Study on the correlation between serum Angptl2 level and carotid plaque nature in Type 2 diabetes

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Objective: To analyze the correlation between serum Angptl2 level and carotid plaque nature in Type 2 diabetes. Methods: 118 cases of Type 2 diabetes patients hospitalized in our hospital from August 2012 to December 2015 were the subjects of observation group, were accompanied with different degree of carotid plaque through B ultrasound and CT coronary arterial angiography examination, and were divided into unstable plaque group (n=56) and stable plaque group (n=62) according to the degree of plaque, and 97 cases of patients with Type 2 diabetes alone (not complicated with carotid plaque) who received blood glucose regulation treatment in our hospital during the same period were the control group. Serum Angptl2 levels and the values of carotid plaque nature-related indexes of all groups were detected, and the correlation between the two was further analyzed. Results: Serum Angptl2 level of observation group was significantly higher than that of control group, and serum Angptl2 level of unstable plaque group was higher than that of stable plaque group; serum Fbg, HbA1c and bigET-1 values of observation group were higher than those of control group while DBIL and RHI values were lower than those of control group; serum cystatin c and visfatin values of observation group were higher than those of control group while ApoA1 and MPO values were lower than those of control group; serum ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer values of observation group were higher than those of control group; serum Angptl2 level was directly proportional to Fng, HbA1c, bigET-1, cystatin c, ApoA1, visfatin, ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer levels, and inversely proportional to DBIL, RHI and MPO values. Conclusion: Angptl2 level is significantly abnormal in Type 2 diabetes patients with carotid plaque, has direct correlation with plaque nature-related indexes, and is the reliable index to judge patients’ condition and predict the outcome.

ABSTRACT

1. Introduction

Blood glucose and blood lipid disorders, etc in patients with type 2 diabetes can lead to the lipid deposition in carotid artery and gradual formation of plaques, unstable plaques fall off, enter into blood circulation, block heart, kidney, lung and other important organs and lead to function failure. Patients with type 2 diabetes are the high-risk group of artery plaque formation and cardiovascular events, and plaque properties should be monitored in real time so as to determine the intervention plan and make clear the disease process[1,2]. Angptl2 is secreted by endothelial cells, is activated under hypoxic condition and induces inflammatory reaction, increases blood cholesterol levels and promotes the formation of atherosclerosis. Angptl2 is considered to be the independent risk factor for the formation of atherosclerosis, and has a direct correlation with plaque nature. In the research, the correlation between serum Angptl2 level and carotid plaque nature in Type 2 diabetes was mainly analyzed, hereby reported as follows.

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2. Information and methods

2.1. General information

A total of 118 cases of Type 2 diabetes patients hospitalized in our hospital from August 2012 to December 2015 were the subjects of observation group, were accompanied with different degree of carotid plaque through B ultrasound and CT coronary arterial angiography examination, 60 cases were male and 58 cases were female, they were 49-76 years old and the average was (63.28±7.11) years. Strong-echo and flat plaques were defined as stable plaques \((n=62)\), and low-echo and irregular plaques were defined as unstable plaques \((n=56)\). 97 cases of patients with Type 2 diabetes alone (not complicated with carotid plaque) who received blood glucose regulation treatment in our hospital during the same period were the control group, 50 cases were male and 47 cases were female, they were 47-75 years old and the average was (62.76±7.09) years. Differences in baseline information were without statistical significance between two groups, \(P>0.05\).

2.2. Observation indexes

Biochemical automatic analyzer was used to detect fibrinogen (Fbg), glycosylated hemoglobin (HbA1c), bid endothelin-1 (bigET-1), direct bilirubin (DBIL), cystatin C and apolipoprotein A1 (ApoA1), and calculate endothelial function index (RHI). Enzyme-linked immunosorbent assay (ELISA) was used to detect Angptl2, visfatin, myeloperoxidase (MPO), anticardiolipin antibody (ACA), macrophage migration inhibitor (MIF), soluble CD40 ligand (sCD40L) and pregnancy-associated plasma protein-A (PAPP-A) levels; enzyme-linked immunosorbent-double antibody sandwich was used to detect CXC chemokine receptor 16 (CXCR16) level; immunoturbidimetric assay was used to detect D-dimer and homocysteine (t-HCY) levels.

