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Original Research Article

Efficacy of atorvastatin in the management of atherosclerotic cardiovascular disease (ASCVD)

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Abstract

Purpose: *To investigate the efficacy of atorvastatin in the treatment of atherosclerotic cardiovascular disease (ASCVD)*

Methods: *A total of 158 patients who underwent coronary angiography in the Department of Cardiology, First Affiliated Hospital of Hebei North University, China were divided into acute myocardial infarction (AMI, n = 42), unstable angina pectoris (UAP, n = 70), and control (n = 46) groups. Atorvastatin (40 mg) was administered to the patients in AMI and UAP groups for 40 days. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, phospholipase A2 (PLA2), YKL40, and clinical efficacy were evaluated after treatment.*

Results: *Acute myocardial infarction group (AMI) had significantly higher TC, LDL-C, non-HDL-C, PLA2, and YKL40 levels compared to UAP and control ($p < 0.05$). Also, HDL-C, TG, and TG/HDL-C were significantly higher in AMI and UAP compared to control group ($p < 0.05$). In coronary heart disease, TG/HDL-C had the highest sensitivity, and LDL-C had the highest specificity. Furthermore, TC, LDL-C, and TG significantly decreased in both AMI and UAP groups ($p < 0.05$), while HDL-C remained unchanged ($p > 0.05$).*

Conclusion: *Atorvastatin effectively improves lipid profiles in ASCVD patients, and markers such as PLA2 and YKL40 effectively predict ASCVD risk. Further larger-scale, long-term studies are needed to validate the effectiveness of combining lipid and inflammatory biomarkers for ASCVD risk prediction and management.*

Keywords: *Atherosclerotic cardiovascular disease, Blood lipids, YKL40, Phospholipase A2, Atorvastatin*

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INTRODUCTION

The current economic developments have led to changes in lifestyle of the population, with accelerated urbanization and an aging population being the most prominent factors. A growing concern is the prevalence of unhealthy lifestyles among residents, leading to a high incidence of atherosclerotic cardiovascular

disease (ASCVD). Over three decades spanning from 1990 to 2019, there has been a significant increase in global burden of cardiovascular mortality. During this period, the number of deaths attributable to cardiovascular disease (CVD) increased from 12.1 million to 18.6 million, reflecting approximately a 1.5-fold increase [1]. This poses significant challenges to public health and healthcare systems. Atherosclerotic cardiovascular disease is a major chronic disease affecting the health of middle-aged and elderly population. Its development is closely related to risk factors such as hypertension, lipid abnormalities, glucose abnormalities, obesity, and unhealthy lifestyles [2].

One of the primary risk factors in the occurrence and development of ASCVD is lipid abnormalities [3]. Latest data from the World Health Organization (WHO) indicated that more than 50 % of coronary heart disease cases globally are linked to elevated cholesterol levels [3]. Active treatment of lipid abnormalities reduces the incidence of coronary heart disease effect. The preferred clinical approach for treatment is the use of oral statin drugs, which are the most commonly used medications worldwide for treatment and prevention of cardiovascular diseases. Atorvastatin, as a commonly used lipid-lowering medication, has been widely applied in the treatment of ASCVD.

Reducing low-density lipoprotein cholesterol (LDL-C) levels, effectively decreases the formation and progression of atherosclerotic plaques, thus lowering the risk of cardiovascular effects. Also, atorvastatin raises high-density lipoprotein cholesterol (HDL-C) levels and inhibits inflammatory responses, offering new prospects for ASCVD treatment [4,5]. However, a single blood lipid indicator may not comprehensively reflect the complex pathogenesis of ASCVD.

Recent research has indicated a close association between blood lipid levels and serum inflammatory factors. Elevated levels of LDL-C and triglycerides (TG) are not only independent risk factors for ASCVD but also closely related to sustained activation of inflammatory responses, accelerating endothelial dysfunction and arterial wall damage. Inflammatory factors such as phospholipase A2 (PLA2) and Chitinase-3-like protein 1 (YKL-40) play significant roles. Also, PLA2 induces vasoconstriction and cell aggregation, leading to acute inflammatory responses and directly participating in the development of atherosclerosis [6-7]. Chitinase-3-like protein (YKL-40) is involved in endothelial dysfunction and vascular remodeling processes, ultimately contributing to the occurrence of arterial sclerosis and accelerating plaque instability [8]. Therefore, this study investigated the efficacy of atorvastatin using blood lipids combined with serum inflammatory factors for ASCVD.

