Original Article
Correlations among plasma insulin concentration, insulin sensitivity and coronary artery ectasia

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Abstract: Objective: To clarify the correlations between plasma insulin and coronary artery ectasia (CAE). Methods: Between January 2013 and January 2017, 100 patients with confirmed CAE were enrolled in this study and assigned to the case group, whereas 50 concomitant patients with negative coronary angiography were assigned to the control group. The plasma insulin concentrations were compared between the two study groups. All the patients with CAE were stratified into subgroups of insulin resistance and insulin sensitivity in accordance with the homeostasis model assessment-insulin resistance (HOMA-IR) index. Comparative analyses of plasma insulin concentration, body mass index (BMI), systolic and diastolic blood pressure, and levels of triglyceride, and the levels of overall cholesterol and high-density lipoprotein cholesterol were conducted between the case group and the control group. The proportions of CAE lesions of different grades were also compared between the two study groups. Pearson correlation analysis was performed to assess the correlations among plasma insulin concentration, HOMA-IR index and coronary artery calcification scores. Results: As compared with the controls, the patients with CAE had significantly higher plasma insulin concentrations (P=0.005); the plasma insulin concentration (P=0.013), BMI (P=0.039), systolic and diastolic blood pressure (P=0.025, 0.030), levels of triglyceride (P=0.014) and overall cholesterol (P=0.033) were substantially higher, but the high-density lipoprotein cholesterol level was significantly lower in the patients with insulin resistance than in those with insulin sensitivity (P=0.024). The patients with insulin resistance mostly presented with CAE of Grade I and II whereas those with insulin sensitivity with CAE of Grade III and IV, and the differences were statistically significant (P<0.001); Pearson correlation analysis indicated a positive correlation was noted between coronary artery calcification scores and plasma insulin concentration (r=0.664, P=0.003), so was between coronary artery calcification scores and HOMA-IR index (r=0.712, P=0.002). Conclusion: Plasma insulin is correlated with CAE, and it may be involved in the development of CAE.

Keywords: Coronary artery ectasia, insulin, insulin resistance, hyperinsulinemia

Introduction

Coronary artery ectasia (CAE) is the local or diffuse dilatation of epicardial coronary arteries induced by reduced coronary artery wall adaptation, genetic susceptibility and immune complex action [1, 2]. CAE is a clinically rare coronary artery lesion with the prevalence ranging from 0.3% to 5.3% [3, 4]. Currently, some scholars hold that CAE and coronary atherosclerosis are partly similar in pathological changes and clinical outcomes, as the former is a variant of the latter [5]. Clinical studies reveal that the dilated coronary artery causes slow coronary flow, myocardial blood insufficiency, and susceptibility to thrombosis, thereby presence of myocardial infarction and other complications [6].

The pathogenesis of CAE remains unclear. Insulin has been proven to play a decisive role in the development of atherosclerosis. Insulin is one of the important factors that cause cardiovascular disease [7]. Insulin protects vascular endothelial cells under normal physiological conditions. Plasma insulin concentrations are low in patients with diabetes mellitus complicated with coronary heart disease (CHD). Active insulin supplementation alleviates the progression of coronary atherosclerotic lesions.
to stenosis [8]. Patients with insulin resistance are frequently present with hyperinsulinemia, which is one of the independent risk factors for CHD. Among non-diabetic patients, acute myocardial infarction (AMI) occurred in up to 29.22% of patients with insulin resistance, and insulin resistance is an independent risk factor for mortality in patients with AMI [9, 10]. Insulin resistance leads to pathological changes such as vascular endothelial dysfunction and injuries, as well as the vascular smooth muscle hyperplasia [11, 12]. However, few reports have been involved in the role of plasma insulin in the pathogenesis of CAE, and the correlation between plasma insulin and CAE has not been mentioned. Therefore, the purpose of this study was to tentatively confirm whether there were correlations among CAE, plasma insulin concentration and resistance by examining plasma insulin concentrations and resistance in patients with CAE. This study will bring some insights into the studies on prevention and treatment of CAE.

Materials and methods

Patients

The eligible patients provided written informed consent and the protocol of this study was approved by the Hospital Ethics Committee.

