

Serum Level of Endogenous Secretory Receptor for Advanced Glycation End Products and Other Factors in Type 2 Diabetic Patients With Mild Cognitive Impairment

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OBJECTIVE—Determine the serum levels of endogenous secretory receptor for advanced glycation end products (esRAGEs) in patients with type 2 diabetes and mild cognitive impairment (MCI) and in control patients with type 2 diabetes but no MCI, and examine the relationship of esRAGE and MCI with other clinical factors.

RESEARCH DESIGN AND METHODS—A total of 101 patients with type 2 diabetes who were hospitalized in the Department of Endocrinology at Fujian Provincial Hospital between January 2010 and January 2011 were enrolled. There were 58 patients with MCI and 43 patients without MCI (control). Serum levels of esRAGE were measured using an enzyme-linked immunosorbent assay (ELISA). Other clinical parameters were also measured.

RESULTS—Type 2 diabetic patients with MCI had a longer duration of diabetes; elevated HbA_{1c}, total cholesterol (CHOL), LDL cholesterol (LDL-C), triglyceride (TG), intima-media thickness, C-reactive protein (CRP), and brachial-ankle pulse wave velocity (ba-PWV); and lower ankle brachial index (ABI) and esRAGE relative to the control group. Among patients with MCI, the Montreal Cognitive Assessment (MoCA) score was positively correlated with serum esRAGE but negatively correlated with CHOL. Spearman rank correlation analysis indicated that esRAGE was positively correlated with MoCA score and ABI but negatively correlated with ba-PWV, CHOL, TG, and CRP in all subjects.

CONCLUSIONS—Our results suggest that esRAGE may be a potential protective factor for dyslipidemia, atherosclerosis, and MCI in patients with type 2 diabetes.

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The condition of mild cognitive impairment (MCI) was first described in 1999 as a common disorder of aging adults that increases the risk for dementia and Alzheimer disease (AD) (1). Patients with MCI progress into dementia at an annual rate of 15.0% (1). There are approved treatments for AD, but not for MCI, although numerous clinical trials

are investigating treatments for both conditions (2). The high worldwide prevalence of MCI, AD, and dementia points to the need to understand the pathogenesis of these disorders.

The elevated serum glucose of patients with diabetes leads to nonenzymatic glycosylation of lipids and proteins and formation of advanced glycation end products

(AGEs) (3). The accumulation of AGEs and their binding to receptors for AGE (RAGEs) on the plasma membrane triggers a series of reactions implicated in the development of disorders, such as diabetes complications and AD (4). In recent years, the endogenous soluble receptor for AGE (esRAGE) has been identified as a tissue-specific, soluble, alternative splicing isoform of RAGE that is primarily present in circulation (5). The cell-protecting function of esRAGE is attributed to its ability to capture extracellular AGEs (6).

In the current study, we measured serum esRAGE levels in adult patients with type 2 diabetes and MCI and in a control group with type 2 diabetes but no MCI, and examined the association of esRAGE with clinical factors.

RESEARCH DESIGN AND METHODS

Study subjects

We selected 101 patients with type 2 diabetes (diagnosed by 1999 World Health Organization criteria). The mean patient age was 63.45 ± 8.38 years, and all patients were hospitalized in the Department of Endocrinology at Fujian Provincial Hospital between January 2010 and January 2011. This study was approved by the hospital internal review board, and all subjects provided written informed consent. Complete medical records were available for all patients. The exclusion criteria were as follows: presence of a CNS disease that could cause MCI, history of head trauma, history of inflammatory or infectious brain disease, depression, drug or alcohol abuse or dependence, and use of possible or known cognition-impairing drugs in the previous month. Based on the criteria established by the 2006 European Alzheimer's Disease Consortium (7) and the Montreal Cognitive Assessment (MoCA) scoring system, 58 patients (30 males and 28 females) had MoCA scores <26 and were selected as type 2 diabetes with MCI group; the

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other 43 patients (24 males and 19 females) had MoCA scores of 26 or greater and were selected as the type 2 diabetes without MCI group (control). Current and past medical histories, personal backgrounds, and medications were recorded for all subjects.

Measurement of esRAGE, AGEs, and other clinical parameters

Serum samples were isolated from fasting subjects and stored at -80°C prior to analysis. The serum levels of esRAGE and AGE were measured by ELISA kits from R&D Systems (Minneapolis, MN). For esRAGE, the intra-assay coefficient of variation (CV) was $<10\%$ and the interassay CV was $<4\%$; for AGEs, the intra-assay CV was 5.8% and the interassay CV was 9.8% . Blood lipids, C-reactive protein (CRP), urine microalbumin, and HbA_{1c} levels were quantified using an automatic biochemical analyzer (Bio-Rad, Benicia, CA). Waist circumference, height, and body weight were measured, and BMI (kg/m^2) was calculated.

