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Original Article

Relationship between Procalcitonin, Homocysteine and Severity of Coronary Artery Disease in Type 2 Diabetic Patients

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SUMMARY

Background: To investigate the relationship between procalcitonin, homocysteine and severity of coronary artery disease (CADs) in type 2 diabetic patients (T2DM).
*Methods:*A total of 121 patients with type 2 diabetes were divided into diabetic group, diabetic patients with coronary heart disease group (patients with stable angina pectoris and acute coronary syndrome group and combined group), another 50 healthy controls were analyzed between the clinical data, according to the number of coronary lesions, Gensini score group and multiple regression analysis of diabetes mellitus PCT and Hcy levels in patients with coronary artery disease.
Results: There was a statistically significant difference in diabetes course, BMI, Glu, HbA1c, Hcy, PCT between the T2DM-CHD groups compared with the C and T2MD groups. Gensini scores of the SAP and ACS groups were significantly positively correlated with Hcy and PCT levels ($r = 0.137$, $r = 0.232$, $r = 0.526$, $r = 0.545$, $p < 0.05$). Two, three coronary lesions group Hcy and PCT levels were higher than those of the C group ($p < 0.05$). Multivariate logistic regression analysis showed that HbA1c (OR 1.58, 95% CI 1.16–2.80, $p = 0.016$), Hcy (odds ratio [OR] 2.27, 95% CI 1.24–2.53, $p = 0.002$) and PCT (OR 1.86, 95% CI 1.29–3.98, $p = 0.024$) were the independent influence factor of Gensini score in T2DM-CHD patients.
Conclusion: This study shows that the severity of CADs with the increase of PCT and Hcy levels in patients with T2DM-CHD. It is of great value in predicting CADs.

1. Introduction

With the development of social economy in recent years, the aging process has accelerated, and the number of obese people has increased, diabetes has a global growth trend, and the incidence has gradually increased, leading to an increase in the number of patients with diabetes combined with cardiovascular disease. Therefore, prevention and treatment of diabetes must prevent cardiovascular disease.[1]

When diabetes mellitus combined with CHD often has more serious disease conditions, poorer prognosis, and higher mortality.[2] With the development of diagnosis and treatment of CHD, percutaneous coronary intervention (PCI) has become one of the most effective methods for coronary revascularization,[3,4] the results are still unsatisfactory in high-risk subgroups of patients.[5] Therefore, early warning the severity of coronary artery diseases (CADs) is still a challenging task.[6,7]

Recent studies have shown that high homocysteine (Hcy) is an important risk factor for cardiovascular diseases, due to increased thrombogenicity, oxidative stress status and endothelial dysfunction.[8,9] However, the progressive contribution of hyperhomocysteinemia on CADs is still under debate. Procalcitonin (PCT) is a biomarker for the diagnosis of sepsis. In recent studies have shown that in cardiovascular events, different degrees of increase of PCT can be detected,[10–12] so it can be seen that PCT levels were correlate with the extent of atherosclerosis in patients with CHD and were even associated with an adverse outcome.[13–15]

However, in the patients with type 2 diabetes mellitus (T2DM) combined with CHD, the correlations of PCT and Hcy with the severity of CADs are rarely investigated. In present study, we detected the levels of PCT and Hcy in T2DM-CHD patients and analyzed their relationships between CADs, aiming to provide certain theoretical basis for predicting the severity of CADs.

2. Materials and methods

2.1. Objects

A total of 121 T2DM patients diagnosed and admitted in the Department of Cardiology, the Affiliated Zhengzhou People's Hospital of Southern Medical University, from January 2014 to January 2015 were retrospectively analyzed. According to the coronary angiographic results after admission, 46 patients were divided into the T2DM group and 75 patients were divided into the T2DM-CHD group. In the T2DM-CHD group, 39 T2DM patients were combined with stable angina pectoris (Subgroup SAP), and 36 T2DM patients were combined with acute coronary syndrome (Subgroup ACS). At the same time, 50 healthy people with sex- and age-matching were

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set as the control group (C). Inclusion criteria: the diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies, fasting glycaemia > 126 mg/dL, random glycaemia > 200 mg/dL or Hb A1c > 6.5%.[16] The diagnosis of CHD was confirmed by coronary angiography on admission: at least one main coronary stenosis more than 50% revealed by coronary angiography and met the diagnostic guidelines of ACC/AHA in 2007.[17] Exclusion criteria: combined with secondary hypertension, various blood system diseases, infection, hyperthyroidism or hypothyroidism, obstructive sleep apnea syndrome, liver or kidney dysfunction, severe cardiac insufficiency, malignancy, or stroke; had folic acid, vitamin B12, or other drugs that may affect plasma Hcy within 3 months. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Southern Medical University. Written informed consent was obtained from all participants.

