Effect of doubling-dose atorvastatin intervention on lipid metabolism, insulin resistance and carotid atherosclerosis in patients with type 2 diabetes mellitus

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1. Introduction

In addition to the typical blood sugar fluctuation, abnormal lipid metabolism co-exists in most patients with type 2 diabetes, so the probability of carotid atherosclerosis is high in such patients, progression is quicker than that in non-diabetic patients, and early intervention measures should be taken to optimize the treatment outcome[1,2]. Atorvastatin is a common drug for hyperlipidemia treatment, and many studies have confirmed the drug helps reduce the risk of angina pectoris, myocardial infarction, stroke, congestive heart failure, etc.[3,4]. The common starting dosage of atorvastatin is 10 mg, maximum dose is 80 mg, different doses are selected according to different conditions, but there is no clear conclusion at present about the optimal dose of atorvastatin for patients with type 2 diabetes. In the research, different doses of atorvastatin were used for the treatment of patients with type 2 diabetes mellitus complicated by carotid atherosclerosis, and discussed from three aspects of lipid metabolism, insulin resistance and carotid atherosclerosis degree, now reported as follows.
2. Information and methods

2.1 Case information

118 patients with type 2 diabetes mellitus treated in our hospital between May 2013 and December 2016 were enrolled as research subjects, and the patients signed the consent form themselves. According to the random number table, the enrolled patients were divided into the single dose group (n=59) who received single-dose atorvastatin therapy and the double dose group (n=59) who received doubling-dose atorvastatin therapy. Single dose group included 32 male cases and 27 female cases, they were 41-78 years old, and the course of type 2 diabetes was 5-19 years; double dose group included 31 male cases and 28 female cases, they were 40-79 years old, and the course of type 2 diabetes was 4-17 years. The differences in gender, age and course of type 2 diabetes were not statistically significant between two groups of patients (P>0.05), and the study was discussed and approved by the ethics committee of the hospital.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with the diagnosis of type 2 diabetes; (2) with atherosclerosis lesions confirmed by carotid artery ultrasound; (3) without previous history of myocardial infarction or cerebral infarction; (4) cooperating with treatments and inspections the whole time. Exclusion criteria: (1) associated with atorvastatin allergy; (2) associated with systemic infectious diseases; (3) associated with malignant tumor disease.

2.3 Therapy

Both groups of patients received routine hypoglycemic therapy, single dose group of patients received atorvastatin (Pfizer Pharmaceutical Co., Ltd., approved by H20051407), with therapeutic dose of 20 mg/time, 1 time/d; double dose group of patients received atorvastatin with therapeutic dose of 40 mg/time, 1 time/d, and both therapies lasted for 3 months.

2.4 Observation indexes

Before and after treatment, 3.0 mL fasting cubital venous blood was extracted from two groups of patients, added to the heparin anticoagulant tube and centrifuged in low-temperature centrifuge (Felles Photonic Instruments China, the article number 02) at 2500 r/min for 10 min, and upper serum was kept and cryopreserved in -70 °C environment for test. Automatic biochemical analyzer (Skillsmodel Biotech Beijing Co., Ltd., the article number of Catalyst One) was used to determine lipid metabolism indexes in it, including total cholesterol (TC), triglyceride (TG), free fatty acid (FFA), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C); serum levels of insulin resistance indexes were measured, including the fasting insulin (INS), islet β-cell secretion index (HOMA-β) and insulin resistance index (HOMA-IR). Nephelometry was used to determine the serum levels of carotid atherosclerosis-related parameters, including visfatin, osteoprotegerin (OPG), cystatin C (CysC) and high mobility group B1 (HMGB1).