Measurement of atherosclerosis

A VP 1000 automated atherosclerosis analyzer (Colin Medical Technology Corp., Komaki, Japan) was used to measure brachial-ankle pulse wave velocity (ba-PWV) and ankle brachial index (ABI). The PWV between two recording sites is related to arterial wall distensibility, so the severity of atherosclerosis can be determined by vessel evaluation and wave analysis. The blood pressure cuffs were tied at both elbows and ankles to measure ba-PWV and ABI. The higher of the two ba-PWV values and the lower of the two ABI values were used for statistical analysis.

Intima-media thickness determination

Color Doppler ultrasound was used to locate the thickest site of the carotid artery intima-media and to measure the thickness at this site, two other upstream sites, and one site that was 1 cm downstream, each of which were measured six times to obtain average values.

Statistical analyses

All data and parameters are presented as means and SDs and were analyzed using SPSS version 13.0. Data with normal and homoscedastic distributions were analyzed by Student *t* test, and those with nonnormal distribution or heteroscedastic distributions were analyzed by the Wilcoxon rank-sum test. The χ^2 test was used to compare the incidences of certain events,

such as smoking. The factors influencing MoCA score were analyzed using Pearson correlation analysis for normally distributed variables and Spearman rank correlation for nonnormally distributed variables. The factors influencing serum esRAGE were analyzed by Spearman rank correlation analysis. A *P* value of 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of enrolled patients

Table 1 shows the demographic and clinical characteristics of enrolled type 2 diabetic patients with and without MCI. There were no significant differences between the groups in age, sex, BMI, waist circumference, morning urinary microalbumin, HDL cholesterol (HDL-C), duration of hypertension, and history of smoking ($P > 0.05$). Compared with the control group, patients with MCI had a significantly longer duration of diabetes; elevated total cholesterol (CHOL), LDL cholesterol (LDL-C), triglyceride (TG), CRP, intima-media thickness (IMT), and ba-PWV; and lower ABI ($P < 0.01$ for all). HbA_{1c} was also higher in the MCI group ($P < 0.05$). The serum esRAGE level was significantly

lower in the MCI group ($P < 0.01$), and the serum AGE level was significantly lower in the control group ($P < 0.05$) (Table 1).

We also assessed the use of medications by all enrolled patients (Table 2). The results indicate no significant differences in medication use between the two groups.

Correlation of MoCA scores and other clinical indicators

Next, we assessed the association of MoCA scores with different variables by use of Pearson correlation analysis for normally distributed variables and Spearman rank correlation analysis for nonnormally distributed variables (Table 3). The results indicated that MoCA score was positively correlated with serum esRAGE level ($r = 0.942$), but negatively correlated with CHOL ($r = -0.364$) and AGEs ($r = -0.275$) (Table 3). MoCA was not significantly correlated with patient age, duration of diabetes, HbA_{1c}, BMI, waist circumference, blood lipids, CRP, IMT, ba-PWV, or ABI ($P > 0.05$ for all).

Correlation of esRAGE and other clinical indicators

Finally, we performed Spearman rank correlation analysis of esRAGE (dependent

Table 1—Demographic and clinical characteristics of type 2 diabetic patients with and without MCI

	Type 2 diabetes with MCI	Type 2 diabetes without MCI (control)
Number of patients	58	43
Male/female	30/28	24/19
Age (years)	63.90 \pm 8.73	62.84 \pm 7.94
Duration of type 2 diabetes (years)	11.19 \pm 4.73	5.19 \pm 3.55**
BMI (kg/m^2)	24.19 \pm 2.85	23.07 \pm 2.98
Waist circumference (cm)	86.22 \pm 9.08	84.61 \pm 9.47
HbA _{1c} (%)	9.35 \pm 2.40	8.19 \pm 1.94*
CHOL (mmol/L)	5.31 \pm 1.36	4.52 \pm 1.24**
LDL (mmol/L)	3.24 \pm 1.01	2.57 \pm 1.11**
TG (mmol/L)	2.05 \pm 2.33	1.34 \pm 1.05**
HDL (mmol/L)	1.15 \pm 0.39	1.33 \pm 0.52
IMT (mm)	1.19 \pm 0.17	1.05 \pm 0.19**
CRP (mg/L)	9.37 \pm 14.12	2.54 \pm 6.64**
ABI	1.09 \pm 0.12	1.17 \pm 0.08**
ba-PWV (cm/s)	2,090.76 \pm 536.817	1,646.60 \pm 423.626**
Morning urine microalbumin (mg/L)	117.46 \pm 411.68	89.91 \pm 343.30
Duration of hypertension (years)	7.44 \pm 9.48	5.76 \pm 8.45
Had ever smoked (%)	18/58 (31.03%)	11/43 (25.58%)
Current smoking (%)	13/58 (22.41%)	6/43 (13.95%)*
Habitual alcohol drinking (%)	10/58 (17.24%)	7/43 (16.28%)
esRAGE ($\mu\text{g}/\text{L}$)	3.51 \pm 2.91	7.82 \pm 5.24**
AGEs (ng/L)	1,999.08 \pm 1,207.48	1,377.08 \pm 905.37*

The Student *t* test, Wilcoxon rank-sum test, or χ^2 test was used to test for significant differences. * $P < 0.05$. ** $P < 0.01$.