2.2. Biochemical measurements

The blood was collected from each fasting for more than 8-hour subject in the morning for the detection of biomarkers. Glucose, HbA1c, UA, Blood count and Lipid concentrations were measured using routine methods.[18] Plasma homocysteine was measured using a competitive immunoassay with direct chemiluminesce-nce detection (Shanghai Medical Devices Co. Ltd., Shanghai, China). The lower detection limit was 0.5 μmol/L. Serum PCT was determined on high-sensitivity immunoluminometric assay (BRAHMS Aktiengesellschaft Co. Ltd., Hennigsdorf, Germany); analytical assay sensitivity: 0.01 ng/ml; functional assay sensitivity [20.0% inter-assay variation coefficient]: 0.05 ng/ml).

2.3. Coronary angiography

Coronary angiography was performed by a digital subtraction angiography (DSA) machine (General Electric Company, Connecticut, America). Coronary angiography was performed in left or right radial or femoral arteries in all patients. CADs were visually judged by at least 2 cardiologist physicians (qualified for intervention therapy), and instruments can be used to measure the lesion-involved site, blood supply scope, stenosis degree, or lesion length if necessary.

2.4. Data collection and definition

The collected data include the demographic information, CHD risk factors, medical history, biomarkers, or coronary angiographic information. All the data were collected by two independently trained investigators so as to ensure the accuracy of the original data entry.

BMI is defined as body weight (kg)/height (m^2), and according to the standards issued by WHO, BMI within 18.5-24.9 is defined as normal, 25–29.9 as overweight, and > 30 as obesity.[19] We suggested that Chinese populations may need different BMI standards, which was the limit of our study, but this limit did not affect the comparison of BMI among the patients. Low level of HDL-C is defined as < 1.04 mmol/L.[20] Significant stenosis is defined at least one main coronary stenosis more than 50%, and multi-vessel disease is defined as > 2 vessels with significant stenosis in coronary angiography.[21] The severity of vascular stenosis is calculated using the Gensini score, and the total Gensini score of CADs is the product of the scores of all branches and their corresponding weighting factors.[22]

2.5. Statistical analysis

The normally distributed continuous variables or approximate normal distribution variables were expressed as mean ± standard deviation. The categorical variables were expressed as frequency or constituent ratio. The continuous variables were analyzed by the unpaired t test or Mann Whitney U test. The categorical variables were compared using the chi-square test or Fisher's exact test. The intergroup comparison used the single-factor ANVOA. The correlations among indexes used Pearson correlation analysis, and multivariate logistic regression analysis was used to predict the factors that can help to identify T2DM-CHD, with bilateral $p < 0.05$ considered as statistical significance. All the analyzes were performed using SPSS19.0 software (IBM, Armonk, New York).

3. Results

3.1. General clinical data

The comparison of general clinical data among the groups are shown in Table 1. Diabetes course in Subgroup ACS is higher than Group T2DM ($t = 2.21$, $p = 0.03$), BMI in Subgroup ACS is higher than Group C ($t = 2.04$, $P = 0.04$); Glu in Subgroup ASP and ACS are higher than Group C and T2DM ($t = 6.01$, $t = 6.14$, $t = 5.30$, $t = 5.31$, $p < 0.01$), HbA1c in Subgroup ASP and ACS are higher than Group C and T2DM ($t = 8.08$, $t = 7.69$, $t = 9.96$, $t = 9.54$, $p < 0.01$), among which HbA1c in Subgroup ACS are higher than Subgroup ASP ($t = 2.62$, $p = 0.01$, Table 1).