2.5 Statistical methods

Statistical software in the study was SPSS 20.0, and the data were recorded and calculated by the professionals. Lipid metabolism indexes, insulin resistance indexes, carotid atherosclerosis-related parameters and other measurement data were in terms of (mean ± SD), and comparison between groups was by t test. P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Lipid metabolism indexes

Comparison of serum lipid metabolism indexes TC, TG, FFA, LDL-C and HDL-C contents between two groups of patients before and after treatment was as follows: before treatment, differences in serum TC, TG, FFA, LDL-C and HDL-C contents were not statistically significant between two groups of patients (P>0.05); after treatment, serum TC, TG, FFA and LDL-C contents of both groups were lower than those before treatment while HDL-C contents were higher than those before treatment, serum TC, TG, FFA and LDL-C contents of observation group were lower than those of control group while HDL-C content was higher than that of control group, and differences were statistically significant (P<0.05), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>TC</th>
<th>TG</th>
<th>FFA</th>
<th>LDL-C</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose group</td>
<td>59</td>
<td>Before treatment</td>
<td>4.93±0.56</td>
<td>2.17±0.35</td>
<td>45.38±6.18</td>
<td>3.16±0.43</td>
<td>1.15±0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>4.25±0.51</td>
<td>1.69±0.26</td>
<td>37.23±4.51</td>
<td>2.48±0.32</td>
<td>1.28±0.16</td>
</tr>
<tr>
<td>Double dose group</td>
<td>59</td>
<td>Before treatment</td>
<td>4.92±0.52</td>
<td>2.14±0.32</td>
<td>45.71±5.98</td>
<td>3.19±0.41</td>
<td>1.13±0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>3.72±0.41*</td>
<td>1.43±0.17*</td>
<td>30.14±3.76*</td>
<td>1.97±0.25*</td>
<td>1.47±0.19*</td>
</tr>
</tbody>
</table>

Note: compare with same group before treatment, *P<0.05; compared with single dose group after treatment, †P<0.05.
become an important cause of diabetic cardiovascular events \[7,8\]. Extremely high, and carotid atherosclerosis can appear later and metabolism, so the probability of hyperlipidemia complication is glucose metabolism in patients with type 2 diabetes can directly Comparison of serum carotid atherosclerosis-related index contents between two groups of patients before and after treatment. Table 3. Comparison of serum carotid atherosclerosis-related index contents between two groups of patients before and after treatment. Table 2. Comparison of serum insulin resistance index levels between two groups of patients before and after treatment. 3.2 Insulin resistance indexes Comparison of serum insulin resistance indexes INS (mU/L), HOMA-β and HOMA-IR levels between two groups of patients before and after treatment was as follows: before treatment, differences in serum INS, HOMA-β and HOMA-IR levels were not statistically significant between two groups of patients \((P>0.05)\); after treatment, serum INS and HOMA-IR levels of both groups were lower than those before treatment while HOMA-β levels were higher than those before treatment, serum INS and HOMA-IR levels of observation group were lower than those of control group while HOMA-β level was higher than that of control group, and differences were statistically significant \((P<0.05)\), shown in Table 2. 3.3 Carotid atherosclerosis-related indexes Comparison of serum carotid atherosclerosis-related indexes visfatin (ng/mL), OPG (pg/mL), CysC (pg/mL) and HMGB1 (ng/mL) contents between two groups of patients before and after treatment was as follows: before treatment, differences in serum visfatin, OPG, CysC and HMGB1 contents were not statistically significant between two groups of patients \((P>0.05)\); after treatment, serum visfatin, OPG, CysC and HMGB1 contents of both groups were lower than those before treatment, serum visfatin, OPG, CysC and HMGB1 contents of observation group were lower than those of control group, and differences were statistically significant \((P<0.05)\), shown in Table 3. 4. Discussion Atorvastatin is one of the most common clinical cholesterol-lowering drugs, and has been successfully applied to patients with hyperlipemia complicated by multiple diseases\[5,6\]. Abnormal blood glucose metabolism in patients with type 2 diabetes can directly promote lipid accumulation and increase the difficulty in lipid metabolism, so the probability of hyperlipidemia complication is extremely high, and carotid atherosclerosis can appear later and become an important cause of diabetic cardiovascular events\[7,8\]. Patients with type 2 diabetes mellitus complicated by carotid atherosclerosis are routinely given atorvastatin, but the dose has been controversial. In the study, atorvastatin 20 mg and 40 mg were provided each time for three consecutive months, and the clinical effects were compared between the two so as to clarify the best dose of atorvastatin and lay foundation for subsequent clinical practice. In patients with type 2 diabetes mellitus, about 20%-90% of patients are with hyperlipemia, which is mainly characterized by the increased levels of TC, TG, FFA and LDL-C as well as the decreased levels of HDL-C\[9,10\]. The TC and TG increase are mainly because that a large amount of FFA flows into the liver and accelerates the synthesis of TC and TG, and meanwhile, the lipoprotein lipase activity declines, and the TC and TG degradation decrease. LDL-C is the main carrier of cholesterol and the main form of cholesterol entering into cells, the enhanced oxidative stress in patients with diabetes makes it hard for related receptors to identify LDL-C, and its decomposition and removal pathways are blocked\[11\]. The main purpose of HDL-C is to transfer the cholesterol from extrathoracic tissues to the liver for metabolism under the action of apolipoprotein A, the accelerated apolipoprotein A decomposition in patients with type 2 diabetes decreases the HDL-C function and content, and then and low blood HDL-C disease appears\[12\]. In the study, the contents of lipid metabolism indexes were compared between two groups of patients at first, and it was found that after treatment, serum TC, TG, FFA and LDL-C contents of observation group were lower than those of control group while HDL-C content was higher than that of control group, it indicates that 40 mg/time of atorvastatin can be more effective to optimize the abnormal lipid metabolism of patients with type 2 diabetes, and it is speculated to be associated with the dosage dependence of the drug. Decreased insulin sensitivity and insulin resistance are the basic mechanisms of the occurrence and development of type 2 diabetes, and previous studies have shown that there can be insulin resistance in patients with severe obesity, so it is speculated that abnormal lipid metabolism can be counterproductive in the glucose metabolism of patients with type 2 diabetes and increase insulin resistance\[13,14\], INS, HOMA-β and HOMA-IR are the three indicators most closely related to insulin resistance, there are generally the increased levels of INS and HOMA-IR as well as the decreased level of HOMA-β in patients with type 2 diabetes mellitus, and the specific change degree is directly related to the illness of diabetes\[15,16\]. In the study, insulin resistance was compared between the two groups of patients before and after treatment, and it was found that after treatment,
serum INS and HOMA-IR levels of both groups were lower than those before treatment while HOMA-β levels were higher than those before treatment, showing that atorvastatin lipid-lowering therapy can effectively alleviate the degree of insulin resistance in patients with type 2 diabetes. Further comparison showed that after treatment, serum INS and HOMA-IR levels of observation group were lower than those of control group while HOMA-β level was higher than that of control group, showing that doubling-dose atorvastatin can more effectively relieve the insulin resistance and optimize the glucose metabolism process in patients.

