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Insulin Resistance and Cognitive Impairment in Non-Diabetic Patients

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Background: Type 2 diabetes mellitus (DM2) is associated with cognitive impairment. Peripheral insulin resistance is known to be the major contributor to the progression of hyperglycemia and DM. However, the relationship between insulin resistance (IR) and the risk of cognitive decline in non-diabetic patients is not clear so far. **Methods:** We analyzed 18 Alzheimer disease (AD) patients, 19 mild cognitive impairment (MCI) patients, and 24 cognitively healthy controls without diabetes. We examined their demographic characteristics, current and past illness and Mini-Mental State Examination (MMSE). We also examined insulin resistance index (Homeostasis Model Assessment of Insulin Resistance, HOMA-IR) as an indicator of IR and a factor associated with cognitive decline. **Results:** Levels of HOMA-IR were significantly different among the 3 groups (p<0.05) and HOMA-IR levels detected in the AD group were higher than those in the MCI and control groups. They were negatively correlated with the MMSE (p<0.01) and significantly connected with the cognitive decline subjects (r=-0.351, p<0.01). Multiple regression analysis revealed that the level of HOMA-IR was independently associated with cognitive decline (p<0.05). **Conclusions:** HOMA-IR levels were related to cognitive decline and these results suggest that HOMA-IR may be an important risk factor of dementia.

Key Words: *Insulin resistance, Dementia, Risk factor*

INTRODUCTION

Type 2 diabetes mellitus (DM2) is associated with mild to moderate decrement in cognitive function as well as with an increased risk of causing dementia. Since the pancreas cannot secrete enough insulin to overcome insulin resistance (IR) and prevent this events, peripheral insulin resistance is known to be the major contributor to the progression of hyperglycemia and DM2 [1-3]. Hyperinsulinemia without hyperglycemia is an indication of IR; it means a pre-diabetic stage. Peripheral hyperinsulinemia and IR causing higher insulin levels in the CNS can increase tau hyperphosphorylation and tangle formation; it leads to an increase Aβ oligomers. This consequently results in neuroinflammation and neurodegeneration [4-7].

Several studies showed those who have hyperinsulinemia without diabetes suffer more often from executive dysfunctions and slower psychomotor speed [5, 8]. However, these associations are not consistent and the relationship between IR and cognitive function in non-diabetic patients has not yet been elucidated.

The purpose of the present study is to examine the clinical correlation between IR and cognitive decline and to evaluate the predictive value of IR in non-diabetic patients with cognitive decline.

MATERIALS AND METHODS

Patients with Alzheimer's disease (AD, n=18) and mild cognitive impairment (MCI, n=19) were recruited. Neuropsychological testing, detailed structured interviews, and

clinical examinations were performed. All patients underwent neuroradiological testing together with the usual battery of blood screening tests to exclude treatable causes or other causes of dementia. The severity of dementia was assessed by the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR). MCI diagnoses were made in accordance with the Peterson et al. [9] criteria and probable AD diagnoses met the NINDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) criteria [10, 11]. Cognitively healthy controls (n=24) were consecutively recruited from individuals who attended a health screening in the outpatient clinics of participating institutions. The controls were also tested with the MMSE to exclude unknown cognitive disturbances and all scored above 27 points. We excluded all patients or controls who were treated for DM and newly diagnosed as having DM; they had conditions, which could potentially influence plasma insulin levels and fasting glucose levels, such as renal insufficiency, marked obesity (BMI>30 kg/m^2), glycated hemoglobin (HbA1c) level of ≥6.5%, or thyroid disease.

Samples were collected from venous blood after a 12 hr-overnight fast and then blood chemistry was performed. Fasting plasma glucose level was measured by the glucokinase method and insulin level by a radioimmunoassay. IR was calculated by the homeostatis model assessment of insulin resistance (HOMA-IR) proposed by Matthews et al. [10], with using the following formula: HOMA-IR=fasting insulin (U/mL)×fasting plasma glucose (mg/dL)/405.

