Original Article
Associations of the insulin level and insulin resistance with the severity of coronary artery ectasia

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Abstract: Objective: To investigate the roles of insulin in coronary artery ectasia (CAE) and the association of insulin with the severity of CAE. Methods: The participants with CAE (n=80) or coronary arteriosclerosis (n=80), or healthy controls (n=80) undergoing coronary angiography in our hospital from March 2015 to March 2017 were enrolled in the current study. The fasting insulin (FINS) levels and the homeostasis model assessment-insulin resistance (HOMA-IR) index were compared among the three groups, and Spearman correlation analysis was conducted for clarifying the association of the insulin level with the severity of CAE. The patients with CAE were stratified into subsets of insulin resistance and insulin sensitivity in accordance with HOMA-IR, and the two subsets of patients were compared in systolic blood pressure (SBP), diastolic blood pressure (DBP), FINS, triglyceride (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), as well as the severity of CAE lesions. In addition, Spearman correlation analysis was made for exploring the relationship between the severity of CAE and the HOMA-IR. Results: The FINS and HOMA-IR levels in the patients with CAE were remarkably higher than those of the patients with coronary arteriosclerosis and healthy controls (both P<0.05). SBP, DBP, FINS, TG, TC and LDL-C were substantially higher, but HDL-C was lower in the CAE patients with insulin resistance than in those with insulin sensitivity (all P<0.05); big differences in the subtypes of CAE lesions were also observed between the CAE patients with insulin resistance and those with insulin sensitivity (P<0.001). On Spearman correlation analysis, the severity of CAE was positively correlated with HOMA-IR (r=0.73, P<0.001), the plasma insulin level was also positively correlated with the severity of CAE (r=0.69, P<0.002). Conclusion: Insulin might be associated with the onset of CAE and its severity, with higher insulin level indicating more severe CAE.

Keywords: Insulin, coronary artery ectasia, severity of lesions, association

Introduction

Coronary artery ectasia (CAE) is a vascular disease primarily manifested as diffusive or focal dilation of the coronary arteries in the epicardium caused by such factors as arteriosclerosis, inflammation, immunodeficiency or congenital diseases [1-3]. The diameter of an ectatic coronary artery can be 1.5 folds of that of a normal coronary artery. Most scholars hold that CAE and coronary atherosclerosis have much in common in pathological changes and clinical outcomes and CAE is a variant of atherosclerosis [4-6]. Currently, the diagnosis of CAE is mainly based on coronary angiography; on diagnostic coronary angiography, the detection rate of CAE in patients with ischemic symptoms ranges from 0.3% to 4.9% [7]. The major manifestations of CAE include sudden angina, arrhythmia and even sudden death, but there may be no clinical symptoms. Nevertheless, the pathogenesis of CAE is unclear, and most of the relevant findings are speculative and unauthoritative. According to a study, CAE is associated with the plasma insulin levels [8]. However, few reports are involved in the association. Therefore, in this study, we made a retrospective analysis on the clinical records of CAE patients admitted in our hospital, and investigated the roles of insulin in the development of CAE and
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the correlation of insulin with the severity of CAE, with an expectation that this study might bring some insights into clinical practice.

Materials and methods

Participants

All the participants in this study provided written informed consent and the study was approved by the Hospital Ethics Committee.

A total of 160 patients with CAE or coronary arteriosclerosis undergoing coronary angiography in our hospital between March 2015 and March 2017 were recruited as participants in this study. Among the enrolled patients, 80 patients with CAE were assigned to the CAE group, 80 patients with coronary arteriosclerosis were assigned to the coronary arteriosclerosis group. Patients were eligible for enrollment if they had chest tightness, pain and other symptoms, and had myocardium blood-supply insufficiency on electrocardiography and the treadmill exercise test; their symptoms of CAE were confirmed on coronary angiography and their complete clinical records were available. Patients were excluded if they had confirmed aortic dissection, pulmonary embolism or other cardiovascular diseases, had demonstrable organic heart disease, were present with the clinical symptoms of heart failure and left ventricular ejection fraction <40%; took recent nitrates and other drugs for dilatation of coronary artery, or had severe hepatic renal dysfunction, coagulation disorder or malignancy. In addition, 80 concomitant healthy volunteers were included as controls in the normal group.

