

The Relationship Between Serum VCAM-1 and Alzheimer's Disease in Patients with Type 2 Diabetes Mellitus

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Background: Previous studies have reported that diabetes mellitus (DM) is a risk factor for Alzheimer's disease (AD). Vascular cell adhesion molecule-1 (VCAM-1) plays an important role in the pathological process of atherosclerosis. The aim was to elucidate the relationship between serum VCAM-1 and early AD in DM patients.

Methods: Serum samples for VCAM-1 were tested in 208 DM patients. All included DM patients were followed up for a median of 36 months prospectively. The prognostic value of serum VCAM-1 for predicting AD events was analyzed by using Cox proportional hazard.

Results: Serum VCAM-1 was independently associated with AD history after adjusting for related confounding factors in patients with DM at baseline by using the logistic regression analysis (OR=1.861; 95% CI, 1.435–2.539; $P_{\text{trend}}=0.020$). The Cox proportional hazard model suggested that VCAM-1 was a prognostic factor for AD events in the DM patients (HR=2.728; 95% CI, 1.785–5.439; $P_{\text{trend}}<0.001$). Stratified analysis showed that the significant association between AD event and serum VCAM-1 in DM patients was not affected by CVD history.

Conclusion: Our results showed that higher VCAM-1 levels were significantly related to a higher risk of AD events in DM patients. The serum biomarker might be beneficial to predict AD early. Serum VCAM-1 might be a good biochemical parameter for predicting AD in DM.

Keywords: diabetes mellitus, Alzheimer's disease, vascular cell adhesion molecule-1, prognostic value

Introduction

Epidemiological and biological evidence has suggested an obvious link between type 2 diabetes mellitus (DM) and Alzheimer's disease (AD).^{1,2} Patients with DM tend to have a higher rate of cognitive decline and a higher risk of developing various dementia.^{3,4} Cognitive deficits in patients with DM mainly affect the areas of executive function, learning and memory and mental flexibility and speed. Although the mechanism for elucidating this relationship is not fully clear, increasing inflammation and oxidative stress in DM play important roles in causing an increased risk of AD.⁵ The early detection of AD in DM patients has an important role on develop strategies to improve prognosis.

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin (Ig) superfamily of proteins, is composed of several extracellular Ig-like domains that contain a 19-amino-acid carboxyl-terminus cytoplasmic domain and a single type

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I transmembrane domain.^{6–8} VCAM-1 is involved in combination with other inflammatory factors in regulating inflammatory responses and immune surveillance. Existing evidence has shown that VCAM-1 can be considered an inflammatory marker for predicting cardiovascular diseases (CVDs) such as ischemic heart disease, stroke and microangiopathy, however, few studies suggested that this marker can improve risk prediction for AD, which has been confirmed as a chronic vascular inflammatory disease. Importantly, VCAM-1 has also been regarded as an inflammation marker and a risk factor for atherosclerotic diseases.^{9–12} Therefore, higher VCAM-1 level is hypothesized to be associated with a higher risk of AD.

In summary, DM is the state of chronic inflammatory response and is considered a chronic inflammatory disease.^{13–16} Considering the close relationship between VCAM-1 and inflammatory response,^{6–12} we hypothesized that serum VCAM-1 may be associated with an increased risk of AD events in DM patients. We aimed to evaluate whether higher serum levels of VCAM-1 contribute to increased risk of AD events in patients with DM.