To determine the cut-off point of HOMA-IR as a predictor of cognitive decline, receiver operating characteristic (ROC) analyses were performed. The determined cut-off point of HOMA-IR was 2.26 (sensitivity 61.1%, specificity 90.9%).

Results represented themselves as mean±standard deviation. Statistical analyses were done using SPSS® Ver. 12.0 for Windows. Non-normally distributed variables were analyzed by using nonparameteric analysis. An overall comparison with differences between HOMA-IR levels of the 3 groups was performed through Kruskal-Wallis analysis and correlations between the study variables were analyzed by Spearman's test. Multivariate analyses were performed to determine the factors related to cognitive decline. Statistical significance was considered at $p<0.05$.

RESULTS

The demographic characteristics and risk factor profiles of the study subjects are shown in Table 1. There were no sig-

Table 1. Clinical characteristics of patients and controls

	AD (n=18)	MCI (n=19)	Normal (n=24)	*p* value
Age (yr)	74.7±5.1	70.2±9.1	70.6±4.4	0.062
Male (%)	5 (28)	10 (52)	13 (75)	0.189
Education (yr)	4.1±3.8	5.2±4.8	6.8±6.1	0.707
hypertension (%)	10 (55)	8 (42)	10 (42)	0.241
Dyslipidemia (%)	4 (22)	2 (10)	4 (17)	0.174
smoker (%)	2 (11)	5 (26)	2 (8)	0.699
MMSE	17.2±4.8	25.5±2.9	28.7±1.0	<0.01
CDR	1.1±0.3	0.5±0.1	0.01±0.2	<0.01
Fasting glucose (mg/dL)	100.4±9.5	100.1±7.6	95.2±5.3	0.017
Fasting insulin (μU/mL)	11.2±7.4	6.7±4.5	5.5±2.3	0.019
HOMA-IR	2.7±1.7	1.7±1.1	1.3±0.5	0.012
hsCRP	5.0±4.7	2.1±3.0	1.0±0.7	0.005
Total cholesterol (mg/dL)	206.5±31.3	186.7±36.0	172.4±29.6	0.008
Triglyceride (mg/dL)	167.0±93.5	126.0±95.0	184.4±106	0.046
HDL-cholesterol (mg/dL)	48.4±11.3	86.1±14.6	44.6±12.6	0.123
LDL-cholesterol (mg/dL)	128.8±25.2	111.6±36.3	95.6±19.9	0.002

AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, mini-mental status examination; CDR, clinical dementia rating; HOMA-IR, homeostasis model asessment of insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein.

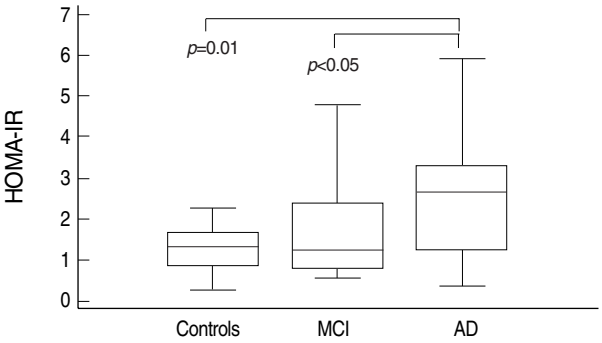

Fig. 1. Box and whisker plots of HOMA-IR in study subjects.