Insulin measurement and the homeostasis model assessment-insulin resistance (HOMA-IR) index

The HOMA-IR was tested in the early morning by the enzyme-linked immunosorbent assay (ELISA) when all the participants in the three groups were fasting. The HOMA-IR of the patients in the CAE group was calculated with the use of the following formula: HOMA-IR=Fasting plasma glucose* fasting insulin/22.5 [4].

Stratification and comparison of patients with CAE

Patients with CAE were stratified into subgroups of insulin resistance and insulin sensitivity in terms of HOMA-IR. Insulin resistance is defined as when the HOMA-IR is greater than 2.69. Systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin (FINS), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) of the patients were compared between the two subgroups.

Determination of the severity of CAE in patients

According to the findings of coronary angiography, the severity of CAE lesions in the patients was rated into four grades in the order from severity to mildness [5]. Grade I was defined as the presence of two-vessel or three-vessel diffuse CAE; Grade II was defined as the presence of one-vessel diffuse CAE and one-vessel focal CAE; Grade III was defined as the presence of single-vessel diffuse CAE; Grade IV was defined as the presence of single-vessel focal CAE. The differences in the severity of CAE lesions were compared between the CAE patients with insulin-resistance and those with insulin-sensitivity.

Outcome measures

Height, weight, and blood pressure of all the participants were measured. Venous blood (5 mL) was drawn from the elbow vein of each participant after 12 h fasting, and placed into the EDTA anticoagulant tube, followed by plasma centrifugation at 3, 000 r/min for 15 min and storage at -20°C. The plasma insulin levels were tested by the ELISA, strictly following the instructions on the ELISA Kits (R&D science, US). The blood lipid levels were detected by AU5800 automatic biochemical analyzers.

Statistical analysis

All the data in this study were analyzed by the SPSS statistical software, version 19.0. Measurement data with normal distribution were described as mean ± standard deviation; one-way analysis of variance (ANOVA) with post hoc LSD-t tests were used for inter-group comparisons if more than two groups were involved and the independent samples t-test was used for between-group analysis when only two groups were involved. Count data were expressed as rates, with the chi-square tests for inter-group comparisons if more than two groups were involved and the chi-square partition tests for between-group comparisons when only two
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The significance level was set as \( \alpha = 0.05 \), and \( P < 0.05 \) was deemed significantly different.

Results

Baseline and clinical characteristics of the participants

Among the participants in the CAE group, 50 were male and 30 were female, with an age between 54 and 70 years (mean, \( 60.14 \pm 2.43 \) years); among those in the coronary arteriosclerosis group, 47 were male and 33 were female, with an age between 52 and 68 years (mean, \( 59.36 \pm 3.43 \) years); among the participants in the normal group, there were 52 males and 28 females, with an age ranging from 51 to 72 years (mean, \( 57.32 \pm 1.67 \) years). The three groups of participants were largely well-balanced in gender, age, hypertension, hyperlipidemia, diabetes mellitus, as well as the history of drinking and smoking (all \( P > 0.05 \)), so they were comparable (Table 1).

FINS and HOMA-IR

The levels of FINS and HOMA-IR in the CAE group were substantially higher than those of the coronary arteriosclerosis group and the normal group (all \( P < 0.05 \), Table 2).

General indexes of CAE patients with insulin resistance or insulin sensitivity

SBP, DBP, FINS, TG, TC and LDL-C in the CAE patients with insulin resistance were remarkably higher than those with the insulin sensitivity (all \( P < 0.05 \); HDL-C in the CAE patients with insulin resistance was strikingly lower than that of those with insulin sensitivity (\( P < 0.05 \), Table 3).

Subtypes of CAE lesions among patients with insulin resistance or insulin sensitivity

Among the ACE patients, CAE of Grade I and II were noted in the majority of the patients with insulin resistance, while CAE of Grade III and IV were in most of those with insulin sensitivity. The differences were statistically significant (\( P < 0.001 \), Table 4).