Table 2—Comparison of drug use by type 2 diabetic patients with and without MCI

	Type 2 diabetes with MCI	Type 2 diabetes without MCI (control)
Number of patients	58	43
Insulin dose (units)	20.86 ± 17.48	19.81 ± 20.40
The use of insulin (%)	39/58 (67.24%)	26/43 (60.47%)
Oral hypoglycemic drugs (%)	36/58 (62.07%)	32/43 (74.42%)
Sulfonylureas (%)	11/58 (18.97%)	9/43 (20.93%)
Nateglinide or repaglinide (%)	8/58 (13.79%)	7/43 (16.28%)
Biguanides (%)	29/58 (50.00%)	23/43 (53.49%)
Thiazolidinediones (%)	3/58 (5.17%)	2/43 (4.65%)
α-Glucosidase inhibitor (%)	23/58 (39.66%)	24/43 (55.81%)
Antihypertensive medications (%)	41/58 (70.69%)	25/43 (58.14%)
Diuretics (%)	12/58 (20.69%)	6/43 (13.95%)
β-Blockers (%)	11/58 (18.97%)	6/43 (13.95%)
Calcium channel blockers (%)	21/58 (36.21%)	19/43 (44.19%)
Angiotensin-converting enzyme inhibitors (%)	14/58 (24.14%)	6/43 (13.95%)
Angiotensin II receptor blockers (%)	17/58 (29.31%)	14/43 (32.56%)
α1-Blockers (%)	5/58 (8.62%)	0/43 (0.00%)
Antiplatelet medications (%)	37/58 (63.79%)	23/43 (53.49%)
Lipid-lowering medications (%)	37/58 (63.79%)	27/43 (62.79%)

The Student *t* test, Wilcoxon rank-sum test, or χ^2 test was used to test for significant differences. All *P* values were >0.05.

variable) with other clinical indicators (independent variables) in all 101 patients. The results indicated that esRAGE was positively correlated with MoCA score and ABI ($r = 0.803$ and $r = 0.214$, respectively), but negatively correlated with ba-PWV, CHOL, TG, and CRP ($r = -0.371$, $r = -0.303$, $r = -0.274$, and $r = -0.308$, respectively) (Table 4). There was no significant correlation of esRAGE with age, duration of diabetes, HbA_{1c}, BMI, waist circumference, HDL, LDL, or IMT ($P > 0.05$ for all).

CONCLUSIONS—Our study of patients with type 2 diabetes indicated that MCI was associated with duration of diabetes; elevated levels of HbA_{1c}, CHOL, LDL, TG, IMT, CRP, ABI, ba-PWV, and esRAGE; and low levels of serum AGEs. In agreement with our results, numerous other studies have also reported associations of diabetes with vascular brain

damage (8), degenerative nerve disease (9), cognitive decline (10,11), and dementia or MCI (12). In addition, MCI is associated with the onset, longer duration, and greater severity of diabetes (13). Diabetic patients have increased levels of AGEs, inflammation, and oxidative stress, all of which can affect blood supply to the brain. We observed an association between hyperlipidemia and MCI perhaps because hyperlipidemia itself causes denaturation of neurons responsible for cognitive function, or because hyperlipidemia accelerates the progression of atherosclerosis, which leads to MCI (14).

In agreement with our results, other studies (15) reported that sustained hyperglycemia, as indicated by elevated HbA_{1c}, is an independent risk factor for

Table 3—Relationship of MoCA score with other clinical indicators in patients with type 2 diabetes and MCI

	MoCA score	
	<i>r</i>	<i>P</i>
esRAGE	0.942	<0.001
AGEs	-0.275	0.005
CHOL	-0.364	0.005

Table 4—Relationship of esRAGE with other clinical indicators in type 2 diabetic patients with and without MCI (n = 101)

	esRAGE	
	<i>r</i>	<i>P</i>
AGEs	-0.236	0.017
MoCA score	0.803	0.000
ABI	0.214	0.032
ba-PWV	-0.371	0.000
CHOL	-0.303	0.002
TG	-0.274	0.006
CRP	-0.308	0.002

impairment of cognitive function. There may be several pathogenic mechanisms underlying this process, including accumulation of sorbitol and development of a hyperosmotic state in nerve cells that leads to edema and impaired brain function (16), insulin resistance syndrome (17), impaired insulin homeostasis in the brain (18), and/or hyperinsulinemia (19).