Materials and Methods

Study Population

We collected 208 hospitalized patients with DM from Zutangshan Hospital and Taizhou Second People's Hospital in China because of DM between January 2015 and December 2016. We have enough data to analyze the relationship of serum VCAM-1 levels with AD events in DM patients. All included patients with DM were prospectively followed up for a median period of 36 months (range=2–40). AD was detected by two neurologists according to the diagnostic criteria: (1) clinical examination and the cognitive scale test confirmed the presence of dementia; 2) two or more cognitive impairments and progressive deterioration; 3) unconsciousness disorder; 4) the onset of the disease was from 40 to 90 years old, mostly after 65 years old; and 5) other systemic and brain diseases that cause progressive memory and cognitive impairment were excluded.¹⁷ Of all the patients with DM, 54 had an AD history. Twenty-two patients with DM were excluded because of neoplastic diseases, severe lung diseases, severe liver diseases or other reasons. Data on the clinical characteristics were collected from medical records or patient interview. Additionally, 223 healthy subjects were collected as the control group who were compared with patients with DM for serum VCAM-1 levels. There was no significant difference

in age or sex between patients with DM and healthy subjects. According to the Declaration of Helsinki guidelines, the Ethics Committee from Zutangshan Hospital and Taizhou Second People's Hospital supported this study. We have written informed consent from all included DM patients.

Follow-Up

All DM patients were followed up for a median of 36 (range 2–40) months prospectively. DM patients were followed up by reviewing telephone or medical record 4 times a year until AD events (diagnosis of AD) happened. The AD events in this study were endpoint events that were diagnosed by two neurologists, consistent with other specialists in radiology and neuropsychology.

Measurement of VCAM-1

Fasting blood samples were collected from all included subjects after admission. According to the manufacturers' instructions at the commencement of the study, serum VCAM-1 levels were tested using ELISA kits (Abcam, UK). All blood samples were measured twice. The mean of two measurements was used for analysis (coefficient of variation of precision [CV], <5%; detection limit, 5 ng/mL).

Laboratory Measurements

The blood samples obtained from the DM patients in the first morning after admission were also detected for fasting blood glucose (FBG), hemoglobin (Hb), HbA1c (glycosylated hemoglobin), LDL (low-density lipoprotein), high-density lipoprotein (HDL), albumin (ALB) and hs-CRP (hs-C-reactive protein) by use of the Siemens ADVIA 2400 automatic biochemistry analyzer (Siemens AG). Estimated glomerular filtration rate (eGFR) was calculated by using The Modification of Diet in Renal Disease (MDRD) formula.¹⁸

Statistical Analyses

Data analysis in our study was used by SPSS 25.0. P values equal to or less than 0.05 were considered statistically significant. Mann–Whitney *U*-test was performed to analyze the data that were not normally distributed. Independent *t*-test was performed to analyze normally distributed data. Categorical variables were analyzed by chi-square test. In multivariable analyses, serum VCAM-1 levels were categorized by quartiles (quartile 4: ≥ 75 th percentile, quartile 3: ≥ 50 th to 75th percentile, quartile 2: ≥ 25 th to 50th percentile, quartile 1: < 25 th percentile). Multivariate logistic regression analysis was used for analyzing the relationship between

Table 1 Baseline Characteristics of Patients with DM and Control Subjects

Variables	Healthy Control Subjects (n=223)	Patients with DM (n=208)	P value
Age (years)	63.6 (58.7–73.2)	64.3 (59.9–74.8)	0.307
Gender (male), n (%)	112 (50.2)	109 (52.4)	0.249
VCAM-I (ng/mL)	631.5±127.8	934.4±205.2	<0.001

Abbreviations: DM, diabetes mellitus; VCAM-I, vascular cell adhesion molecule-I.

serum VCAM-1 levels and AD history in DM patients at baseline. The Cox proportional hazard analysis was performed to evaluate whether serum VCAM-1 is a potential prognostic factor for AD events in DM patients.

Results

Clinical Characteristics of Patients with MD

Serum levels of VCAM-1 in patients with DM (934.4±205.2 ng/mL) were significantly higher than 223 subjects who

were selected as the healthy subjects (631.5±127.8 ng/mL, Table 1). The clinical characteristics of DM patients are shown in Table 2. According to with and without AD events (N=62), all DM patients (N=208) were separated into two groups. Patients with AD events had higher BMI, higher rate of male and CVD history and tend to be older, current smoker, current drinker than patients without AD events ($P<0.05$). Patients with AD events had lower serum levels of HDL, ALB, and Hb and higher VCAM-1, HbA1c, FBG, hs-CRP and LDL than those without AD events ($P<0.001$).