Correlation between CAE severity and HOMA-IR

According to the subtypes of CAE lesions, the severity of CAE was classified into 4 grades (Grade I, II, III, and IV). Spearman correlation

Table 1. Baseline and clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAE group</th>
<th>CA group</th>
<th>Normal group</th>
<th>F/X2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (n)</td>
<td>50/30</td>
<td>47/33</td>
<td>52/28</td>
<td>0.673</td>
<td>0.714</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>60.14±2.43</td>
<td>59.36±2.43</td>
<td>57.32±1.67</td>
<td>1.307</td>
<td>0.338</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.13±2.54</td>
<td>24.83±2.46</td>
<td>24.56±2.34</td>
<td>0.041</td>
<td>0.960</td>
</tr>
<tr>
<td>Hyperlipidemia (n)</td>
<td>21</td>
<td>30</td>
<td>24</td>
<td>2.444</td>
<td>0.295</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>31</td>
<td>43</td>
<td>29</td>
<td>5.851</td>
<td>0.054</td>
</tr>
<tr>
<td>DM (n)</td>
<td>10</td>
<td>24</td>
<td>22</td>
<td>5.718</td>
<td>0.057</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>18</td>
<td>17</td>
<td>15</td>
<td>0.354</td>
<td>0.838</td>
</tr>
<tr>
<td>Drinking (n)</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>1.214</td>
<td>0.545</td>
</tr>
</tbody>
</table>

Note: CAE denotes coronary artery ectasia, CA coronary arteriosclerosis, and DM diabetes mellitus.

Table 2. FINS and HOMA-IR of the participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAE group</th>
<th>CA group</th>
<th>Normal group</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FINS (mU/L)</td>
<td>18.76±3.34</td>
<td>10.54±2.34</td>
<td>8.31±1.39</td>
<td>14.686</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.72±1.52</td>
<td>3.34±1.07</td>
<td>2.63±0.94</td>
<td>15.763</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Note: CA group denotes coronary arteriosclerosis group; compared with the coronary arteriosclerosis group, \( *P<0.001 \); compared with the normal group, \( #P<0.001 \).

Table 3. General indexes of CAE patients with insulin resistance or insulin sensitivity

<table>
<thead>
<tr>
<th>Variable</th>
<th>IR (n=46)</th>
<th>IS (n=34)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>146.32±14.51</td>
<td>132.67±10.13</td>
<td>2.114</td>
<td>0.045</td>
</tr>
<tr>
<td>DBP</td>
<td>96.33±4.53</td>
<td>82.31±6.24</td>
<td>3.149</td>
<td>0.035</td>
</tr>
<tr>
<td>FINS</td>
<td>27.10±3.21</td>
<td>7.47±3.51</td>
<td>2.460</td>
<td>0.024</td>
</tr>
<tr>
<td>TG</td>
<td>2.98±0.49</td>
<td>1.23±0.34</td>
<td>5.082</td>
<td>0.007</td>
</tr>
<tr>
<td>TC</td>
<td>5.64±0.92</td>
<td>4.65±0.76</td>
<td>2.291</td>
<td>0.036</td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.57±0.58</td>
<td>2.34±0.28</td>
<td>3.308</td>
<td>0.030</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.83±0.36</td>
<td>1.54±0.14</td>
<td>3.184</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Note: IR denotes insulin resistance, and IS insulin sensitivity.
Table 4. Subtypes of CAE lesions among patients with insulin resistance or insulin sensitivity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case (n)</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>46</td>
<td>25</td>
<td>14</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>IS</td>
<td>34</td>
<td>3</td>
<td>4</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>X²</td>
<td>36.464</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: IR denotes insulin resistance, and IS insulin sensitivity.

Figure 1. Scatter plot of CAE severity and HOMA-IR.

Figure 2. Scatter plot of CAE severity and the plasma insulin level.

analysis indicated that HOMA-IR was positively correlated with the severity of CAE (r=0.73, P=0.001; Figure 1), so was the plasma insulin level (r=0.69, P=0.002; Figure 2).