2.3. Statistical methods

Data obtained in the research was analyzed by SPSS23.0 software, measurement data was in terms of Mean ± SD. Comparison between two groups was by \(t\) test, correlation analysis was by unary linear analysis and \(P<0.05\) was set as the standard of statistical significance in differences.

### 3. Results

#### 3.1 Serum Angptl2 levels

The average serum Angptl2 level of observation group was \((2.93±0.23)\) ng/mL, Angptl2 level of stable plaque group was \((1.56±0.12)\) ng/mL, and Angptl2 level of unstable plaque group was \((3.27±0.28)\) ng/mL. Serum Angptl2 level of control group was \((0.96±0.09)\) ng/mL. Serum Angptl2 level of observation group was significantly higher than that of control group, and serum Angptl2 level of unstable plaque group was higher than that of stable plaque group \((P<0.05)\).

#### 3.2 Fbg, HbA1c, bigET–1, DBIL and RHI

Serum Fbg, HbA1c and bigET-1 values of observation group were higher than those of control group while DBIL and RHI values were lower than those of control group; serum Fbg, HbA1c and bigET-1 values of unstable plaque group were higher than those of stable plaque group while DBIL and RHI values were lower than those of stable plaque group \((P<0.05)\), shown in Table 1.

#### 3.3 Cystatin c, ApoA1, visfatin and MPO

Serum cystatin c and visfatin values of observation group were higher than those of control group while ApoA1 and MPO values were lower than those of control group, serum cystatin c and visfatin values of unstable plaque group were higher than those of stable plaque group while ApoA1 and MPO values were lower than those of stable plaque group \((P<0.05)\), shown in Table 2.

#### 3.4 ACA, MIF, sCD40L, PAPP–A, CXCR16, t–HCY and D–dimer

Serum ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer values of observation group were higher than those of control group, ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer values of unstable plaque group were higher than those of stable plaque group \((P<0.05)\), shown in Table 3.

#### 3.5 Correlation between Angptl2 and carotid plaque–related indexes

Unary linear regression showed that serum Angptl2 level was directly proportional to Fng, HbA1c, bigET-1, cystatin c, ApoA1, visfatin, ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer levels, and inversely proportional to DBIL, RHI and MPO values \((P<0.05)\).

### Table 1

Comparison of Fbg, HbA1c, bigET-1, DBIL and RHI levels among groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fbg (mg)</th>
<th>HbA1c (%)</th>
<th>bigET-1 (pmol/L)</th>
<th>DBIL (μ mol/L)</th>
<th>RHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>273.81±24.76*</td>
<td>6.93±0.67*</td>
<td>0.26±0.02*</td>
<td>4.87±0.43*</td>
<td>1.98±0.15*</td>
</tr>
<tr>
<td>Stable plaque</td>
<td>241.28±21.28</td>
<td>6.47±0.59</td>
<td>0.22±0.02</td>
<td>5.21±0.45</td>
<td>2.07±0.19</td>
</tr>
<tr>
<td>Unstable plaque</td>
<td>289.36±24.17</td>
<td>7.32±0.69*</td>
<td>0.39±0.03*</td>
<td>3.76±0.35*</td>
<td>1.76±0.13*</td>
</tr>
<tr>
<td>Control</td>
<td>213.91±20.64</td>
<td>6.01±0.57</td>
<td>0.17±0.02</td>
<td>6.73±0.59</td>
<td>2.34±0.22</td>
</tr>
</tbody>
</table>

*\(P<0.05\).
Comparison of cystatin c, ApoA1, visfatin and MPO levels among groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cystatin c (mmol/L)</th>
<th>ApoA1 (mmol/L)</th>
<th>Visfatin (g/L)</th>
<th>MPO (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>1.88±0.17*</td>
<td>0.93±0.11*</td>
<td>218.39±18.34*</td>
<td>18.48±1.76*</td>
</tr>
<tr>
<td>Stable plaque</td>
<td>1.65±0.14</td>
<td>1.02±0.12</td>
<td>193.74±17.53</td>
<td>27.36±2.49</td>
</tr>
<tr>
<td>Unstable plaque</td>
<td>2.27±0.23*</td>
<td>0.76±0.08*</td>
<td>264.18±23.59*</td>
<td>14.27±1.39*</td>
</tr>
<tr>
<td>Control</td>
<td>1.03±0.12</td>
<td>1.32±0.12</td>
<td>156.38±14.21</td>
<td>31.29±2.76</td>
</tr>
</tbody>
</table>

*P<0.05.

