ORIGINAL ARTICLE

Relationship of plasma homocysteine, soluble intercellular adhesion molecule-1, high mobility group box 1 protein with carotid intima-media thickness in elderly patients with type 2 diabetes mellitus

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ABSTRACT

Objective: To explore the relationship of plasma homocysteine (Hcy), soluble intercellular adhesion molecule-1 (sICAM-1) and high mobility group box 1 protein (HMGB1) with carotid intima-media thickness (c-IMT) in elderly patients with type 2 diabetes mellitus.

Methods: A total of 100 elderly patients who were diagnosed as type 2 diabetes mellitus in Baogang Hospital of Inner Mongolia from June 2017 to May 2020 were chosen as research objects. According to c-IMT, they were divided into the normal group (n = 35), the mild to moderate group (n = 41) and the severe group (n = 24). The expression levels of plasma Hcy, sICAM-1 and HMGB1 were compared between groups respectively. Pearson's correlation coefficient was used to analyze the relationship of plasma Hcy, sICAM-1, HMGB1 with c-IMT.

Results: The comparison in plasma Hcy, sICAM-1, HMGB1 and c-IMT among the three groups of patients was of statistical significance ($p < .05$). The results of correlation analysis showed that the expression levels of plasma Hcy, sICAM-1 and HMGB1 were positively correlated with c-IMT in elderly patients with type 2 diabetes mellitus ($r = .627, .598, .614$; $p < .05$).

Conclusions: The expression levels of plasma Hcy, sICAM-1 and HMGB1 are abnormally increased in elderly patients with type 2 diabetes mellitus, and related to c-IMT, which can provide a strong evidence for clinical diagnosis and treatment by detecting their levels in clinical practice.

Key Words: Type 2 diabetes mellitus, Carotid intima-media thickness, Homocysteine, Soluble intercellular adhesion molecule-1, High mobility group box 1 protein

1. INTRODUCTION

Macrovascular complications, with atherosclerosis as the underlying lesion, including cerebral basilar and coronary diseases, are one of the most important causes of death in elderly patients with type 2 diabetes mellitus.[1] At present, it is clinically believed that atherosclerosis is essentially an aseptic inflammatory disease involving multiple organ systems and closely related to carotid intima-media thicken-

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ing and plaque formation.[2] Therefore, it is significant to study the inflammatory factors of atherosclerosis. Carotid intima-media thickness (c-IMT), as an early marker reflecting systemic atherosclerosis, is associated with the occurrence and development of macrovascular complications in elderly patients with type 2 diabetes mellitus.[3] Homocysteine (Hcy), as a metabolic intermediate of sulfur-containing amino acids in the human body, is also an independent risk factor for atherosclerosis.[4,5] It has been reported that adhesion molecules are related to atherosclerosis, and their expression on active endothelial cells is the key to leukocyte accumulation, the local infiltration-induced tissue injury and inflammatory responses, of which, soluble intercellular adhesion molecule-1 (sICAM-1) has its representative meaning as its typicality.[6] Studies have reported that high mobility group box 1 protein (HMGB1), as a proinflammatory factor, can promote disease progression and plaque rupture by activating a variety of inflammatory cells to release proinflammatory factors to maintain and amplify the inflammatory responses in aseptic inflammation.[7] This study was designed to explore the relationship of Hcy, sICAM-1 and HMGB1 with c-IMT in elderly patients with type 2 diabetes mellitus, which can provide a strong evidence for clinical diagnosis and treatment. Now it was reported as follows.

2. DATA AND METHODS

2.1 General information

A total of 100 elderly patients who were diagnosed as type 2 diabetes mellitus in Baogang Hospital of Inner Mongolia from June 2017 to May 2020 were chosen as research objects. All patients met the diagnostic criteria related to type 2 diabetes in Internal Medicine.[8] Exclusion criteria were as follows: Patients with acute diabetic complications; patients with severe chronic diabetic complications; patients with malignant tumors; patients with severe cardiovascular and cerebrovascular diseases; patients with liver and kidney dysfunction. According to c-IMT, they were divided into the normal group (n = 35, c-IMT = 0.9-1.0 mm), the mild to moderate group (n = 41, c-IMT = 1.0-1.2 mm) and the severe group (n = 24, c-IMT $\geq$ 1.2 mm). In the normal group, there were 20 male and 15 female cases, aged 61-83 years, with an average age of (70.5 $\pm$ 9.3); the course of diabetes was 1-10 years, with an average of (5.5 $\pm$ 1.6) years. In the mild to moderate group, there were 22 male and 19 female cases, aged 60-81 years, with an average age of (70.6 $\pm$ 9.8); the course of diabetes was 1-9 years, with an average of (5.7 $\pm$ 1.4) years. In the severe group, there were 14 male and 10 female cases, aged 62-80 years, with an average age of (71.2 $\pm$ 9.2); the course of diabetes was 1-11 years, with an average of (5.1 $\pm$ 1.3) years. There was no statistically significant difference in the general data among the three groups (p > .05), and it was comparable. The research was approved by Ethics Committee of Hospital.

2.2 Research methods

2.2.1 *The measurement of Hcy, sICAM-1 and HMGB1*

In the morning, 5 ml of cubital venous blood was drawn under fasting state and centrifuged (3,000 r/min, 10 min), with a centrifugation radius of 15 cm, and serum and plasma were separated for examination. Plasma Hcy, sICAM-1, and HMGB1 levels were measured by enzyme-linked immunosorbent assay, and the kits were purchased from Biosourze, USA. The operation was performed in strict accordance with the instructions.