3.2. Comparison of Hcy and PCT among different groups

The levels of Hcy in Subgroup SAP and ACS are higher than Group C and T2DM ($t = 4.91$, $t = 2.07$, $t = 6.83$, $t = 4.13$, $p < 0.05$). The levels of PCT in Subgroup SAP and ACS are higher than Group C and T2DM ($t = 6.44$, $t = 7.19$, $t = 8.49$, $t = 6.79$, $p < 0.05$). The levels of Hcy and PCT in Subgroup ACS are higher than Subgroup ASP ($t = 2.16$, $p = 0.03$; $t = 4.04$, $p < 0.01$). The correlation coefficients of Hcy level with Gensini scores of SAP and ACS Group were $r = 0.137$, $r = 0.232$ ($p < 0.05$). The correlation coefficients between PCT level and Gensini scores of SAP and ACS Group were $r = 0.526$, $r = 0.545$ ($p < 0.05$), the Gensini scores of the two groups were significantly positively correlated with Hcy and PCT levels. The Hcy, PCT and Gensini score in the three-vessel disease group were higher than those in the Group C and single-vessel disease group ($t = 6.14$, $p < 0.01$; $t = 2.62$, $p = 0.01$). There were significant differences in PCT and Gensini scores between the two lesions and the single-vessel disease group ($t = 7.67$, $p < 0.05$; $t = 3.60$, $p < 0.05$, Table 2). That is, with the increase of the number of coronary lesions, Hcy, PCT and Gensini scores raised.

3.3. Comparison of Hcy and PCT among different Gensini score groups

Compared with Hcy and PCT, there was a statistical difference between each Gensini score group and the C group (all $p < 0.05$, Figs. 1, 2). The higher levels of Hcy and PCT in Gensini score Group, the more coronary artery lesions, and the more severe coronary artery stenosis.

3.4. Multivariate logistic regression analysis

The multivariate logistic stepwise regression analysis was performed with such clinical biochemical indexes as the diabetes

Table 1
Comparison of general information and biomarkers among groups[a].

Item	C (n = 50)	T2DM (n = 46)	T2DM-CHD (n = 75)	
			SAP (n = 39)	ACS (n = 36)
Age, years	57.24 ± 9.34	58.43 ± 10.56	57.45 ± 9.13	58.53 ± 10.21
M/F, n (%)	35/15	28/18	23/16	26/10
Smoking, n (%)	11 (22.0)	14 (30.4)	22 (56.4)	23 (63.9)
History of stroke, n (%)	-	2 (4.3)	1 (2.6)	1 (2.8)
Hypertension, n (%)	-	3 (6.5)	2 (5.1)	2 (5.6)
Hyperlipidemia, n (%)	-	36 (78.3)	31 (79.5)	29 (80.6)
Family history of CHD, n(%)	-	1 (2.2)	1 (2.6)	2 (5.6)
Chronic kidney disease, n (%)	-	2 (4.3)	1 (2.6)	1 (2.8)
Diabetes course (year)	-	7.53 ± 2.12	8.64 ± 3.75	9.11 ± 4.23[2)]
BMI (kg/m^2)	25.01 ± 4.07	25.46 ± 5.23	26.21 ± 7.01	27.75 ± 8.23[1)]
Glu ($mmol·L^{-1}$)	5.54 ± 2.87	5.67 ± 2.41	9.42 ± 3.21[1)2)]	9.53 ± 4.12[1)2)]
TC ($mmol·L^{-1}$)	4.43 ± 0.54	4.12 ± 1.33	4.47 ± 0.51	4.56 ± 0.62
TG ($mmol·L^{-1}$)	1.51 ± 0.42	1.65 ± 0.55	1.61 ± 0.45	1.59 ± 0.61
LDL-C ($mmol·L^{-1}$)	2.71 ± 0.62	3.03 ± 1.01	2.63 ± 0.71	2.93 ± 1.01
HDL-C ($mmol·L^{-1}$)	1.01 ± 0.21	1.12 ± 0.28	1.03 ± 0.22	1.12 ± 0.31
HbA1c/%	5.61 ± 0.81	5.68 ± 0.77	7.22 ± 1.07[1)2)]	7.96 ± 1.37[1)2)3)]
UA ($\mu mol·L^{-1}$)	321.21 ± 56.34	321.33 ± 54.61	327.23 ± 60.61	319.35 ± 58.02
SCr (μmol/L)	78.80 ± 18.97	78.96 ± 19.40	79.08 ± 20.19	79.66 ± 19.27
Folic acid ($ng·ml^{-1}$)	15.21 ± 6.89	18.24 ± 6.76	18.43 ± 7.12	17.13 ± 6.89
VB12 ($pg·ml^{-1}$)	252.12 ± 67.12	268.24 ± 68.23	256.48 ± 65.32	261.42 ± 69.31
Hemoglobin ($g·L^{-1}$)	113.23 ± 11.24	118.51 ± 17.26	117.21 ± 13.26	116.12 ± 15.46

Note: Compared with Group C, [1)] $p < 0.05$; compared with Group T2DM, [2)] $p < 0.05$; compared with Subgroup ASP, [3)] $p < 0.05$.
BMI, body mass index; Glu, glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; UA, uric acid.
[a] All the data were expressed as mean ± standard deviation, median, quartile, or percentage.