From January 2013 to January 2017, 100 patients with confirmed CAE treated in the Department of Cardiology in the affiliated Hospital of Qingdao University were recruited in this study. There were 70 males and 30 females, with an age ranging from 36.7 to 65.4 years (mean, 55.3±3.9 years), and the disease course of 1.5 to 5.3 years (mean, 2.6±1.1 years). Inclusion criteria included an age of over 18 years and the dilated coronary artery diameter in non-obstructive lesions exceeding 1.5 folds or over of normal coronary artery on coronary angiography. Patients were ineligible for enrollment if they had pericarditis, myocarditis, type I diabetes mellitus, hypertrophic cardiomyopathy, aortic aneurysm, malignant tumor, coronary artery stenosis, previous cardiac surgery, incomplete clinical medical records or were unable to follow the protocol. Fifty patients with negative coronary angiography were assigned to the control group. Negative coronary angiography was defined as no evident coronary stenosis (less than 50%) or dilatation.

Coronary angiography

Coronary angiography was conducted on all patients via a femoral artery puncture by the Judkins technique. During coronary angiography, the contrast medium used was iopamidol Injection 370, the device was a digital subtraction angiography and no drugs like nitrates were used for dilatation of coronary vessels. Quantitative coronary angiography was applied to examine the dilatation of coronary arteries. The criteria for classification of the CAE grading are as follows: two or three coronary arteries with diffuse dilatation was classified as Grade I, one coronary artery with diffuse dilatation and one coronary artery with local dilatation was defined as Grade II; single coronary artery with diffuse dilatation was defined as Grade III; single coronary artery with local or segmental dilatation was defined as Grade IV. Coronary artery calcification scores were used to evaluate the severity in CAE. The coronary artery calcification score was defined as the product of the calcified area and the density integral of calcification lesions.

Randomization

The patients in the experiment group were stratified into the insulin resistance subgroup and the insulin sensitivity subgroup according to the Homeostasis model assessment-insulin resistance (HOMA-IR) index [12]. The CAE patient was present with insulin resistance when the HOMA-IR index was greater than 2.69.

Detection of plasma insulin concentration

The plasma insulin concentrations of the patients were compared between the experimental group and the control group. At 12 h after fasting, 5 mL of venous blood was drawn from the elbow vein of each patient, and then input in an EDTA anticoagulant tube. The plasma was centrifuged at 3000 r/min for 15 min, followed by storage at -20°C. Insulin concentration assessment was performed with the use of the ELISA, strictly following the instructions on the ELISA kits (R & D Science, USA).

Detection of monitoring indicators

Body mass index (BMI), systolic and diastolic blood pressure, triglyceride, overall cholesterol
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Table 1. Comparison of baseline characteristics of patients between the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Group</th>
<th>M/F (n)</th>
<th>Age (year)</th>
<th>DM (n)</th>
<th>Hypertension (n)</th>
<th>Hyperlipidemia (n)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>55.3±3.9</td>
<td>70/30</td>
<td>55.3±3.9</td>
<td>0</td>
<td>47</td>
<td>6</td>
<td>25.8±1.2</td>
</tr>
<tr>
<td>DM (n)</td>
<td>0</td>
<td>37/13</td>
<td>54.7±3.1</td>
<td>6</td>
<td>26</td>
<td>7</td>
<td>24.6±1.3</td>
</tr>
<tr>
<td>Hyperlipidemia (n)</td>
<td>0.261</td>
<td></td>
<td>0.209</td>
<td>13.691</td>
<td>0.334</td>
<td>2.695</td>
<td>1.175</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>0.610</td>
<td>0.845</td>
<td>&lt;0.001</td>
<td>0.564</td>
<td>0.101</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Note: M denotes male, F female, DM diabetes mellitus.

Figure 1. Comparison of plasma insulin concentrations between the case group and the control group. *P<0.05, compared with the control group.

Figure 2. Comparison of insulin concentrations between the insulin resistance subgroup and the insulin sensitivity subgroup. *P<0.05, compared to the insulin sensitivity subgroup.

Statistical analysis

All statistical data were analyzed with the application of the SPSS software, version 20.0. Count data were expressed as percentages or rates, with the chi-square tests for between-groups comparisons. Measurement data were described as mean ± standard deviation, with the independent samples t-tests for between-groups comparisons. Pearson correlation analysis was performed to evaluate the correlations among CAE, plasma insulin concentration and HOMA-IR index. A P value of less than 0.05 was deemed as statistically significant.

Results

Patient characteristics

Sex ratio, age, BMI, hypertension and hyperlipidemia of patient were generally well-balanced between the case group and the control group (All P>0.05). The proportion of patients with type II diabetic mellitus in the case group decreased substantially compared with that in the control group (P<0.001, Table 1).

Plasma insulin concentrations between the case group and the control group

The plasma insulin concentration (36.5±7.4 mU/L) in the case group was remarkably higher than that (13.7±4.1 mU/L) in the control group (t=5.627; P=0.005), as shown in Figure 1.

