Changes in Homocysteine Levels Affect Serum Lipid Response to Atorvastatin in Patients With Acute Coronary Syndrome: A Retrospective Observational Study

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Abstract

Objective: The present study investigated whether changes in serum homocysteine (Hcy) levels modify the effects of atorvastatin treatment on blood lipid parameters in patients with acute coronary syndrome (ACS). Methods: A total of 159 patients with ACS who received regular, long-term treatment with 20 mg/d atorvastatin were included. Depending on the changes in Hcy parameters, they were divided into Hcy reduction (HR) and Hcy elevation (HE) groups. Results: After long-term atorvastatin treatment, total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and Hcy levels were decreased (P < .05), and the ApoAI level was increased (P < .01). Correlation and stratified analysis showed that Hcy or hyperhomocysteinemia was correlated with blood lipids. In both the HE and HR groups, the TC, LDL-C, and ApoB levels after treatment were lower than those before treatment (P < .01), and the ApoAI level was increased compared with that before treatment (P < .05). There was no difference in the reduction of TC, LDL-C, and ApoB levels or in the increase of ApoAI level (Pinteraction > .05) between the 2 groups. However, there was a clear opposite trend of the effect of atorvastatin on TG and high-density lipoprotein cholesterol (HDL-C) levels between the HR and HE groups (Pinteraction < .05). In the HR group, the HDL-C level was increased (P < .05), and TGs were decreased compared with those before treatment (P < .01). Nevertheless, in the HE group, the HDL-C level was decreased (P < .05), and TGs (P < .05) were increased compared with those before treatment. Conclusion: The effects of atorvastatin on TGs and HDL-C depend on changes in Hcy levels. Patients with a reduced Hcy level after atorvastatin treatment had more favorable lipid parameters.

Keywords
acutecoronary syndrome, atorvastatin, lipid, homocysteine

Introduction

The prevalence and death rate of cardiovascular disease in China are still on the rise according to the “Report on Cardiovascular Diseases in China 2018.” Notably, acute coronary syndrome (ACS) accounts for 50% of cardiovascular deaths and is the most common and high-risk type of coronary heart disease (CHD), including unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. Despite the development of percutaneous coronary intervention (PCI) technology, patients still have a high incidence of major adverse cardiovascular events after ACS. The CHD mortality rate of urban and rural residents in China has gradually been increasing since 2012.1 Therefore, drug therapy for secondary prevention of CHD is one of the key treatment measures used to reduce the incidence of ACS regardless of PCI therapy. Atorvastatin is a lipid-lowering agent from ß-hydroxy ß-methyl glutaryl-CoA inhibitors. At the standard dosage, this drug reduces total cholesterol (TC) levels by 20% to 30%, low-density lipoprotein cholesterol (LDL-C) levels by 21% to 60%, and triglyceride (TG) levels by 7% to 37% and increases high-density lipoprotein cholesterol (HDL-C) levels by approximately 5% to 10%.2 At present,
Materials and Methods

Data Collection and Laboratory Methods

Drug Information

Research Groups

Table 1: Clinical Information of Selected Patients.

| Factor                        | Parameter |
|-------------------------------|-----------|
| Age, year                     | 62.36 ± 10.94 |
| Gender, male/female           | 108/51    |
| BMI, kg/m²                    | 23.42 ± 3.68 |
| Hypertension                  | 63        |
| Diabetes                      | 12        |
| Time after PCI (month)        | 9.34 ± 3.65 |
| ST-segment elevation myocardial infarction | 58 |
| Non-ST-segment elevation myocardial infarction | 42 |
| Unstable angina               | 59        |

