



Influencing Mechanism of Large-dose of Atorvastatin in Serum Visfatin, MMP-9, and Blood Fat Levels of Patients with Acute Coronary Syndromes

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ABSTRACT

The research was conducted to analyze the clinical effects and corresponding molecular mechanisms of short-term treatment of acute coronary syndromes (ACS) by different doses of atorvastatin. In the research, a total of 90 ACS patients were included as the samples and divided into an experimental group (conventional treatment+60mg/per time/late atorvastatin), control group 1 (conventional treatment+25mg/per time/late atorvastatin), and control group 2 (25mg/per time/late atorvastatin) according to different doses of atorvastatin. After that, their blood fat and inflammatory factors before and after treatment were analyzed. Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels of the experimental group were inferior to those of control groups 1 and 2 in the 5th and 7th days ($P<0.05$). After treatment, visfatin, matrix metalloproteinase-9 (MMP-9), and brain natriuretic peptide (BNP) of patients in the experimental group and control groups 1 and 2 were notably inferior to those in control groups 1 and 2 ($P<0.05$). Besides, interleukin-6 (IL-6) and hyper-sensitive C-reactive protein (hs-CRP) of patients in the experimental group and control groups 1 and 2 were inferior to those in control groups 1 and 2 after treatment ($P<0.05$). Based on the above results, the short-term treatment by large-dose atorvastatin could reduce blood fat and inflammatory factor levels of ACS patients more effectively than by conventional dose, and further inhibit inflammatory reactions and improve patient prognosis with safety and feasibility.

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Introduction

Acute coronary syndrome (ACS) refers to a group of clinical manifestation syndromes caused by ischemia in the blood supply area, which results from lesions in the coronary artery. The commonest symptom is atherosclerosis which results in atheromatous plaque. If atheromatous plaques are unstable or ruptured, a thrombus will occur. Complete or incomplete blocking of blood vessels affects the myocardial blood supply in their blood supply areas and leads to corresponding clinical manifestations (1-3). ACS is a clinically common disease with high incidence, including myocardial infarction and angina pectoris, which are manifested as sternum stuffy pain, squeezing, or compression. Furthermore, these symptoms even threaten people's lives and safety (4-7). The main causes of ACS include atherosclerosis, plaque rupture, platelet aggregation, thrombosis, and vasospasm. In recent years, the incidence of ACS is gradually rising, especially among patients with diabetes mellitus, hypertension, smokers, and chronic heavy drinkers. In addition, most clinical research demonstrates that inflammatory reactions and inflammatory cell infiltration are two of the major causes of ACS (8,9). ACS has acute onset with fast progress, and thus posing great threats to patients' lives. Hence, an emergency treatment for patients must be performed as quickly as possible. Once patients suffer from angina pectoris which can't be alleviated by taking nitroglycerin or other suspec-

ted symptoms, they must see a doctor right away to ask for diagnosis and treatment to avoid delaying the disease (10).

ACS is an internal medicine emergency, and the therapeutic effects on it depend mainly on whether patients are diagnosed and treated quickly. Therefore, ACS should be detected as early as possible, and patients need to be hospitalized as soon as being diagnosed with ACS. Besides, the treatment and cure measures should be strengthened before hospitalization (11). Clinical drug treatment methods include antiplatelet therapy, antithrombin, anti-myocardial ischemia, and thrombolysis. Statins are the most effective lipid-lowering drugs at present, including simvastatin, fluvastatin, atorvastatin, and rosuvastatin. These drugs not only can effectively reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), but can also lower triglyceride (TG) and elevate high-density lipoprotein cholesterol (HDL-C) to some degree (12,13). It is proposed in relevant studies that the long-term adjustment of TC and TG levels in the patient's body can stabilize plaques effectively and improve the incidence of inflammations and adverse reactions. As a result, medium and long-term treatment with statins is very effective (14-16). Atorvastatin is the newly synthesized and selective 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor. Besides, it is acknowledged by the medical field that it shows more significant therapeutic effects than natural microbial fermentation and semi-synthesized statins. At the initial phase of atorvastatin use, outstanding

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lipid regulation qualified rate is obtained. However, there are some disadvantages, including high-dose requirements and many poor prognosis events (17). Hence, the clinical effects of atorvastatin on ACS disease are discussed from the perspective of different doses in the research.