The Relationship Between VCAM-I Levels and AD History in All Included Patients with DM

To analyze the association between VCAM-1 and AD history in DM patients, multivariate logistic regression analysis was used (Table 3). The crude model suggested that after no adjustment was made, higher serum levels of VCAM-1 were associated with a higher risk of AD history.

Table 2 Clinical Characteristics in 208 DM Patients at Baseline

Variables	All DM Patients (n=208)	DM without AD Events (n=146)	DM with AD Events (n=62)	P value
Age (years)	64.3 (59.9–74.8)	62.5 (57.9–71.4)	67.8 (62.6–80.3)	<0.001
Gender (male), n (%)	109 (52.4)	74 (50.7)	35 (56.5)	0.028
BMI	25.7 (22.5–26.9)	23.9 (20.2–24.6)	27.3 (24.1–29.7)	<0.001
Current smoker, n (%)	33 (15.9)	16 (11.0)	17 (27.4)	<0.001
Current drinker, n (%)	66 (31.7)	44 (30.1)	22 (35.5)	0.029
Admission systolic BP (mmHg)	126.5 (111.4–147.9)	125.8 (104.8–139.8)	127.4 (115.6–153.1)	0.107
Admission diastolic BP (mmHg)	77.5 (70.1–85.4)	75.3 (64.2–81.4)	79.3 (73.4–86.5)	0.223
CVD history				
Hypertension, n (%)	52 (25.0)	31 (21.2)	21 (33.9)	0.013
Coronary heart disease, n (%)	32 (15.4)	22 (15.1)	10 (16.1)	0.314
Stroke, n (%)	19 (9.1)	8 (5.5)	11 (18.0)	<0.001
Others, n (%)	10 (4.8)	7 (4.7)	3 (4.9)	0.557
Laboratory measurements				
eGFR (mL/min/1.73 m ²)	56.8 (45.1–63.7)	56.9 (45.3–63.9)	56.7 (45.0–63.6)	0.780
Hs-CRP (pg/mL)	7.2 (2.5–13.4)	5.6 (2.0–9.3)	9.7 (3.6–17.5)	<0.001
Hb (g/L)	106 (92–121)	114 (99–128)	103 (87–115)	<0.001
ALB (g/L)	37.2 (35.7–40.3)	38.3 (36.3–43.3)	35.4 (33.3–38.5)	<0.001
FBG (mmol/L)	10.5±2.3	9.2±1.4	13.2±2.6	<0.001
HbA1c (%)	5.9 (5.7–6.3)	5.8 (5.6–6.1)	6.3 (5.9–6.6)	0.004
HDL (mmol/L)	1.5±0.31	1.7±0.60	1.2±0.14	<0.001
LDL (mmol/L)	2.68±1.03	2.27±0.93	2.78±1.32	<0.001
VCAM-I (ng/mL)	934.4±205.2	758.8±153.6	1249.5±267.3	<0.001

Notes: Data are presented as mean ± SD for normally distributed data, as median (interquartile range) for nonnormally distributed data, and as n (%) for categorical variables.

Abbreviations: DM, diabetes mellitus; AD, Alzheimer's disease; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; hs-CRP, hs-C-reactive protein; ALB, albumin; FBG, fasting blood glucose on admission; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VCAM-I, vascular cell adhesion molecule-I.