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention.
Table 2. Changes in Serum Lipids and Homocysteine Levels After Atorvastatin Treatment.a

| Parameter      | Pretreatment | Posttreatment | Discrepancy | F    | P   |
|----------------|--------------|---------------|-------------|------|-----|
| TC, mmol/L     | 4.81 ± 1.09  | 3.91 ± 0.81   | −0.91 ± 1.13| 101.243 | .000 |
| TGs, mmol/L    | 1.82 ± 1.49  | 1.46 ± 0.73   | −0.36 ± 1.45| 9.834 | .002 |
| HDL-C, mmol/L  | 1.08 ± 0.28  | 1.09 ± 0.26   | 0.006 ± 0.24| 0.105 | .746 |
| LDL-C, mmol/L  | 3.02 ± 0.78  | 2.24 ± 0.62   | −0.78 ± 0.86| 132.254 | .000 |
| ApoAI, g/L     | 1.13 ± 0.23  | 1.20 ± 0.20   | 0.07 ± 0.22 | 16.430 | .000 |
| ApoB, g/L      | 0.98 ± 0.23  | 0.76 ± 0.19   | −0.21 ± 0.23| 129.972 | .000 |
| Hcy, μmol/L    | 14.31 ± 5.96 | 13.41 ± 5.04  | −0.90 ± 4.25| 7.099 | .009 |

Abbreviations: Apo, apolipoprotein; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Results

Changes in Blood Lipid Levels and Hcy Levels After Atorvastatin Treatment

The blood lipid levels of TC, TGs, LDL-C, and ApoB were significantly decreased after atorvastatin treatment (P < .005). The ApoAI level was increased compared with the level before treatment (P < .005). However, there was no statistically significant difference in HDL-C levels (P > .05). After atorvastatin treatment, the serum Hcy level was significantly decreased compared with the level before treatment (P < .05), as shown in Table 2.

Correlation Between Hcy Levels and Blood Lipid Levels

Before atorvastatin treatment, Hcy levels were negatively correlated with HDL-C levels (t = −0.192, P = .015), while there was no significant correlation between levels of Hcy and TC, TGs, LDL-C, ApoAI, or ApoB, as shown in Table 3.

Hyperhomocysteinemia and Serum Lipid Levels

After adjustment for sex, age, and BMI, a statistical analysis performed between the normal Hcy and HHcy groups divided according to whether the serum Hcy concentration was greater than 15 μmol/L indicated that the levels of serum TGs in the HHcy group were significantly higher than those in the normal Hcy group and that the levels of serum HDL-C and ApoAI in the HHcy group were significantly lower than those in the normal Hcy group (P for all < .05; Table 4).

The Interaction Between the Change in Hcy Level and the Lipid-Lowering Effect

The patients were divided into HE group or HR group according to the change in Hcy level after treatment with atorvastatin, and the effect of atorvastatin on lipid regulation was compared between the 2 groups. In the HE and HR groups, the levels of TC, LDL-C, and ApoB significantly decreased, and the ApoAI level significantly increased after treatment compared with the levels before treatment (P < .01). There were no significant differences in the effects of lowering TC, LDL-C, and ApoB and increasing ApoAI between the 2 groups (Pinteraction > .05). In the HE group, the TG levels after treatment were significantly higher than those before treatment (P < .05), while in the HR group, the TG levels after treatment were significantly lower than those before treatment (P < .01); the effects of atorvastatin on TG levels in the 2 groups were noticeably in
contrast ($P_{\text{interaction}} < .05$). In the HE group, the HDL-C levels after treatment showed a decreasing trend compared with the levels before treatment ($P < .05$). In the HR group, the HDL-C levels after treatment were significantly increased compared with the levels before treatment ($P < .05$). The effects of atorvastatin on HDL-C levels between the 2 groups were significantly opposite one another ($P_{\text{interaction}} < .05$), as shown in Table 5.

### Discussion

Epidemiological investigations have shown that increased TC, TG, LDL-C, and ApoB levels and decreased HDL-C and ApoAI levels were independent risk factors for CHD. Prospective intervention studies have found that reducing levels of TC, TGs, LDL-C, and ApoB, and increasing HDL-C and ApoAI levels can reduce the risk of atherosclerosis. Our study found that after statin treatment, TC, TG, LDL-C, and ApoB, and increasing HDL-C and ApoAI levels decreased significantly, and ApoAI levels increased significantly; however, the HDL-C levels did not change significantly after treatment. At present, the guidelines in China recommend that the target LDL-C level should be less than 1.8 mmol/L for very high-risk patients with arteriosclerotic cardiovascular disease (ASCVD). After an average of 9 months of lipid-lowering treatment in our study population, the average LDL-C level did not fully meet this standard. The data show that only 51 (32.1%) people met this standard. A recent study collected data on the status of target lipid attainment in high-risk patients with ASCVD with a history of myocardial infarction or revascularization in nearly 200 hospitals in China, and the results showed that 98% of these patients were treated with statins alone. Similar to our data, only 30% of them met the LDL-C standard. The control of LDL-C by single-dose statin therapy for very high-risk patients with ASCVD is generally insufficient. It is suggested that we should strengthen lipid-lowering efforts in high-risk patients with ASCVD who still fail to meet the standard after treatment with conventional doses of statins.