To conclude, the commonly adopted drug methods in the clinical treatment of ACS, and the development and application of statins receive more and more attention. Based on the situation, a total of 90 ACS patients treated in hospitals between March 2020 and October 2021 were included as the subjects in the research. They were enrolled into three groups, including the experimental group (30 cases), control group 1 (30), and control group 2 (30). In addition, 15 healthy volunteers were selected and included in the blank group. In the research, patients were offered drug treatment with different doses of atorvastatin. By the comparison of their blood fat and inflammatory factors before and after treatment, the clinical effects and corresponding molecular mechanism of the short-term treatment by different doses of atorvastatin on ACS patients are discussed.

Materials and Methods

Subjects

90 ACS patients treated in Qingdao Municipal Hospital between March 2020 and October 2021 were selected as the subjects. According to different doses of atorvastatin, they were enrolled into the experimental group (30 cases), control group 1 (30 cases), and control group 2 (30 cases). Besides, 15 healthy volunteers undergoing physical examination in the hospital during the same period were included and enrolled in the blank group. In the experimental group, patients were performed with conventional treatment+60mg/per time/late atorvastatin, conventional treatment+25mg/per time/late atorvastatin were performed on patients in control group 1, and those in control group 2 were treated with conventional treatment+15mg/per time/late atorvastatin. Before the treatment, patients and their family members had been informed of the contents of this research, and patients had agreed to engage in it and then signed informed consent forms.

The patients were included based on the following criteria. A. patients didn't receive other drug treatments. B. Patients' family members allowed them to engage in the experiment. C. Patients' clinical data were complete. D. Patients had agreed to engage in the research and signed informed consent forms.

The patients were excluded based on the following criteria. A. Patients suffered from complicated serious congestive heart failure. B. Patients suffered from complicated organic heart disease. C. Patients suffered from serious liver and kidney abnormalities. D. Patients suffered from complicated stroke or peripheral vascular disease. E. Patients suffered from rheumatoid arthritis and other immunological diseases. F. Patients were lactating women.

Experimental termination conditions were as follows. A. Patients suffered from drug allergies or serious gastrointestinal tract reactions during treatment. B. Creatine kinase level was over ten times normal during treatment. C. Transaminase level was over three times more than normal during treatment.

Detection methods of visfatin in serum

The operation process was as follows. Firstly, 96-well enzyme-linked immunosorbent assay (ELISA) plates were added with 45 μ L standard peptides, 20 μ L rabbit visfatin-immunoglobulin G (IgG), 20 μ L biotinylated peptides, and 45 μ L samples or control, and then placed at 25°C for 2 hours. Secondly, the mixed solution was added with 250 μ L buffer solution and then washed three times. After that, it was added with 80 μ L substrate solution (Western Blot) before being placed at 25°C for 1 hour. Finally, it was added with 2N hydrogen chloride (HCl) to terminate the reaction. Next, the absorbance at 450nm was recorded by a multi-functional enzyme-labeled instrument, and the concentration of visfatin in serum was calculated by standard curve.

Detection methods of serum matrix metalloproteinase-9 (MMP-9)

Double-antibody ELISA method was adopted to detect MMP-9 levels in patients. The operation process was as follows. Firstly, reaction plates were added with 80 μ L standard and 80 μ L samples and then mixed for 30 seconds before being cultured at 37°C for 2 hours. Secondly, reaction plates were washed with scrubbing solution three times, and then each well was added with the diluted IX Biotin (80 μ L). After being mixed for 30 seconds, it was cultured at 37°C for 2 hours. After that, the reaction plates were washed again. Thirdly, each well was added with diluted 1X HRP (80 μ L), and then it was mixed for 30 seconds before being cultured at 37°C for 2 hours. Then, the reaction plates were washed again. Fourthly, each well was added with 40 μ L color liquid A and 40 μ L color liquid B. After being mixed for 10 seconds, it was cultured at 37°C in dark for 20 minutes. Finally, each well was added with 80 μ L termination liquid and mixed for 30 seconds. After that, the absorbance at 450nm was recorded.