<table>
<thead>
<tr>
<th>Groups</th>
<th>ACA</th>
<th>MIF (g/L)</th>
<th>sCD40L (ng/mL)</th>
<th>PAPP-A (mIU/L)</th>
<th>CXCR16 (8 g/L)</th>
<th>t-HCY (µ mol/L)</th>
<th>D-dimer (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>1.67±0.13*</td>
<td>23.15±2.09*</td>
<td>154.38±14.36*</td>
<td>11.83±1.39*</td>
<td>2.67±0.23*</td>
<td>22.38±1.96*</td>
<td>2.17±0.18*</td>
</tr>
<tr>
<td>Stable plaque</td>
<td>1.57±0.14</td>
<td>21.27±2.09</td>
<td>132.29±12.07</td>
<td>9.36±0.87</td>
<td>2.16±0.19</td>
<td>19.27±1.76</td>
<td>1.42±0.13</td>
</tr>
<tr>
<td>Unstable plaque</td>
<td>2.15±0.19*</td>
<td>27.15±2.68*</td>
<td>192.37±18.55*</td>
<td>14.28±1.59*</td>
<td>3.09±0.31*</td>
<td>27.49±2.34*</td>
<td>2.39±0.22*</td>
</tr>
<tr>
<td>Control</td>
<td>1.43±0.13</td>
<td>19.76±1.85</td>
<td>104.38±10.76</td>
<td>8.24±0.79</td>
<td>1.65±0.14</td>
<td>11.39±1.27</td>
<td>0.78±0.06</td>
</tr>
</tbody>
</table>

*P<0.05.

4. Discussion

Patients with type 2 diabetes are the high-risk group of cardiovascular events, and a study shows that because of blood glucose level and lipid metabolism disorders, patients with type 2 diabetes will have carotid plaques with course prolonging, and the unstable plaques rupture into blood circulation can lead to vascular embolization and functional loss in important organs[3]. Angptl2 is the glycoprotein secreted by endothelial cells and highly expressed in the heart, lungs, kidneys and skeletal muscles, Angptl2 is stimulated and expressed in hypoxia state, and it will further induce angiogenesis and endothelial cell migration. Study confirms that Angptl2 can induce vascular inflammation in vivo, induce mononuclear macrophage chemotaxis via integrin signaling pathways, and activate inflammatory cascade in endothelial cells. On the other hand, Angptl2 can increase the level of cholesterol in blood circulation and promote the formation of atherosclerosis. It is currently considered that Angptl2 level is the independent risk factor of macro-vascular complications in patients with type 2 diabetes, and its directivity effect on carotid plaque nature and loss risk has caught clinical attention[4,5]. Above research results showed that serum Angptl2 level of observation group was higher, and with the decrease of plaque stability, Angptl2 value increased.

Type 2 diabetes mellitus patients associated with carotid plaques may show change levels of a series of serum factors, which plays an important role in plaque formation, and also indicates the risk of cardiovascular events in patients. Fibrinogen (Fbg) is the liver-synthesized protein involved in blood coagulation process, and Fbg destructs red blood cells adsorption to endothelial cell by thrombin, ultimately promoting the occurrence of artery thrombosis[5]. Glycated hemoglobin (HbA1c) is a binding product of hemoglobin and blood glucose in red blood cells, is directly proportional to patients’ blood glucose concentration, can keep 120 d, and can reflect patients’ blood glucose levels within a period of time. Big endothelin-1 (bigET-1) is a precursor of endothelin, has longer half-life than endothelin, and can reflect endothelin levels and vascular damage state within a period of time. Direct bilirubin (DBIL) mainly comes from the degradation of hemoglobin, belongs to powerful antioxidant, has a variety of cell protection effects, eliminates oxygen free radicals to inhibit LDL oxidation, and plays an effective anti- atherosclerosis role[6]. Endothelial function index (RHI) is predictor of cardiovascular events, and a study shows that RHI value is negatively correlated with blood glucose and lipid levels, and also has certain negative correlation with the plaque nature[7]. Above research results showed that serum Fbg, HbA1c and bigET-1 values of observation group were higher while DBIL and RHI values were lower, and with the decrease of plaque stability, the change trend of above factors was more significant.