Table 3 The Association Between the AD History and VCAM-I in 208 Patients with DM by Logistic Regression Analysis

Variables	Crude	Model 1	Model 2
VCAM-I levels (ng/mL)			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	1.525 (1.231–1.799)	1.356 (1.227–1.719)	1.326 (1.223–1.604)
Quartile 3	1.587 (1.346–1.996)	1.526 (1.3301–1.967)	1.456 (1.294–1.862)
Quartile 4	2.175 (1.574–3.570)	1.954 (1.513–3.104)	1.861 (1.435–2.539)
P-trend	<0.001	0.003	0.020

Notes: Crude: No adjustment. Model 1: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP and CVD history. Model 2: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP, CVD history and laboratory measurements.

Abbreviations: DM, diabetes mellitus; AD, Alzheimer's disease; VCAM-I, vascular cell adhesion molecule-I; BMI, body mass index; BP, blood pressure.

The results in Model 1 were similar to those of the crude model after adjustments for age, sex, BMI, current smoker, current drinker, admission systolic and diastolic BP and CVD history were made. Model 2 suggested that this association was still significant and changed minimally after adding laboratory measurements to Model 1.

Prognostic Value of Serum VCAM-I Levels for AD Events in All DM Patients by Using Cox Proportional Hazard Analysis

All included DM patients (N=208) were followed up for a median of 36 months prospectively. Sixty-two of all included patients had AD events. Kaplan-Meier analysis showed that DM patients with serum levels of VCAM-I above the mean (934.4 ng/mL) had a significantly higher risk of AD events than those with serum levels of VCAM-I below the mean value (data not shown; Log rank test, $P<0.001$). To further assess the independent association between serum VCAM-I and AD events in DM patients, multivariate Cox proportional hazard regression model was performed (Table 4). Multivariate Cox proportional hazard analysis showed that after adjustments were made for age, sex, BMI, current smoker, current drinker,

admission systolic and diastolic BP, CVD history and laboratory measurements, VCAM-I was a potential prognostic factor for predicting AD events (HR=2.728; 95% CI 1.785–5.439; $P_{\text{trend}}<0.001$). Stratified analysis by adding CVD history as a covariate showed that the significant association of serum VCAM-I with AD events in DM patients was not affected by CVD history (Table 5).

We used a sensitivity analysis to assess the relationship between VCAM-I with AD events in DM patients who had no previous AD history (n=154). In these DM patients, all AD events were 21. Importantly, Kaplan-Meier survival curves suggested that the rate of AD events was still higher in DM patients with VCAM-I levels above the mean, compared with patients below the mean value (data not shown). The multivariate Cox analysis showed that DM patients who had higher VCAM-I levels had a higher risk of AD events (data not shown).

Discussion

Our findings suggested that DM patients with AD events tended to have higher serum levels of VCAM-I than those DM patients without AD events. Multivariate logistic regression analysis suggested that serum VCAM-I levels were independently associated with AD history in DM patients. Multivariate Cox proportional hazard analysis

Table 4 Cox Proportional Hazard Analysis for Predicting AD Events in 208 Patients with DM

Variables	Crude	Model 1	Model 2
VCAM-I levels (ng/mL)			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	2.122 (1.512–3.802)	1.974 (1.424–3.318)	1.699 (1.321–3.200)
Quartile 3	2.571 (1.855–4.360)	2.217 (1.634–4.125)	2.165 (1.567–3.560)
Quartile 4	3.263 (2.214–6.261)	2.957 (1.875–5.982)	2.728 (1.785–5.439)
P-trend	<0.001	<0.001	<0.001

Notes: Crude: No adjustment. Model 1: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP and CVD history. Model 2: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP, CVD history and laboratory measurements.

Abbreviations: DM, diabetes mellitus; AD, Alzheimer's disease; VCAM-I, vascular cell adhesion molecule-I; BMI, body mass index; BP, blood pressure.