2.2.2 *c-IMT examination*

PHILIPS33 color Doppler ultrasound machine and L11-3B 7.5 MHz probe were used for examination. Each patient was placed in supine position, with the headrest padded behind the neck, the head deviated backward and the neck fully exposed. c-IMT, plaque, stenosis and blood flow were measured subsequentially. The c-IMT was assessed in 3 segments: the distal common carotid (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider) and the proximal internal carotid arteries (1 cm section of the internal carotid artery immediately distal to the flow divider). The mean value of c-IMT was taken on the basis of the measurements on both sides.

2.3 Statistical methods

SPSS 22.0 statistical software was applied to the analysis of the data in this research. The measurement data were represented by mean $\pm$ standard deviation ($\bar{x} \pm$ s), One-way ANOVA was applied to the comparison among multiple groups, and SNK-q test was used in the comparison between two groups. Pearson's correlation analysis was applied to the correlation analysis. The difference p < .05 was of statistical significance.

3. RESULTS

3.1 The comparison in the expression levels of plasma Hcy, sICAM-1 and HMGB1 among the three groups

The comparison in plasma Hcy, sICAM-1, HMGB1 and c-IMT among the three groups of patients was of statistical significance (p < .05) (see Table 1).

3.2 The relationship of plasma Hcy, sICAM-1, HMGB1 with c-IMT

The results of correlation analysis showed that the expression levels of plasma Hcy, sICAM-1 and HMGB1 were positively correlated with c-IMT in elderly patients with type 2 diabetes mellitus relationship (r = .627, .598, .614; p < .05).

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Table 1. The comparison in the expression levels of plasma Hcy, sICAM-1, HMGB1 and c-IMT among the three groups ($\bar{x} \pm s$)

Group	Hey/μmol·L^{-1}	sICAM-1/μg·L^{-1}	HMGB1/ng·ml^{-1}	c-IMT/mm
c-IMT Normal Group	15.87±5.19	453.16±65.36	15.27±7.69	0.95±0.04
c-IMT Mild to moderate group	22.74±7.83	503.26±108.94	24.69±10.98	1.11±0.04
c-IMT Severe group	26.49±6.12	605.87±125.47	32.87±13.14	1.27±0.03
F Value	20.216	15.570	20.352	515.831
p Value	< .05	< .05	< .05	< .05

4. DISCUSSION

Atherosclerosis is the underlying disease of macrovascular complications in elderly patients with type 2 diabetes mellitus.[9] c-IMT is currently recognized as an objective index that can well reflect systemic atherosclerosis, and its degree of thickening is closely related to cardiovascular diseases such as cerebral infarction and coronary heart disease.[10] Therefore, the early and timely identification of the change in c-IMT to understand the progression of atherosclerosis are important for the prevention and treatment of macrovascular complications in elderly type 2 diabetes mellitus. Hcy, a sulfur-containing amino acid generated by demethylation of intracellular methionine, can damage the vascular endothelium by producing peroxides and superoxide, change the coagulation factor function, cause macrophage reactions and fat accumulation in the vascular wall.[11,12] In this study, plasma Hcy was associated with c-IMT in elderly patients with type 2 diabetes mellitus, suggesting that it is involved in the early atherosclerosis formation. In patients with type 2 diabetes mellitus, glycation end products can increase the sensitivity of endothelial cells to Hcy injury, both of which are involved in the vascular endothelial injury in diabetic patients. Meanwhile, the high level of Hcy in the body results in aggravated direct glucose toxicity, massive peroxide and superoxide production, damages the vascular endothelial cells and stimulates the growth of vascular smooth muscle, thereby promoting the occurrence and development of atherosclerosis.

sICAM-1 is a type of adhesion molecules on the surface of cells, such as vascular endothelial cells.[13] The level of sICAM-1 in diabetic patients was significantly increased, which may be related to their long-term hyperglycemia and dyslipidemia. Some studies have reported that the elevated sICAM-1 level is associated with atherosclerosis.[14] On the basis of that, this study analyzed the relationship between sICAM-1 and c-IMT, showing that the elevated plasma sICAM-1 level was proven to be associated with c-IMT. The abnormally elevated level of sICAM-1 in diabetic patients can mediate the viscosity of vascular endothelial cells and monocytes, cause vascular endothelial injury, increase vascular permeability, enhance platelet aggregation, promote thrombosis, participate in atherogenesis, and play an important role in the occurrence and development of macrovascular complications.

The results of this study showed that the level of plasma HMGB1 was proved to be associated with c-IMT. HMGB1 plays an important role in the pathological development of diabetes and its complications.[15] In diabetic patients, after the immune attack of pancreatic β-cells, local inflammatory cell infiltration is increased accordingly, with HMGB1 released and the expression upregulated. During the progression of atherosclerotic lesions, the activated macrophages and smooth muscle cells are the main sources of HMGB1, which accumulate in the blood, induce the generation of a large number of inflammatory cytokines, maintain and amplify the inflammatory response, and promote the progression of atherosclerosis.

5. CONCLUSION

The expression levels of plasma Hcy, sICAM-1 and HMGB1 are abnormally increased in elderly patients with type 2 diabetes mellitus, and related to c-IMT, which can provide a strong evidence for clinical diagnosis and treatment by detecting their levels in clinical practice.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

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