Detection of blood fat

Patients were forbidden to eat and drink for over 8 hours. After venous blood was extracted, a fully automatic biochemical analyzer (Jinan Hanfang Medical Equipment Co., Ltd) was adopted to detect TC, TG, HDL-C, and LDL-C levels.

Observation indexes

The general data of patients were recorded (gender, age, height, weight, previous medical history, diagnosis type, and body mass index (BMI)). Besides, blood plasma inflammatory factor interleukin-6 (IL-6), hypersensitive C-reactive protein (hs-CRP), and serum brain natriuretic peptide (BNP) of patients before and after treatment were recorded. Myalgia and other adverse events during the treatment of patients were followed and recorded.

Statistical methods

Data processing was analyzed by SPSS 19.0. Measurement data were denoted by mean \pm deviation ($\bar{x}\pm s$), and enumeration data were denoted by percentage mark (%). Pairwise comparison was analyzed by the one-way variance analysis method. $P<0.05$ or $P<0.01$ revealed that the differences demonstrated statistical significance.

Results

Comparison of general data on patients in four groups

General data were compared. According to Figure 1, the pairwise comparisons among the age, gender, hypertension, diabetes mellitus, smoking history, hyperlipidemia, systolic pressure, diastolic pressure, white blood cell (WBC) count, and fetal bovine serum (FBS) of patients among experimental group and control groups 1 and 2 all demonstrated no statistical significance ($P>0.05$). Pairwise comparisons among the age, gender, hypertension, diabetes mellitus, systolic pressure, diastolic pressure, and FBS among the experimental group, control groups 1 and 2, and the blank group also showed no statistical significance ($P>0.05$). Besides, smoking history, hyperlipidemia, and WBC count in the experimental group and control groups 1 and 2 were all markedly superior to those in the blank group ($P<0.05$).

Changes in blood fat of patients before and after treatment

Figure 2 demonstrates the changes in blood fat of patients before and after treatment. According to this figure, TC, LDL-C, and TG levels of patients in the experimental group and control, groups 1 and 2 showed a descending trend over time. In contrast, HDL levels of patients in the experimental group and control groups 1 and 2 all showed a rising trend over time. TC and LDL-C of patients in the experimental group were obviously inferior to those in control groups 1 and 2 in the 5th and 7th days ($P<0.05$). Besides, the differences in TG and HDL levels among the three groups indicated no statistical significance ($P>0.05$).

Visfatin levels of patients before and after treatment

Figure 3 shows the changes in blood fat of patients before and after treatment. According to Figure 3, visfatin levels of patients in the experimental group and control groups 1 and 2 all showed a descending trend over time. Besides, visfatin levels of patients among the above groups

after treatment were obviously inferior to those in control groups 1 and 2 ($P<0.05$).

MMP-9 of patients before and after treatment

Figure 4 displays the changes in MMP-9 of patients before and after treatment. MMP-9 levels of patients in the experimental group and control groups 1 and 2 all showed a descending trend over time. Besides, MMP-9 levels of patients among the above groups after treatment were notably inferior to those in control groups 1 and 2 ($P<0.05$).

The inflammatory factor of patients before and after treatment

According to Figures 5 and 6, IL-6 and hs-CRP of patients in the experimental group and control groups 1 and 2 all showed a descending trend over time. What's more, the IL-6 and hs-CRP of patients among the above groups after treatment were obviously lower than those in controls 1 and 2 ($P<0.05$).