Comparison of plasma insulin concentrations between the insulin resistance subgroup and the insulin sensitivity subgroup

The plasma insulin concentration was 50.2 ±12.2 mU/L in the insulin resistance subgroup (n=60), and 15.9±5.1 mU/L in the insulin sensitivity subgroups (n=40), hence there were significant disparities in plasma insulin concentrations between the two subgroups (t=3.287, P=0.013; Figure 2).
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Table 2. Comparison of basic markers between the insulin resistance subgroup and the insulin sensitivity subgroup

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>BMI (kg/m²)</th>
<th>Blood pressure (mmHg)</th>
<th>Lipid level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>IRS</td>
<td>60</td>
<td>26.5±1.4</td>
<td>145.4±17.4</td>
<td>91.4±6.7</td>
</tr>
<tr>
<td>ISS</td>
<td>40</td>
<td>25.1±1.1</td>
<td>127.8±16.2</td>
<td>75.2±5.3</td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>2.311</td>
<td>2.526</td>
<td>3.285</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.039</td>
<td>0.025</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Note: IRS denotes insulin resistance subgroup, ISS insulin sensitivity subgroup.

Figure 3. Comparison of the proportions of different grades of CAE lesions between the two subgroups. *P<0.05, compared to the insulin sensitive group.

Discussion

Although the prevalence of CAE is relatively low, it brings such great harm that it has drawn growing attention from scholars [13, 14]. Previous clinical studies have showed that the major pathological characteristics of CAE are coronary artery intima thickening, destruction and reduced thickness of media, extracellular matrix degradation and severe atherosclerosis [15]. Vascular maladaptation leads to vascular remodeling or dilation [16].

Over recent years, the findings from most studies indicate that the level of inflammatory cytokines is related to CAE [17, 18]. Conversely, the association of CAE with insulin concentration is rarely reported. Insulin resistance and hyperinsulinemia play crucial roles in the pathogenesis of cardiovascular disease; insulin resistance, in particular, has been a hotspot of studies on cardiovascular disease. According to a study, the incidence of myocardial infarction was markedly higher in patients with high fasting plasma insulin concentrations than in those with low corresponding concentrations, regardless of male or female [19]. The incidences of hypertension and hyperlipidemia in CAE patients with diabetic mellitus are much higher than those of CAE patients without dia-

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On the Spearman correlation analysis, plasma insulin concentration was positively correlated with coronary artery calcification scores (r=0.664, P=0.003), as were HOMA-IR index and coronary artery calcification scores (r=0.712, P=0.002). This suggests that plasma insulin concentration and HOMA-IR index are closely related to the severity in CAE.
abetic mellitus. The results of the current study revealed that none of the enrolled CAE patients were complicated with diabetes mellitus. Hamirani et al. and Boles et al. held that contrary to patients with coronary atherosclerosis, the proportion of patients with diabetic mellitus is lower among CAE patients and is negatively correlated with the presence of diabetic mellitus [20, 21]. This is similar to the result of our current study. Our current study also demonstrated that the plasma insulin concentrations were markedly higher in the CAE patients than controls. These results suggest that insulin may play a decisive role in the pathogenesis of CAE.

When it comes to coronary heart disease, the coronary artery lesions mostly manifest diffuse stenosis in patients with insulin resistance and their rates of multi-site, multi-vessel and small vessel lesions are remarkably higher than those of patients with insulin sensitivity. According to our current study, patients with insulin resistance primarily presented with Grade I and II of CAE, while those in the insulin sensitivity group with Grade III and IV; the proportions of different grades of CAE lesions varied greatly between the patients with insulin resistance and those with insulin sensitivity. This implies that CAE in patients with insulin resistance are characterized by multi-vessel local or diffuse coronary dilatation. Spearman correlation analysis indicated that plasma insulin concentration and HOMA-IR index were positively correlated with coronary artery calcification scores. This may attribute to the fact that insulin resistance mediates coronary artery endothelial injury, reduces coronary wall compliance and promotes lipid deposition, hence inducing the onset and development of CAE [22]. Additionally, high plasma insulin concentration stimulates vascular endothelial cells to secrete nitric oxide, reduces endothelin secretion and aggravates coronary atherosclerosis.

In conclusion, patients with CAE have elevated plasma insulin concentration. CAE is more severe in patients with insulin resistance than in those with insulin sensitivity. This study fails to delve into the mechanism of insulin in CAE, which should be further elucidated in the future studies.

**Disclosure of conflict of interest**

None.

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