Table 2
Comparison of Hcy and PCT among groups[a].

Category	n	Hcy ($\mu mol·L^{-1}$)	PCT ($ng·ml^{-1}$)	Gensini score
C	50	8.23 ± 3.14	0.04 ± 0.03	-
T2DM	46	10.21 ± 3.89[1)]	0.11 ± 0.07[1)]	-
T2DM-CHD				
SAP	39	12.01 ± 4.12[1)2)]	1.21 ± 0.07[1)2)]	39.97 ± 11.33
ACS	36	14.31 ± 5.10[1)2)3)]	1.29 ± 0.10[1)2)3)]	57.55 ± 14.35[3)]
Branches with lesions				
Single	31	11.22 ± 3.21	0.10 ± 0.04[1)]	18.75 ± 15.71
Two	23	12.63 ± 5.42[1)]	1.12 ± 0.11[1)4)]	34.23 ± 15.56[4)]
Three	21	14.11 ± 4.76[1)4)]	1.21 ± 0.11[1)4)5)]	63.47 ± 26.64[4)5)]

Note: Compared with Group C, [1)] $p < 0.01$; compared with Group T2DM, [2)] $p < 0.05$; compared with Subgroup ASP, [3)] $p < 0.05$,compared with Subgroup Single, [4)] $p < 0.05$,compared with Subgroup Two, [5)] $P<0.05$
Hcy, homocysteine; PCT, procalcitonin.
[a] All the data were expressed as mean ± standard deviation

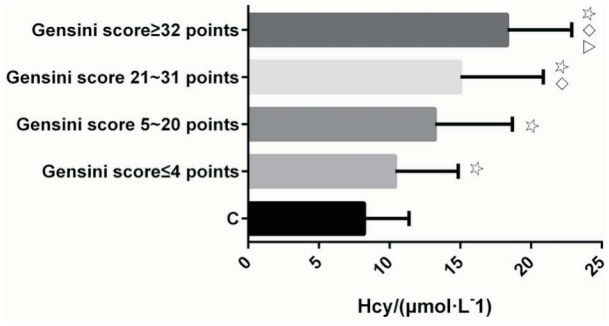

Fig. 1. Comparison of Gensini score in Hcy. The data shown are the means ± standard deviation. Note: Compared with Group C, ☆) p < 0.05; compared with Subgroup ≤ 4 points. ◊) p < 0.05; compared with Subgroup 5~20 points, △) p < 0.05; Hcy, homocysteine.

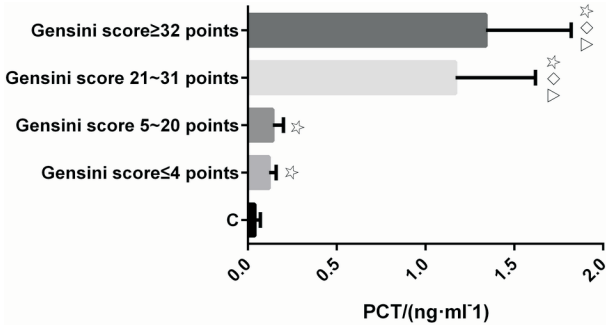

Fig. 2. Comparison of Gensini score in PCT. The data shown are the means ± standard deviation. Note: Compared with Group C, ☆) p < 0.05; compared with Subgroup ≤ 4 points, ◊) p < 0.05; compared with Subgroup 5~20 points, △) p < 0.05; PCT, procalcitonin.

course, BMI, Glu, HbA1c, Hcy, and PCT on admission as the independent variables and the Gensini score as the dependent variable, and the result showed that HbA1c (OR 1.58, 95% CI 1.16–2.80, p = 0.016, Hcy (odds ratio [OR] 2.27, 95% CI 1.24–2.53, p = 0.002) and PCT (OR 1.86, 95% CI 1.29–3.98, p = 0.024), (Table 3) were the independent influence factor of Gensini score in T2DM-CHD patients.

Table 3
Multivariate logistic regression analysis of Gensini score in group T2DM-CHD.