HHcy is considered a new risk factor for atherosclerosis. Folate deficiency is the main cause of HHcy because smoking, drinking, and cooked food dietary habits are common in China, which could lead to absorption disorders of folate and the loss of folate in food; however, folic acid supplementation is not popular in China, so folate, vitamin B6, and B12 deficiencies are not uncommon, resulting in a high proportion of HHcy in the Chinese population. In addition, methylene tetrahydrofolate reductase (MTHFR) is a key enzyme in Hcy metabolism, and the C677T genotype is related to decreased MTHFR activity, reduced remethylation of Hcy to methionine, and an increased Hcy level. In China, one-fourth of the population harbors the MTHFR C677T TT genotype, which is also an important factor leading to a high proportion of HHcy in China. In a recent study carried out by Chinese scholars, folic acid supplementation was shown to significantly reduce the risk of stroke in the hypertensive population in China, and the higher the level of Hcy was, the greater the benefit of folic acid supplementation. Therefore, HHcy is considered to be a stronger key risk factor for cardiovascular and cerebrovascular diseases in the Chinese population than in the Western population, and lowering the Hcy level can confer greater cardiovascular benefits in the
Chinese population. Some studies have shown that statin therapy can reduce human Hcy levels in women with polycystic ovary syndrome,10 renal transplant recipients,12 and patients with hypercholesterolemia.11 In the present study, we analyzed the changes in Hcy levels after atorvastatin treatment and found that the average level of Hcy decreased significantly (from 14.31 ± 5.96 μmol/L to 13.41 ± 5.04 μmol/L, P < .05). However, this association is not evident in some other studies.13,14 To explain these controversies, we must understand that the effect of statins on Hcy was influenced by the baseline level of Hcy,11 which was relatively high in our study, and that this would lead to the efficient therapy of atorvastatin, whereas in other studies, the baseline Hcy level was lower (approximately 10.5 μmol/L), and statin treatment was consequently less efficient. In addition, the effect of statins on Hcy was also influenced by the MTHFR C677T genotype, obesity,11 and the study sample size, so the controversial results of different studies may be influenced by these factors. However, in a meta-analysis of 15 studies, statins indeed caused reductions (3.5%) in Hcy blood concentrations in a large sample.15 The mechanism by which statins reduce Hcy levels in humans has not been fully studied. To the best of our knowledge, only Schroechsnessdal et al16 showed that statins may prevent Hcy accumulation in the blood via immunosuppression in vitro. Although the exact pathophysiological mechanisms underlying the association of the serum Hcy change with statin treatment remain to be further elucidated, in animal experiments, atorvastatin therapy can attenuate Hcy-induced reactive oxygen species accumulation and endothelial cell apoptosis through nicotinamide adenine dinucleotide phosphate oxidase and/or p38MAPK-dependent mechanisms.17,18 Atorvastatin also inhibits Hcy-induced endothelium reticulum stress both in vitro and in vivo.19 Kerstin Wustmann et al even showed that both statin and Hcy-lowering therapy (B-group vitamin supplementation) improved endothelial function in high-risk patients with cardiovascular disease but they act via different mechanisms.20 Thus, atorvastatin may reduce inflammatory factors and oxidative stress by a reduction in Hcy levels or via mechanisms independent of Hcy to achieve antiatherosclerosis effects.