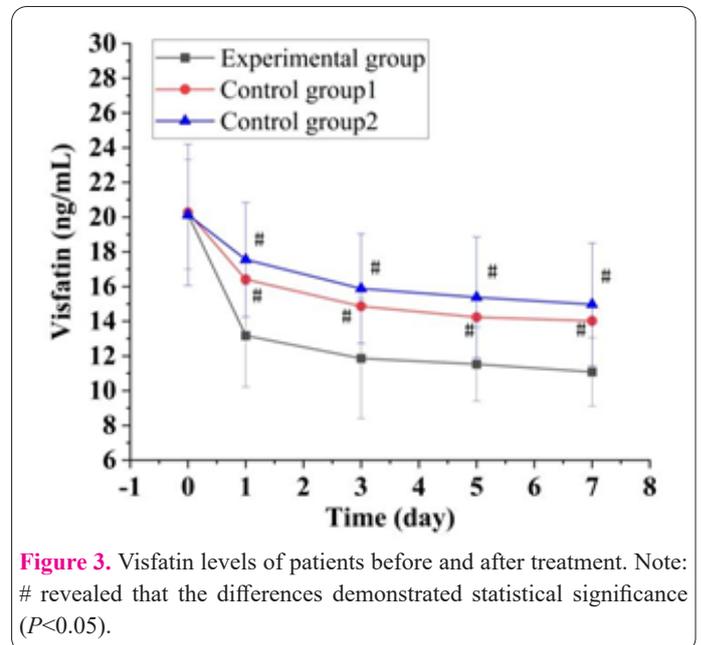
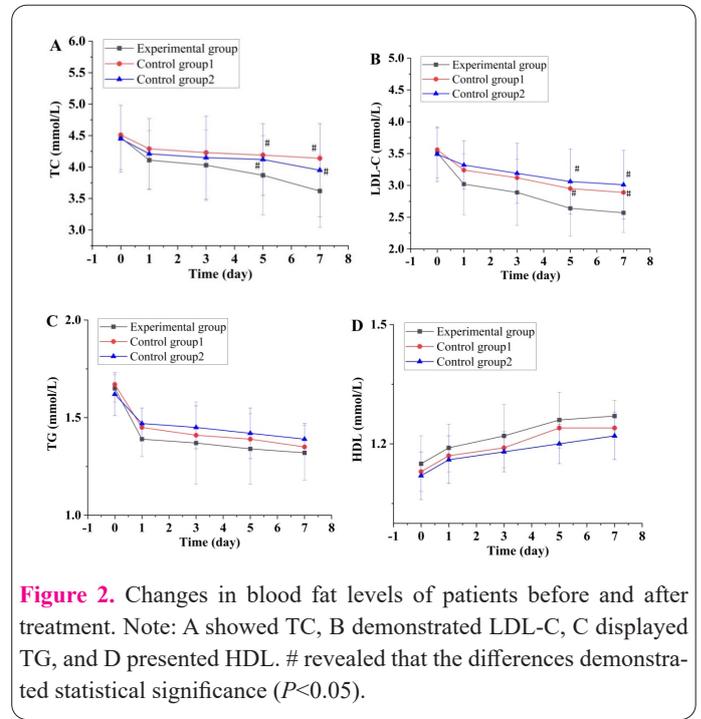
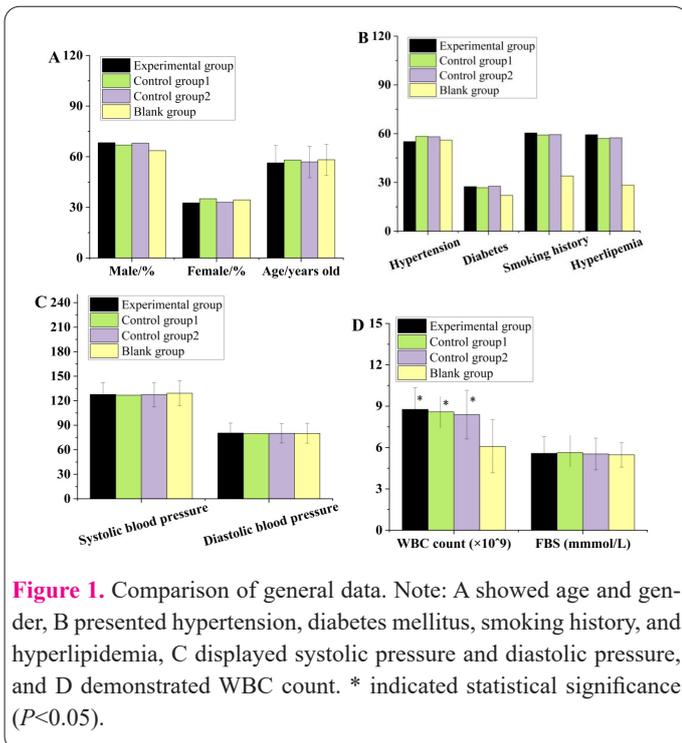