METHODS

Participants

A total of 158 cases (comprising 105 males and 53 females) were admitted to the Department of Cardiology, First Affiliated Hospital of Hebei North University, China between May 2020 to May 2021 and underwent coronary angiography within 24 h who met the diagnostic criteria for AMI and UAP [9]. Patients were randomly divided into acute myocardial infarction (AMI), unstable angina pectoris (UAP), and control (NC) groups based on patient history, biochemical indicators, and coronary angiography results. This study was approved by the Ethics Committee of The Third Central Hospital of Tianjin (approval no. 19979523). Informed consent was obtained from all study participants, and the study was conducted in accordance with the Declaration of Helsinki [10].

Inclusion criteria

Patients who met the diagnostic criteria for AMI and UAP [9].

Exclusion criteria

History of surgery within the prior 6-month period, presence of severe hepatic or renal dysfunction in the medical history, active malignancy, autoimmune disease, prior coronary artery bypass grafting, allergy to atorvastatin, poor treatment adherence, or withdrawal of consent.

Treatment

Patients in the AMI and UAP groups underwent atorvastatin treatment. Both groups received standard atorvastatin calcium (20 mg daily; Pfizer Inc., USA, batch number: National Medical Products Administration Approval No. J20120050, specification: 10 mg/tablet) for 3 months, and changes in blood lipid levels before and after treatment were measured in both groups [11].

Collection of blood specimens

Within a single day from hospital admission and again after treatment, venous blood samples (5

mL) were drawn from all participants in a fasted state. These biological materials underwent centrifugation at 3,200 revolutions per minute for 3 minutes, after which the clarified supernatant was harvested for subsequent analytical procedures.

Biochemical measurements

Venous blood samples (5 mL) were drawn from all participants in a fasted state, centrifuged at 3,200 rpm, for 3 min to obtain the supernatant for biochemical analysis. The Hitachi 7170 automated clinical chemistry platform was used to quantify triglycerides (TG, mmol/L), total cholesterol (TC, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L).

Also, the concentration of phospholipase A2 (PLA2, ng/mL) and glycoprotein YKL-40 (ng/mL) was determined using enzyme-linked immunosorbent assay (ELISA) kits (Beijing Xiehe Biotechnology Co., Ltd).

The atherogenic index, expressed as TG/HDL-C ratio, represented the ratio of serum triglyceride to HDL-cholesterol value. This metric has been validated as a reliable surrogate marker of insulin resistance and is viewed as an indicator of a more pro-atherogenic lipid profile, with higher ratios portending elevated cardiovascular disease risk. Furthermore, non-HDL-C was calculated using Eq 1.

Non-HDL-C = TC - HDL-C …… (1)

This parameter encapsulates cholesterol content across all atherogenic lipoprotein subfractions, encompassing very low-density lipoprotein cholesterol (VLDL-C), LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and cholesterol residing within chylomicron remnants (CMR-C).

Statistical analysis

Data was analyzed using Statistical Packages for Social Sciences (SPSS version 22.0; IBM, Armonk, NY, USA). Normally distributed data were presented in mean ± standard deviation (SD), and group comparisons were done using one-way analysis of variance (ANOVA). Independent samples t-tests were employed for paired group comparisons. Non-normally distributed continuous data were expressed as median (interquartile range), denoted as M (Q1, Q3), and Mann-Whitney U test or Kruskal-Wallis H test was used for group comparisons. Pearson's chi-square test or Fisher's exact probability method was used to assess group differences. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

There was no significant difference in baseline characteristics (gender, and age) across all groups ($p < 0.05$). Assessments of lipid profile parameters revealed that TC and LDL-C levels were significantly higher in AMI group compared to UAP and NC groups ($p < 0.05$). There was no significant difference in HDL-C and TG levels between AMI and UAP groups ($p > 0.05$). However, both AMI and UAP groups exhibited significantly higher HDL-C and TG levels compared to control group ($p < 0.05$; Table 1).

Non-HDL, TG/HDL, PLA2, and YKL40

Levels of non-HDL-C, PLA2, and YKL-40 were significantly higher in AMI group compared to UAP and control groups ($p < 0.05$). Furthermore, there was no significant difference in atherogenic index (TG/HDL-C ratio) between AMI and UAP groups ($p > 0.05$). However, both AMI and UAP groups exhibited significantly higher TG/HDL-C ratios compared to control group ($p < 0.05$; Table 2).

Sensitivity, and specificity for various indicators

The TG/HDL-C showed the highest sensitivity, while LDL-C exhibited the highest specificity (Table 3).

