippocampal atrophy.

Finally, we analyzed the association between brain structural changes and cognitive impairment (Table 4). Hippocampal atrophy was significantly related to low scores on FAB (Wald chi-square = 43.5,  $p < .001$ ) and Kohs' block test (Wald chi-square = 22.3,  $p < .001$ ), but not to MMSE score. Among asymptomatic ischemic brain lesions, SBI affected negatively to MMSE score (Wald chi-square = 5.67,  $p < .05$ ) and Kohs' block test score (Wald chi-square = 9.20,  $p < .01$ ), and DSWMH was associated with stronger depressive state (Wald chi-square = 4.26,  $p < .05$ ). Apathy score was not related to any brain structural changes.

## DISCUSSION

This cross sectional study of neurologically normal volunteers demonstrated that type 2 diabetes was associated with atrophic changes in the hippocampus, but not ischemic vascular changes, whereas hypertension was associated with both atrophic changes and ischemic vascular changes. Type 2 diabetes was associated with lower scores on the frontal lobe and visuospatial function tests, but not with test scores

involving memory or affective domains. In addition, the association of type 2 diabetes with frontal lobe and visuospatial dysfunction was correlated with degenerative pathology since strong relationship was observed between hippocampal atrophy and reduction in those cognitive test scores. Thus, this study supports the notion that hippocampal degenerative change rather than ischemic vascular changes might be the main pathology underlying cognitive impairment, independent of aging, in type 2 diabetic subjects [16].

Several community-based longitudinal studies have reported the association of type 2 diabetes with impairment in multiple domains of cognitive function [17, 18]. A recent study indicated that type 2 diabetes was associated with non-amnesic minimal cognitive impairment [19]. Our previous cross-sectional study also demonstrated that metabolic syndrome was an independent risk factor for impairment of executive functions [20]. Among the components of metabolic syndrome, elevated fasting glucose was the only independent risk factor associated with impairment of executive function [20]. The present study confirms and extends our previous findings in a different population. A large-scale cohort study also demonstrated that type 2 diabetes was significantly associated with lower scores on processing speed and executive functioning, but was not associated with memory function [8].

Our study suggests that type 2 diabetes might promote atrophy of the hippocampus. MRI studies investigating the impact of type 2 diabetes on brain structures have been conducted on people without dementia [7]. These studies demonstrated decreases in brain volume affecting both the white and grey matters in individuals with type 2 diabetes. Although our volumetric measurement did not cover brain areas other than the hippocampus, the medial temporal lobe seems particularly vulnerable to diabetes-related brain atrophy [4, 21]. Postmortem studies determined that insulin resistance in the hippocampus was an early and common feature in patients with AD, and that these impairments in insulin signaling correlated with impaired cognitive performances [22]. Studies using animal models also supported the notion that decrease in insulin receptor expression and/or activity might be common pathologic changes in

type 2 diabetes and AD [23]. Experimental models of type 2 diabetes exhibit evidence of AD-like pathology [23]. Tau phosphorylation and neuronal degeneration are increased in the hippocampus of mice selectively lacking insulin receptor expression in the brain [23]. These cumulative evidences support the hypothesis that hippocampal insulin resistance is a shared pathological feature between type 2 diabetes and AD.

The present study demonstrated that hypertension in addition to type 2 diabetes also contributed to the reduction of the hippocampal volume independently, although this effect was not as strong as that of type 2 diabetes. Rather, hypertension contributed to the ischemic vascular lesions in the brain such as PVH and DSWMH. It is well known that hypertension is a major risk factor for small vessel disease in the brain. Although SBI was associated with the reduction in MMSE and Kohs' test scores, the effect of hypertension to cognitive impairment seems to be ambiguous according to the direct regression analysis (Table 2).

Regarding the ischemic vascular changes, we did not find that type 2 diabetes contributed toward white matter hyperintensity. This is consistent with some [16, 24], but inconsistent with other studies [7, 25]. Long-standing diabetes and poor glycemic control were associated with severe leukoaraiosis [26]. Thus, the underlying mechanisms of cerebrovascular lesions associated with type 2 diabetes might depend on the severity and duration of type 2 diabetes, but did not investigate in this study. Our study suggests that ischemic vascular changes are not associated with diabetes-related cognitive impairments and that degenerative changes are a predominant pathway linking diabetes and cognition [16]. Thus, degenerative pathology rather than cerebrovascular lesions might play a key role in diabetes-related cognitive impairments.

Regarding the association of cognitive impairment with structural brain changes, only low scores on the frontal lobe dysfunction was associated with hippocampal atrophy. Recent brain network analyses have revealed that the medial temporal lobe is one of the core regions involved in the default mode network. This network also included the precuneus, posterior cingulate gyrus, and medial frontal lobe

[27]. It is conceivable that functional impairment of the hippocampus could cause decline in various cognitive functions, including frontal executive functions. The other possibility is that the frontal lobe is also involved in pathological changes in diabetic subjects. However, the frontal lobe was not included as an area of interest in this VBM analysis. Although there is less evidence for frontal lobe atrophy in diabetic subjects so far [16], future studies could reveal frontal structural and functional changes in type 2 diabetic subjects.

The major limitation of this study was its cross-sectional design, which made it difficult to determine the causative relationship between type 2 diabetes, hippocampal atrophy, and cognitive impairments. Longitudinal studies including brain imaging and neuropsychological assessment are needed to understand the mechanisms of the link between type 2 diabetes and cognitive impairments.

## CONCLUSIONS

Our study demonstrated that patients with type 2 diabetes showed reduction in frontal executive and visuospatial functions and this association was correlated with neurodegenerative processes but not ischemic vascular changes. Our study suggested that pharmacological intervention and life-style approaches might effectively prevent neurodegenerative processes and dementia in individuals with type 2 diabetes. This study also indicated the importance of monitoring brain morphological changes in the routine follow-up of type 2 diabetic patients, because both type 2 diabetes and AD are highly prevalent among the elderly.

## FUNDING

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