Figure 2. Changes in blood fat levels of patients before and after treatment. Note: A showed TC, B demonstrated LDL-C, C displayed TG, and D presented HDL. # revealed that the differences demonstrated statistical significance ($P<0.05$).

Figure 3. Visfatin levels of patients before and after treatment. Note: # revealed that the differences demonstrated statistical significance ($P<0.05$).

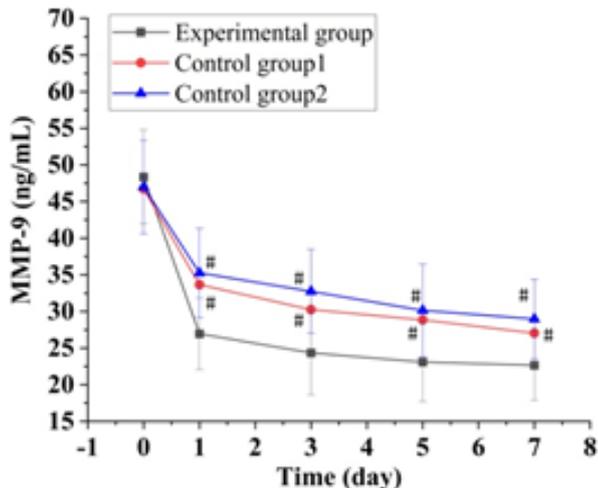


Figure 4. MMP-9 of patients before and after treatment. Note: # revealed that the differences demonstrated statistical significance ($P<0.05$).

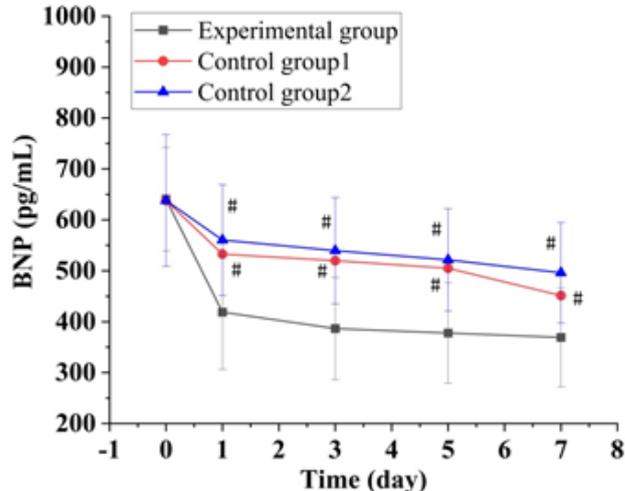


Figure 7. BNP levels of patients before and after treatment. Note: # revealed that the differences demonstrated statistical significance ($P<0.05$).

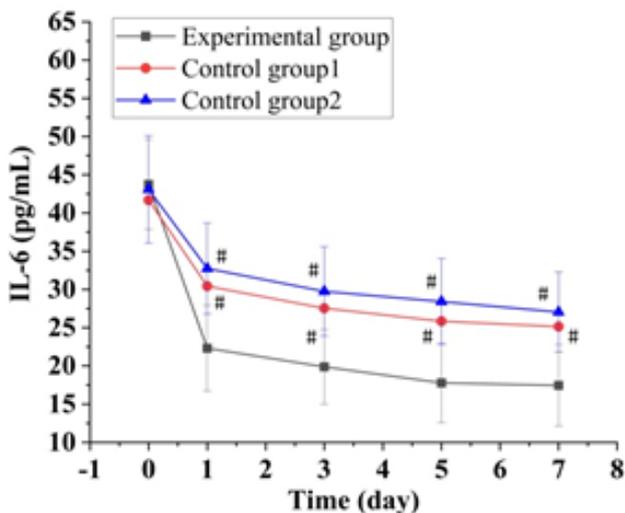


Figure 5. IL-6 of patients before and after treatment. Note: # revealed that the differences demonstrated statistical significance ($P<0.05$).