Recent clinical observations have shown a certain correlation between serum Hcy and blood lipid levels in patients with CHD.21,22 The present study results also show a correlation between Hcy and blood lipid levels before atorvastatin treatment. When the statistical analysis was performed between normal Hcy and HHcy, the levels of serum TGs in the patients with HHcy were significantly higher than those in patients with normal Hcy, and the levels of serum HDL-C and ApoAI in patients with HHcy were significantly lower than those in patients with normal Hcy. Although we have not explored the mechanism of the relationship between Hcy and serum lipid levels (especially HDL-C and ApoAI), recent animal and in vitro cell studies have demonstrated that Hcy can suppress hepatic ApoAI expression via the pexosomes proliferator-activated receptor α-ApoAI pathway.23 Moreover, Hcy could decrease the transcription of ApoAI by stimulating nuclear factor-κB and ApoAI regulatory protein 1 and24 enhancing HDL-C clearance.24 These increased Hcy levels may impair cardiovascular function via the reduction in HDL-C and the impairment of its antioxidant capacity.

Based on the effect of statins on lowering both blood lipids and Hcy and the relationship between Hcy and blood lipid levels, however, whether the lipid-lowering effect of atorvastatin and the reduction in Hcy exist independently or whether there is an interaction between them are still unclear. In the present study, we found that different changes in Hcy levels after statin treatment may lead to different lipid-lowering effects. According to the changes in Hcy, the patients were divided into 2 groups: the HE group and the HR group. The results showed that the Hcy level decreased in most patients (96 patients, 60.4%). A small proportion of patients still showed an upward trend (63 patients, 39.6%). When we further compared the lipid-lowering effect between the HE group and the HR group, we found that the 2 groups showed the same trend in decreasing TC, LDL-C, and ApoB levels and increasing ApoAI levels. In the HE group, the level of TGs after treatment was significantly higher than that before treatment (P < .05). In the HR group, the level of TGs after treatment was significantly lower than that before treatment (P < .01). The effect of atorvastatin on TG levels between the 2 groups showed an opposite trend. In the HE group, the level of HDL-C decreased after treatment (P < .05), and in the HR group, the level of HDL-C increased significantly after treatment (P < .05). Interestingly, the effect of atorvastatin on HDL-C levels between the 2 groups was significantly opposite (P < .05). As mentioned earlier, elevated serum TGs and decreased serum HDL-C levels are risk factors for CHD. These results suggest that after statin treatment, patients with decreased Hcy have more favorable blood lipid levels (increased HDL-C and decreased TGs), while patients with elevated Hcy have more harmful blood lipid levels (decreased HDL-C and increased TGs).

Current studies have shown that even in patients where LDL-C levels are up to standard, there is still a significant risk of macrovascular events and microvascular complications. The Treating to New Targets (TNT) study indicated that when stratified at different HDL-C levels, the incidence of cardiovascular events in patients with low levels of LDL-C was further reduced by 39% in the highest HDL-C level group compared with the lowest HDL-C level group.25 It is suggested that even if the LDL-C level is up to standard, further increases in HDL-C levels can reduce cardiovascular events. Increased levels of TGs have been recognized as a risk factor for ASCVD and are often accompanied by decreased levels of HDL-C8,9, they are the main manifestations of metabolic syndrome and are the major risk factors for ASCVD.26 Therefore, the possible cause of residual cardiovascular risk is closely related to whether statins reduce TGs and increase the level of HDL-C. Our study found that statins have more favorable lipid parameters in patients with reduced Hcy, suggesting that these patients may benefit from reduced Hcy levels by having a lower risk of residual cardiovascular events. However, our study is an observational study, and additional prospective randomized controlled trials are needed to confirm that statin treatment has
better lipid parameters and cardiovascular outcomes in patients with reduced Hcy than in patients with elevated Hcy.

**Conclusion**

The effects of atorvastatin on serum TGs and HDL-C levels depend on the changes in Hcy levels. Patients with decreased Hcy levels after atorvastatin treatment have more favorable lipid parameters. This finding suggests that in the treatment of ACS, we should not only strive to achieve the target LDL-C levels but also pay attention to the benefits of statin therapy in reducing Hcy levels.

**Authors’ Note**

DFW participated in the design, collected the data and the samples, performed the statistical analyses, and drafted the manuscript. YXW and JLD conceived the study and participated in the design. All authors read and approved the final manuscript.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethics Approval and Consent to Participate**

This study was complied with the Declaration of Helsinki and approved by the Institutional Ethics Committee of People’s Hospital of Guangxi Zhuang Autonomous Region. Written informed consent was obtained from the participants.

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