Table 2. Multivariate analysis of independent predictors for cognitive decline

Variables	Odds ratio	95% CI	*p* value
Age >65 yr	2.46	0.44-13.66	0.303
HOMA >2.26	5.62	1.34-23.44	0.018
Fasting glucose ≥104 mg/dL	35.7	3.89-328.14	0.002
Total cholesterol ≥200 mg/dL	0.87	0.14-5.49	0.889
LDL-cholesterol ≥130 mg/dL	0.21	0.02-2.60	0.227
MMSE	10.1	1.08-94.06	0.042

CI, confidence interval; MMSE, mini-mental statue examination; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein.

nificant differences in risk factors between study subjects including age, sex, hypertension, smoking, and family history. Serum glucose, C-reative protein (CRP), and total cholesterol were significantly higher in the cognitive decline subjects than in the non-diabetic control subjects, while LDL-cholesterol was significantly lower in the controls ($p<0.05$).,

The serum levels of HOMA-IR were significantly different between the 3 groups (AD, 2.7 ± 1.7; MCI, 1.7 ± 1.1; controls 1.3 ± 0.5. $p<0.05$) and those of HOMA-IR detected in the AD group were higher than in the MCI and control groups (Fig. 1). In simple correlation analysis, HOMA-IR levels were positively correlated with age ($p<0.01$) and triglyceride ($p<0.05$), whereas they showed a negative correlation with the MMSE between the cognitive decline subjects (r=-0.351, $p<0.01$). There were no significant differences in gender and serum HOMA levels between the 3 groups. The MMSE was negatively correlated with age, the level of total cholesterol, and that of LDL-cholesterol ($p<0.05$), but it did not show any relationship between other vascular r risk factors.

To further quantify the relationship between HOMA-IR and clinical parameters in the study subjects, multiple regression analysis was performed. The level of HOMA-IR and MMSE were independently associated with cognitive decline ($p=0.02$, and $p=0.04$, respectively) (Table 2).

DISCUSSION

Poor cognition is more prevalent in subjects with impaired glucose tolerance and DM2 than in those with a normal glucose metabolism. The progression from normal glucose tolerance to DM2 is a gradual process in which IR plays a crucial role [7]. This study showed that a high HOMA-IR value is associated with cognitive decline in non-diabetic patients. HOMA-IR levels were significantly elevated in AD patients compared to the MCI and control groups and IR may be clinically important as a significant predictor of cognitive decline. We also observed a significant inverse relationship between the MMSE and HOMA-IR, which was independent of age and sex.

IR is the main pathological condition underlying vascular disorders such as diabetes and cerebrovascular or cardiovascular disease and can increase the risk of dementia [1-3]. Although precise mechanisms remain to be elucidated, IR and hyperinsulinemia accelerate AD-related pathology through its effects on Aβ metabolism and tau phosphorylation [3]. Peripheral insulin is transported to the CNS across the blood-brain barrier (BBB) by insulin receptor protein. This transporter is not uniformly distributed throughout the BBB and insulin receptors have been found in the dentate gyrus and hippocampus. Peripheral IR and hyperinsulinemia possibly contributed to the develpment of central IR causing increased insulin levels in the CNS, which sequesters insulin degrading enzyme (IDE); it results in a decrease in Aβ degradation and consequently increase tau phosphorylation and Aβ oligomers. More toxic Aβ oligomers lead to neuroinflammation [3-6, 13-15].

Several studies suggest that IR is closely connected with a decrease in measures of global cognitive functioning or frontal

executive functioning resulting from an abnormal insulin-signaling pathway, even though studies on this association are not consistent [2, 5, 16, 17]. In our study, we observed a significant inverse relationship between the MMSE and levels of HOMA, which was independent of age and sex. However, IR is not a significant determinant of the neuropsychological correlates of frontal or temporal lobe functions (not shown). This is why our sample was from a single hospital study and was small in size and our findings cannot be generalized to other groups or populations, which is the limitation of our study. In addition, although individuals with previously diagnosed diabetes were excluded from the present study, we did perform neither an oral glucose tolerance test nor an euglycemic hyperinsulinemic clamp as a standard test to measure IR. The inclusion of subjects with impaired glucose tolerance may not be ruled out in the present study, but the HOMA index was designed to assess insulin resistance and recently has been widely used.

Although the study limitations should caution against over-interpretation, our results suggest that IR is associated with cognitive decline in non-diabetic patients. Increasing the level of HOMA-IR could be a potentially powerful approach to prevent AD and cognitive decline.

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