Severe glucolipid metabolism can finally cause carotid atherosclerosis in patients with type 2 diabetes, and its persistent progression can lead to cardiovascular and cerebrovascular infarction. The occurrence and aggravation of carotid atherosclerosis can affect the serum contents of many factors, they are also known as "carotid atherosclerosis-related indicators", and to detect the contents of them can objectively reflect the carotid atherosclerosis condition. Visfatin is the adipocytokine specifically highly expressed in visceral adipose tissue, its content also gradually rises along with the progress in obesity, and many studies have shown that Visfatin is closely related to the occurrence of abnormal lipid metabolism, diabetes as well as cardiovascular and cerebrovascular diseases[17]. OPG is a secreted glycoprotein, and a study in recent years has shown that it is closely related to macrovascular lesions, and its content in patients with diabetics is significantly higher than that in normal people[18]. High blood CysC disease is an independent risk factor for cardiovascular diseases, which is probably associated with its effects such as strongly inhibiting the effect of cathepsin B, increasing vascular smooth muscle cell apoptosis and intensifying inflammation[19]. HMGB1-RAGE axis is believed to play an important role in the process of diabetes and its complications, which can damage insulin, make inflammatory factors gather in large blood vessels and accelerate atherosclerosis plaque formation. In the study, serum contents of these carotid atherosclerosis-related parameters were compared between the two groups of patients, and it was found that after treatment, serum visfatin, OPG, CysC and HMGB1 contents of observation group were lower than those of control group, indicating that doubling-dose atorvastatin can more effectively curb the carotid atherosclerosis progression.

Thus it is clear that doubling-dose atorvastatin can effectively optimize the lipid metabolism alleviate the degree of insulin resistance, and also inhibit the carotid atherosclerosis progress in patients with type 2 diabetes, it is of positive clinical significance, and same dose can be recommended in patients with similar condition in the clinical use in the future.

**References**