Cystatin C is a cysteine protease inhibitor, and is the reliable and ideal of endogenous index reflecting glomerular filtration rate. Recent study has shown that there is independent correlation between cystatin c and cerebrovascular events. Apolipoprotein A1 (ApoA1) is the main component of plasma lipoproteins, and in cases of atherosclerosis and diabetes, ApoA1 levels decrease[8]. Visfatin is a newly discovered adipocytokine synthesized by viscera, has insulin-like effect, and has positive significance in both reducing the blood glucose and promoting the synthesis and differentiation of adipose tissue. Research has shown that visfatin is closely related to inflammation, microvascular disease, atherosclerosis, and so on, and as the degree of atherosclerosis is aggravating, visfatin levels rise. Myeloperoxidase (MPO) is stored in neutrophils and monocytes, activated by neutrophil and released into the blood in the form of degranulation, and involved in systemic inflammation as inflammatory mediator[9]. MPO level is directly proportional to the body’s inflammatory state, and promotes atherosclerosis through various channels. Above research results showed that serum cystatin c and visfatin values of observation group were higher while ApoA1 and MPO values were lower, indicating that the change trend of above factors was an important factor causing carotid plaque formation in diabetes.

Anticardiolipin antibody (ACA) mainly acts on the phospholipid composition in vascular endothelial cells, and can change the cell structure and affect cell function. ACA is combined with endothelial cell surface mass and changes the membrane receptor configuration, making endothelial cells lose anticoagulant ability; ACA combination with endothelial cell membrane phospholipids can direct damage
endothelial cells; ACA combination with platelet phospholipid starts the process of thrombosis, and can induce thrombosis in the condition of diabetes[10]. Macrophage migration inhibitor (MIF) is a kind of multifunctional cytokine controlled by the hypothalamus-pituitary system, can inhibit macrophage migration and promote macrophage accumulation, further activates endothelial cells to express a variety of inflammatory factors, and is involved in the process of atherosclerosis. Soluble CD40 ligand (sCD40L) and pregnancy-associated plasma protein-A (PAPP-A) are independent risk factors of unstable plaques, and sCD40L is the glycoprotein of the tumor necrosis factor family, plays a crucial mediating role in the inflammatory response, and participates in the development of atherosclerosis; PAPP-A is Zn$^{2+}$-binding metalloproteinase produced by various activated cells in the unstable plaques and released into the blood, PAPP-A is abundantly expressed in unstable plaques, and its expression level is significantly reduced in the stable plaque. CXC chemokine receptor (16 CXCR16) has the roles of keeping the self stability of body's immune system, participating in inflammation and angiogenesis, and so on, and is one of the pathological basis involved in atherosclerosis[11,12]. CXCR16 expression on macrophage surface can devour oxidized low density lipoprotein and be transformed into foam cells and deposit in the arterial intima, becoming the core of atheromatous plaque. D-dimer is from fibrinolysis under the action of fibrinolytic enzyme, and high level of D-dimer reflects high levels of fibrous protein and higher possibility of thrombosis. A large number of epidemiological investigations have confirmed that homocysteine (t-HCY) is an independent risk factor of atherosclerosis and cardiovascular diseases, and t-HCY can generate superoxide and peroxide, damaging vascular endothelium while changing clotting factors and increasing thrombosis. At the same time, t-HCY accelerates vascular smooth muscle cell proliferation, and promotes atherosclerosis[13,14]. Above research results showed that serum ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer values of observation group were higher, indicating that above indexes were all involved in carotid plaque formation in diabetic patients and were the risk factors of plaque formation and rupture.

Further analysis of the correlation between serum Angptl2 level and the values of carotid plaque nature-related indexes showed that serum Angptl2 level was directly proportional to Fng, HbA1c, bigET-1, cystatin c, ApoA1, visfatin, ACA, MIF, sCD40L, PAPP-A, CXCR16, t-HCY and D-dimer levels, and inversely proportional to DBIL, RHI and MPO values, indicating that in addition to being related to the degree of atherosclerosis, Angptl2 level could also macroscopically represent the degree of disorder of body’s serum plaque nature-related factors, and had positive significance in judging the disease severity of type 2 diabetes patients with carotid plaque and predicting long-term risk of cardiovascular events[15].

To sum up, it is concluded as follows: Angptl2 level is significantly abnormal in Type 2 diabetes patients with carotid plaque, has direct correlation with plaque nature-related indexes, is the reliable index to judge the disease and predict the outcome, and is worth popularization and application in clinical practice in the future.

References