Table 5 Cox Proportional Hazard Analysis for Predicting AD Events in 208 Patients with DM by Stratified Analysis

Variables	Crude	Model 1	Model 2
CVD history			
VCAM-I levels (per 1-SD increase)	2.460 (1.743–4.251)	2.106 (1.523–4.014)	2.052 (1.456–3.4501)
P value	<0.001	0.009	0.025
CVD history			
VCAM-I levels (per 1-SD increase)	3.374 (2.325–6.372)	3.068 (1.964–6.092)	2.839 (1.896–5.546)
P value	<0.001	<0.001	<0.001

Notes: Crude: No adjustment. Model 1: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP. Model 2: Adjusted for age, gender, BMI, current smoker, current drinker, admission systolic and diastolic BP and laboratory measurements.

Abbreviations: DM, diabetes mellitus; AD, Alzheimer's disease; VCAM-I, vascular cell adhesion molecule-I; BMI, body mass index; BP, blood pressure.

suggested that serum VCAM-1 might be potential prognostic factors for predicting AD events.

Type 2 DM and AD are age-related conditions, both characterized by increased incidence and prevalence with aging.^{19,20} DM2 is currently one of the fastest-growing epidemics and is frequently associated with aging, posing an increased rate of AD.^{1,2} AD is the most common neurodegenerative disorder associated with atherosclerosis-related inflammation and oxidative stress.^{21–23} Early detection of AD in patients with DM has important clinical significance, which might help to develop strategies to improve the prognosis for DM patients. As a cell surface protein, VCAM-1 is expressed by several cell types, including macrophages, endothelial cells, dendritic cells and smooth muscle cells.²⁴ Elevated serum VCAM-1 is a result of higher surface expression or increased shedding, which plays an important role in the adhesion and transmigration of leukocytes from the circulation into the surrounding tissue. Existing clinical evidence has suggested that VCAM-1 is associated with various CVDs, including stroke, chronic heart disease and hypertension.^{25–28} Elevated serum levels of VCAM-1 are also significantly linked with atrial fibrillation.^{29,30} Several basic studies have suggested that upregulated VCAM-1 expression in vitro and in vivo potentially contributes to inflammation-related pathological changes.^{31,32}

In this study, we first suggested that serum levels of VCAM-1 at baseline had a close association with AD history, which may be mostly or partly explained by the mechanistic research investigated in previous studies.^{6–8,31,32} These studies have suggested that chronic vascular inflammation caused by DM accelerates the occurrence of AD events. The mechanism of chronic vascular inflammation may be a possible explanation of the increased VCAM-1 levels, which is consistent with our hypothesis and results. The early detection of AD in these

patients may provide an opportunity to develop strategies aiming to reduce the medical burden and improve prognosis. Our results seemed to imply that serum VCAM-1 might be a sensitive biomarker for the early recognition of AD events in patients with DM.

There were some strengths in our study. First, our results showed that multivariate Cox proportional hazard analysis suggested that serum VCAM-1 might be a potential prognostic factor for predicting AD events. Second, we carried out comprehensive follow-up and rigorous adjudication of AD events to ensure the accuracy and reliability of our results. Finally, the serum test is simple and convenient for DM patients. The VCAM-1 assay chosen for this analysis is both widely available and analytically stable.

There were some limitations in our study. First, this is a small-sample study. Large-scale prospective cohort studies need to be further studied and prove the significant association between serum VCAM-1 and AD events in DM patients. The generalizability of our results needs further verification. Second, inflammatory cytokines related to VCAM-1 need to be included in this study and should be performed to identify the prognostic value of these inflammatory marks for predicting AD events. Third, hyperglycemia or other pathological states may increase the inflammatory response so that VCAM-1 levels might thus be altered. Finally, confounding factors such as treatment for AD were not included in this study, which may lead to some biases in our results.

Conclusions

Serum VCAM-1 is a potential prognostic factor for predicting AD events in DM patients. VCAM-1 might help early recognize developing AD in DM patients. Future studies should assess whether VCAM-1 can improve the risk classification of AD events in DM patients.

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Disclosure

The authors report no conflicts of interest for this work.

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