Table 1: Baseline characteristics of patients (mean ± SD, m (Q1, Q3))

Group	AMI (n=42)	UAP (n=70)	Control (n=46)	χ^2/F/Z	*P*-value
Male (n; %)	33 (79%)	44 (63%)	28(61%)	3.82	0.15
Age (years)	61.43±10.91	61.79±8.99	59.07±9.14	1.21	0.30
TC (mmol/L)	5.07±0.87	4.70±0.84*	4.10±1.00*#	13.30	< 0.001
LDL-C (mmol/L)	3.14±0.70	2.79±0.63*	2.50±0.8*#	9.00	< 0.001
HDL-C (mmol/L)	1.08±0.32	1.12±0.28	1.24±0.31*#	3.74	0.026
TG (mmol/L)	1.63 (1.25,2.50)	1.58 (1.18,2.15)	1.31(0.95,1.73)*#	8.83	0.018

*P < 0.05 vs Acute myocardial infarction (AMI), #p < 0.05 vs unstable angina pectoris (UAP)

Table 2: Non-HDL, TG/HDL ratio, PLA2, and YKL40 (mean ± SD or M (Q1, Q3))

Group	AMI (n=42)	UAP (n=70)	Control (n=46)	χ^2/F/Z	*P*-value
Non-HDL-C (mmol/L)	3.99±0.83	3.58±0.77*	2.86±0.94*#	20.99	< 0.001
TG/HDL-C	1.62 (1.04, 2.71)	1.45 (0.95, 2.22)	1.07 (0.68, 1.73)*#	56.64	0.004
PLA2(mg/L)	0.434 (0.340, 0.637)	0.334 (0.227, 0.458)*	0.192 (0.130, 0.336)*#	66.94	< 0.001
YKL40(ng/mL)	0.49 (0.41, 0.64)	0.34 (0.22, 0.47)*	0.16 (0.85, 0.36)*#	43.12	< 0.001

*P < 0.05 compared to AMI, #p < 0.05 compared to UAP

Table 3: Sensitivity, and specificity for various indicators

Indicator	AUC Area	95%CI	Sensitivity	Specificity
TC (mmol/L)	0.708	0.615-0.801	0.804	0.522
TG (mmol/L)	0.643	0.545-0.740	0.902	0.326
LDL-C (mmol/L)	0.661	0.560-0.762	0.598	0.696
HDL-C (mmol/L)	0.375	0.263-0.451	0.411	0.413
HDL-C (mmol/L)	0.751	0.663-0.838	0.821	0.587
TG/HDL-C (ratio)	0.664	0.569-0.760	0.946	0.326
PLA2 (mg/L)	0.745	0.654-0.835	0.911	0.543
YKL40 (ng/mL)	0.762	0.668-0.856	0.804	0.674

Table 4: Blood lipid concentrations (mean ± SD)

Group		AMI (n=42)	UAP (n=70)
TC (mmol/L)	Before treatment	5.07±0.87	4.70±0.84
	After treatment	3.95±0.68	2.82±1.09
T-value		6.573	11.430
P-value		0.001	0.001
LDL-C (mmol/L)	Before treatment	3.14±0.70	2.79±0.63
	After treatment	2.63±0.52	2.32±0.59
T-value		3.790	4.556
P-value		0.001	0.001
HDL-C (mmol/L)	Before treatment	1.08±0.32	1.12±0.28
	After treatment	1.22±0.42	1.26±0.47
T-value		1.718	1.978
P-value		0.089	0.050
TG (mmol/L)	Before treatment	1.63(1.25,2.50)	1.58(1.18,2.15)
	After treatment	1.41(1.08,1.92)	1.32(1.16,2.07)
T-value		1.980	3.021
P-value		0.042	0.031

Blood lipid concentrations

Levels of TC, LDL-C, and TG levels significantly decreased in both AMI and UAP groups after treatment compared to pre-treatment values (p < 0.05). Furthermore, HDL-C levels remained unchanged across all study groups before and after atorvastatin therapy (p > 0.05; Table 4).

DISCUSSION

Currently, commonly used indicators in ASCVD detection still revolve around blood lipids, with LDL-C being the most widely acknowledged plasma lipoprotein-associated with atherosclerosis, and HDL-C recognized as an anti-atherogenic lipoprotein and an important protective factor against coronary heart disease [3]. Elevated levels of TC, TG, LDL-C, and low levels of HDL-C are known to increase the risk of ASCVD. In this study, control group exhibited significantly lower TC, TG, LDL-C, and higher HDL-C levels compared to AMI and UAP groups. This finding reaffirms the existing belief that elevated TC, TG, LDL-C, and low HDL-C levels increase the risk of ASCVD. Furthermore, TC and LDL-C levels were significantly higher in AMI group compared to UAP group, indicating a positive correlation between TC, LDL-C levels, and occurrence of coronary heart disease lesions. In light of this, the 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidemias recommended an LDL-C target

value of a 50 % reduction from baseline and < 1.4 mmol/L for very high-risk ASCVD patients [11]. Similar guidelines were also provided by the 2018 American Heart Association Cholesterol Management Guidelines and the Guidelines for the Diagnosis and Treatment of Lipid Abnormalities in Primary Care (2019) in China [3,12]. However, even in patients achieving appropriate LDL-C targets, the risk of cardiovascular effects remains high, suggesting a significant residual cardiovascular risk.