Our results indicate that type 2 diabetes patients with MCI had significantly elevated IMT and ba-PWV but lower ABI than the control group, indicating a correlation between atherosclerosis and type 2 diabetes-associated MCI. This is consistent with the research of Rafnsson et al. (20), who reported that individuals with peripheral arterial disease had worse cognitive function than healthy controls, and with the research of Hanon et al. (21), who reported a significant relationship of reduced cognitive function and arteriosclerosis (based on PWV) in 308 elderly patients.

Our results also indicate that type 2 diabetic patients with MCI had significantly higher CRP levels than controls, suggesting an association of inflammation and MCI. In agreement with this result, Xu et al. (22) reported that patients with higher serum CRP had lower mini-mental state examination scores and higher risk for development of AD. Other studies have also shown that AD patients have increased brain inflammation and that this leads to deposition of amyloid β-protein (23), formation of senile plaques, and neurofibrillary formation, resulting in damage or death of neurons. Inflammation also increases apolipoprotein E synthesis in stellate cells, which is associated with increased risk of AD (24).

Previous evidence indicates that RAGE has multiple roles in the development of cognitive dysfunction. RAGE appears to promote AD through a positive feedback mechanism with amyloid β-protein (25). Another study reported that low expression of esRAGE in the hippocampus was associated with AD (26). Thus, the mechanism by which AGEs induce MCI in patients with type 2 diabetes may include one or more of the following: 1) AGEs induce oxidative stress directly or by binding to specific receptors such as RAGE, leading to upregulation of nuclear factor-κB and its target genes, resulting in inflammation and neural damage; 2) AGEs induce vascular endothelial dysfunction, and the increased permeability of blood vessels increases accumulation of AGEs in the vascular wall and causes hardening; and

3) AGEs activate microglial cells and damage the microtubular structure, leading to neuron dysfunction.

Recent research has shown that esRAGE counteracts the effects of inflammatory molecules. Dementia patients have lower levels of esRAGE than healthy controls (27). Ghidoni et al. (28) reported that serum esRAGE levels were significantly decreased in MCI patients and even lower in AD patients than in healthy controls. Similar to these reports, our results indicated that esRAGE levels were lower in patients with an MCI group than those with type 2 diabetes alone, suggesting that esRAGE may have a protective effect against diabetic MCI. While the precise mechanism of this relationship remains unclear, one or more of the following may be responsible: 1) chronic hyperglycemia in type 2 diabetic patients with MCI directly inhibits synthesis and secretion of esRAGE; 2) accumulated AGEs bind to esRAGE, which leads to increased clearance of esRAGE; and 3) inflammation, which has been implicated in MCI, can also reduce esRAGE synthesis.

Our results also indicated that the MoCA score was positively correlated with serum esRAGE ($r = 0.942$) and negatively correlated with CHOL ($r = -0.364$) in type 2 diabetes patients with MCI. Thus, measurement of esRAGE and CHOL can be helpful in the prediction and/or diagnosis of MCI in middle-aged and older populations. We also found that esRAGE was negatively correlated with CHOL and TG, consistent with previous studies (29). Thus, esRAGE may be an endogenous factor that protects against oxidative stress-mediated atherosclerosis and endothelial dysfunction in hypercholesterolemia (30). Additionally, Lindsey et al. (31) reported that esRAGE was independently and negatively correlated with coronary atherosclerosis. On the other hand, there is some evidence that elevated esRAGE is associated with increased cardiovascular disease (32,33).

McNair et al. (34) reported that esRAGE was negatively correlated with high-sensitivity CRP (hs-CRP) and tumor necrosis factor- α (TNF- α), but that TNF- α was positively correlated with hs-CRP. This result suggests that the production of esRAGE may be regulated by TNF- α -related hs-CRP. Another study involving 245 type 2 diabetic patients without coronary artery disease shows negative correlation between esRAGE and hs-CRP (35). Consistent with these reports, we found

that esRAGE was negatively associated with hs-CRP ($r = -0.308$).

In conclusion, our study indicates that a lower level of serum esRAGE and a higher level of serum AGE in patients with type 2 diabetes are associated with MCI, dyslipidemia, and atherosclerosis. Thus, we suggest that future investigators consider the hypothesis that therapeutic interventions that increase serum esRAGE may be a novel approach to prevent RAGE-mediated diseases such as MCI and AD.

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G.C. designed the study and reviewed and edited the manuscript. L.C. wrote the manuscript and researched data. B.C. researched data and contributed to discussion. J.L., F.L., L. Li, L. Lin, J.Y., and J.W. researched data. H.H. reviewed and edited the manuscript.

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