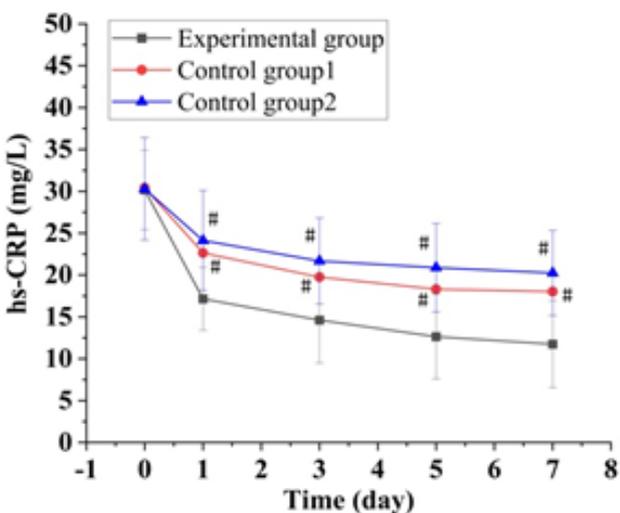


Figure 6. hs-CRP of patients before and after treatment. Note: # revealed that the differences demonstrated statistical significance ($P<0.05$).

levels of patients among the above groups after treatment were obviously inferior to those in control groups 1 and 2 ($P<0.05$).

Adverse reactions of patients after treatment

By follow-up observation, all patients in the experimental group and control groups 1 and 2 didn't undergo adverse events after treatment, including myalgia, rhabdomyolysis, drug allergy, gastrointestinal tract reactions, and malaise. Besides, creatine kinase levels of patients were less than ten times than normal during treatment, and transaminase levels were less than over three times than normal.

Discussion

ACS is the major cause of hospitalization and even death of patients with coronary artery heart disease at present. Unstable coronary atherosclerotic plaque is the basic pathology of the disease (18,19). According to clinical manifestations, atherosclerosis is actually a chronic inflammatory disease. With hyperlipidemia in the human body, inflammation combined with cholesterol causes damage to the endarterium of patients and finally results in atherosclerosis plaques (20-22). Currently, ACS disease is treated mainly by statins. In the research, 90 ACS patients were included as the research samples and enrolled into the experimental group (conventional treatment+60mg/per time/late atorvastatin), control group 1 (conventional treatment+25mg/per time/late atorvastatin), and control group 2 (conventional treatment+25mg/per time/late atorvastatin) according to different doses of atorvastatin. After that, 15 healthy volunteers undergoing physical examination during the same period were enrolled into the blank group. Firstly, clinical data on the research objects in four groups were compared, which demonstrated that the pairwise comparisons of age, gender, hypertension, diabetes mellitus, smoking history, hyperlipidemia, systolic pressure, diastolic pressure, WBC count, and FBS between patients in control groups 1 and 2 all demonstrated no statistical significance ($P>0.05$). The similarities of these baseline situations implemented subsequent contrastive studies feasible (23). In addition, the smoking history,

Serum BNP of patients before and after treatment

According to Figure 7, serum BNP levels of patients in the experimental group and control groups 1 and 2 all showed a descending trend over time. Besides, serum BNP

hyperlipidemia, and WBC count levels of patients in the experimental group and control groups 1 and 2 were all notably superior to those in the blank group ($P>0.05$). The results demonstrated that hazard factors of cardiovascular disease of ACS patients were more significant compared with the healthy population, including smoking history, hyperlipidemia, and WBC count. Besides, the above differences indicated that patients with a smoking history, hyperlipidemia, and high levels of WBC count needed to pay more attention to routine physical examination and disease prevention.