Discussion

As a special subtype of coronary artery disease, the clinical manifestations of CAE are similar to those of coronary atherosclerosis. Clinically, CAE is frequently complicated by coronary atherosclerosis. As a result, most researchers argue that CAE is a variant of coronary atherosclerosis [9-11]. The inflammatory reactions of coronary atherosclerosis contribute to faster degradation of extracellular matrix, which may result in thinning and destruction of the tunica media if involved in the tunica media, thereby leading to disorder of the vascular anatomical structure and ultimately to vascular dilation [12-14].

The results of several recent clinical studies demonstrate that insulin is implicated in the development of arteriosclerosis, and is one of the most important determiners of cardiovascular and cerebrovascular diseases [15, 16]. The incidence of myocardial infarction is remarkably higher in the patients with high fasting insulin levels than those with low fasting insulin levels; therefore, hyperinsulinemia is a dominant contributor in the development of myocardial infarction [17]. Murase et al. held that diabetes mellitus is the only negative factor in the development of CAE [18]. A previous study has confirmed that the insulin secretion in the normal physiological state, together with the regulation of the glucose levels, is associated with an improvement of cardiac microcirculation, inhibition of endothelial cells apoptosis in the coronary arteries and a decrease in the dilation of coronary artery; whereas elevated insulin levels is associated with reductions in endothelial functions of the NO/endothelin system, and promotion of the coronary dilation [19]. Accordingly, we speculated that hyperinsulinemia promoted the development of CAE. In the current study, we compared FINS in HOMA-IR of participants among the CAE group, the coronary arteriosclerosis group and the normal group, and found that the FINS level (18.76±3.34 mU/L) in the CAE group was substantially higher than that of (10.54±2.34 mU/L) the coronary arteriosclerosis group and that (8.31±1.39 mU/L) of the normal group, so was the HOMA-IR level in the CAE group (7.72±1.52 versus 3.34±1.07 and 2.63±0.94). The findings were well aligned with the above-mentioned ideas.

Insulin resistance is primarily manifested as increased insulin secretion as a result of the disorder of glucose metabolism. The pathologi-
cal change of CAE is a complex process in which abnormal dilation and thinning of vascular walls were caused by stimulation from various factors. Insulin resistance damages the vascular endothelial cells, which results in the lipid deposition on the coronary artery walls, leading to a reduction of its compliance to the dilation of coronary artery and activation of the blood coagulation system and finally to the exacerbation of CAE [20]. In the current study, we stratified the patients with CAE into subsets of insulin resistance and insulin sensitivity in terms of their HOMA-IR levels and found that SBP, DBP, FINS, TG, TC and LDL-D in the CAE patients with insulin resistance were substantially higher, but the HDL-C level was lower than those of the CAE patients with insulin sensitivity, which corresponded to the findings reported by Jayanthi et al. [21]. This suggests that hyperinsulinemia might cause disorder of blood pressure and abnormal metabolism of blood lipid. Hence, we speculated that the degree of insulin resistance was associated with the CAE lesions. We compared the pathological subtypes between the CAE patients with insulin resistance and those with insulin sensitivity, and found that the rates of CAE of I and II (more severe CAE) were remarkably higher, but those of III and IV were lower in the CAE patients with insulin resistance than those with insulin sensitivity. Moreover, Spearman correlation analysis was conducted to investigate the correlation of CAE severity with HOMA-IR, and the results revealed that the severity of CAE was positively correlated with HOMA-IR, and the plasma insulin level. Namely, the degree of insulin resistance accelerated the aggravation of CAE, and the severity of CAE rose with the increase in the plasma insulin level in the body. The development of CAE might be associated with the matrix metalloproteinase-9 (MMP-9) and its inhibitor TIMP1 in which thinning of the vascular walls was caused by degradation of the cell matrix. As demonstrated in a study, MMP-9 and TIMP1 reflect the degree of damages to the smooth muscle cells, and their imbalanced expression might be implicated in the pathogenesis of CAE; the MMP-9 and TIMP1 levels are potently correlated with the plasma insulin levels [22].

In conclusion, insulin is implicated in the onset of CAE and correlated with the severity of the disease; insulin resistance aggravates the development of CAE. This study is of significance to the diagnosis and assessment of CAE. However, there are many deficiencies in this study due to its small sample size and relatively limited case selection. Therefore, additional more profound studies are required in the future.

Disclosure of conflict of interest

None.

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