Item	β	*S.E.*	*Wald*	*OR* (95% *CI*)	*p*-value
HbA1c	1.33	0.52	6.61	1.58 (1.16–2.80)	0.016
Hcy	1.83	0.31	6.61	2.27 (1.24–2.53)	0.002
PCT	1.52	0.06	5.29	1.86 (1.29–3.98)	0.024

Note: CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

4. Discussion

In this study, we find that BMI in subgroup ACS is higher than Group C (p = 0.04). Previous studies have shown that obesity is an important risk factor for the development of CHD and is associated with insulin resistance, increased oxidative stress, increased platelet adhesion, and chronic inflammation, all of which contribute to the progression of CHD.[23] Recent clinical studies have found that obesity accelerates the progression of coronary atherosclerosis and increases the incidence of cardiovascular adverse events.[24] Taking the contributive roles of obesity toward atherosclerosis into account, losing weight is very important to change the progress of atherosclerosis in diabetic patients.

Studies have confirmed that the occurrence of vascular disease is closely related to Hcy. Hcy is a sulfur-containing amino acid that is an important intermediate in the metabolism of methionine and cysteine and does not participate in protein synthesis. When the concentration of Hcy metabolic disorder is increased, superoxide products will damage vascular endothelial cells; stimulate the transitional growth of vascular smooth muscle cells, leading to stenosis of the lumen, which will affect blood flow;[25] Hcy can accelerate the oxidation of low-density lipoprotein cholesterol, prompting the cells ingest and accumulate in the cells, thereby increasing the formation of foam cells and aggravating the degree of stenosis of the blood vessels; Hcy can cause changes in the function of blood coagulation factors, increase the adhesion of platelets, induce thrombosis, and lead to the occurrence of acute cardiovascular events.[26] A dense complex with apolipoprotein, which is easily phagocytized by vascular wall macrophages and deposited under the vessel wall, eventually leading to the occurrence of CHD. We found that patients with T2DM, Hcy levels and the severity of CADs are closely related. May be related to insulin resistance. We also found that Gensini scores increased as Hcy levels increased in patients with T2DM, and there was a significant difference in Hcy levels among different groups, confirming that Hcy levels are closely related to CHD. Logistic regression analysis showed that Hcy was an independent risk factor for coronary heart disease. Elevated Hcy level correlated with cardiovascular events, consistent with the results of Wang et al.[27] and Akyürek et al.[28] In summary, Hcy can be used as a noninvasive indicator of CADs.

Inflammatory responses play an important role in coronary atherosclerosis and has been recognized as the pathologic basis of atherosclerosis.[29] Previous study found that in cardiovascular events, there are varying degrees of PCT levels increased, can be used as a new indicator of cardiovascular events.[30] The mechanism of the relationship between serum PCT and coronary lesions may be explained by the activated inflammatory state, which plays a key role in the progression of atherosclerosis. Studies have shown that PCT plays an important role in monocyte adhesion and migration and stimulates the expression of inducible nitric oxide synthase gene in patients with sepsis, representing a key feature of the atherosclerotic process.[31] As a chemoattractant, PCT was originally produced in adherent monocytes, which were then able to accumulate more parenchymal cells for further production of PCT.[32] PCT mRNA is expressed by peripheral blood mononuclear cells, and then directly stimulated by lipopolysaccharide to indirectly stimulate the production of cytokines interleukin-1β, interleukin-2, interleukin-6 and tumor necrosis factor-α, and these inflammatory factors. It also plays a key role in the process of atherosclerosis.[33] We found that patients with simple diabetes had higher levels of PCT than controls, probably due to the fact that diabetes is a metabolic disorder characterized by disturbances in glucose metabolism and is involved in chronic inflammatory injury.[34] Subgroup analysis found that the level of PCT in ACS group were higher than the SAP group, and were higher than the C group and T2DM group, suggesting that there was a relationship between PCT and the incidence of CHD. Therefore, the early detection of PCT levels help monitor the progression of T2DM-CHD.

Previous studies have shown that high-level HbA1c has no significant association with the increase of cardiovascular risk events in patients with DM while not with CHD.[35] Another study reported that T2DM-CHD patients have high-level HbA1c, and their coronary lesions exhibit complex and severe clinical features,[36] consistent with this study. This study also finds that HbA1c is an independent predictor of coronary artery disease in T2DM-CHD patients.

5. Conclusions

In summary, the Hcy, PCT levels is independently associated with CADs. Therefore, the early monitoring of Hcy and PCT levels in patients with T2DM-CHD can predict the progress of CHD, prevention in advance, and has important clinical value in improving long-term prognosis of patients.

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Conflicts of interest

The authors declare no conflict of interest.

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