In the research, blood fat levels of patients before and after treatment were compared, which demonstrated that TC and LDL-C of patients in the experimental group were obviously inferior to those in control groups 1 and 2 in the 5th and 7th days ($P<0.05$). In contrast, the differences in TG and HDL levels between the above groups were not remarkable ($P>0.05$). The findings revealed that the short-term treatment by large-dose atorvastatin could reduce blood fat levels of patients more effectively than by low-dose atorvastatin with significant therapeutic effects. Besides, visfatin levels of patients in the experimental group and control groups 1 and 2 all showed a descending trend over time, which was similar to the results of the study conducted by Wang et al (2019) (24). The effects of atorvastatin on reducing blood fat levels and visfatin levels revealed that different doses of atorvastatin could inhibit visfatin levels of endothelial cells and lymphocytes in unstable plaques. What's more, the visfatin levels of patients in the experimental group and control groups 1 and 2 after treatment were obviously inferior to those in control groups 1 and 2 ($P<0.05$). The differences suggested that the inhibition effects of short-term treatment by large-dose atorvastatin on visfatin generation were more significant than those by low-dose atorvastatin. In addition, the former treatment method was relatively more effective in anti-inflammation and endothelial dysfunction improvement. In the research, MMP-9 levels of patients in the experimental group and control groups 1 and 2 after treatment were notably inferior to those in control groups 1 and 2 ($P<0.05$). The main function of MMP-9 is to degrade and reshape the dynamic balance of the extracellular matrix and can get involved in blood vessel formation by releasing vascular endothelial growth factor (VEGF) (25). The above results demonstrated that the short-term treatment by large-dose atorvastatin could reduce MMP-9 levels in body blood plasma, and the relevant mechanism might be the inhibition of MMP-9 formation by atorvastatin by adjusting macrophages and endothelial cells in unstable plaques, and the further improvements of patient prognosis.

According to the analysis of other inflammatory factors, IL-6 and hs-CRP of patients in the experimental group and control groups, 1 and 2 after treatment were obviously inferior to those in control groups 1 and 2 ($P<0.05$). The results revealed that short-term treatment by large-dose atorvastatin could inhibit the inflammatory reactions of ACS patients more effectively. The relevant mechanism might be the abnormalities of monocytes and endothelial cells by reducing MMP-9 levels in plasma by atorvastatin and the subsequent induction of inflammatory factor reduction (26). BNP is one of the members of the natriuretic peptide family and the most effective neurohormone index for assessing left ventricular functions and their prognosis (27,28). With a higher level of ventricular functions,

the BNP level is higher. In the research, serum BNP levels of patients in the experimental group and control groups 1 and 2 after treatment were notably inferior to those in control groups 1 and 2 ($P<0.05$). The differences indicated that short-term treatment by large-dose atorvastatin demonstrated relatively more positive improvement effects on patient prognosis. In the follow-up visits, it was found that adverse events, including myalgia, rhabdomyolysis, drug allergy, gastrointestinal tract reactions, and malaise, didn't occur among patients in the three groups. In addition, both creatine kinase and transaminase levels didn't exceed the upper limits, which indicated that the treatment of ACS by large-dose atorvastatin was safe and feasible.

Conclusion

In the research, 90 ACS patients were included as the research objects and enrolled into the experimental group (conventional treatment+60mg/per time/late atorvastatin), control group 1 (conventional treatment+25mg/per time/late atorvastatin), and control group 2 (conventional treatment+25mg/per time/late atorvastatin) according to different doses of atorvastatin. After that, 15 healthy volunteers attending physical examinations at the same period were enrolled into the blank group. Blood fat and inflammatory factor levels of patients before and after treatment were analyzed. It was demonstrated that short-term treatment by large-dose atorvastatin could reduce blood fat and inflammatory factor levels of ACS patients more effectively compared with that by conventional dose. Besides, it could inhibit the incidence of inflammatory reactions and improve patient prognosis with safety and feasibility. However, the included patient sample size was limited, and the feasibility of the adoption of a higher dose of atorvastatin was not discussed. Therefore, clinical experiments with larger sample sizes need to be selected for further analysis. To conclude, the contents of this research provided data reference for the clinical selection of the dose of atorvastatin.

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