In this study, HDL-C levels significantly increased in NC, UAP and AMI groups, indicating a positive correlation between non-HDL-C levels and the occurrence of coronary heart disease. Also, there was no significant difference in TG/HDL-C ratio for AMI and UAP groups compared to control. The Framingham study demonstrated that at the same level of non-HDL-C, there was no correlation between LDL-C and coronary heart disease risk [13-14]. Conversely, at the same level of LDL-C, non-HDL-C is strongly correlated with coronary heart disease risk. This study suggests that non-HDL-C is a better predictor of coronary heart disease compared to LDL-C [15]. A meta-analysis in 2012 showed that among patients who achieved LDL-C targets, those who did not achieve non-HDL-C targets (≥ 3.4 mmol/L) had a 32 % increased risk of cardiovascular effects. However, among patients who achieved non-HDL-C targets, those who did not achieve LDL-C targets (≥ 2.6 mmol/L) did not exhibit any significant increase in cardiovascular risk. The results indicate a positive correlation between non-attainment of non-HDL-C targets and higher cardiovascular risk in patients who have achieved LDL-C targets. When LDL-C is within target but non-HDL-C is not, it often suggests elevated plasma TG levels and major carriers of chylomicron remnants cholesterol are lipoproteins rich in TG. Therefore, elevated TG levels are one of the important residual cardiovascular risks after drug intervention.

Evidence showed that low HDL-C levels and a high TG/HDL-C ratio are risk factors for cardiovascular effects in coronary heart disease patients [16]. Compared to individual lipid measurements, TG/HDL-C ratio more accurately reflects lipid levels in patients [14,15]. Thus, TG/HDL-C ratio has been established as a predictive factor for ASCVD, providing more accurate estimation of residual cardiovascular risk in patients with coronary heart disease. Previous studies have pointed out that TG/HDL-C ratio is an independent risk factor for coronary heart disease [17]. Both non-HDL and TG/HDL serve as risk prediction indicators for ASCVD. In addition to non-HDL in atherosclerosis, inflammation is also a key factor in the development of atherosclerosis. Levels of PLA2 and YKL40 were increased in control, UAP and AMI groups. This suggests that PLA2 and YKL40 play important roles in the occurrence and progression of coronary heart disease. Also, PLA2 is primarily synthesized and secreted by macrophages and lymphocytes and also participates in the regulation of inflammatory responses [18].

Since its discovery in 2015, PLA2 has been identified as a crucial pathogenic factor associated with the development of coronary heart disease. The PLA2 levels were increased in patients with coronary heart disease compared to normal individuals, consistent with previous research findings. Moreover, studies have shown that PLA2 levels are higher in vulnerable plaques compared to stable plaques, and it reflects the extent of myocardial injury and inflammatory response becoming a valuable diagnostic and predictive tool, particularly for elderly patients with acute myocardial infarction (AMI) and major adverse cardiovascular events (MACE) [19]. Similarly, YKL40, through its involvement in endothelial dysfunction and vascular remodeling, it ultimately contributes to the development of arterial sclerosis and accelerates plaque instability [8]. Its levels are significantly higher in coronary heart disease patients compared to normal individuals, with higher levels associated with greater plaque instability [9]. Serum YKL-40 levels are significantly elevated in patients with acute coronary syndrome, and the degree of elevation correlates with the progression of coronary artery disease [8]. Also, YKL-40 levels increase with the severity of coronary artery disease (evaluated by the number of affected vessels in coronary angiography) and are independently associated with disease progression. It also serves as a promising predictive factor for high-risk coronary heart disease and should be detected early. This study further investigated the fluctuation in lipid levels before and after 3 months of atorvastatin treatment in patients from the AMI and UAP groups. The results demonstrated that post-treatment levels of LDL-C, TC, and TG were significantly reduced compared to pre-treatment levels ($p < 0.05$), while HDL-C levels increased ($p > 0.05$). This indicated the effective lipid-lowering effect of atorvastatin in ASCVD patients. Atorvastatin is a selective 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, exerting robust lipid-modulating effects by inhibiting HMG-CoA reductase and biosynthesis of cholesterol and lipoproteins in the liver.

Limitations of the study

This study used a relatively small sample size, particularly in AMI and control groups which may limit the generalizability of the findings. Additionally, the short 30-day duration of atorvastatin treatment may not have been sufficient to fully evaluate its long-term effects on lipid profiles and ASCVD risk.

CONCLUSION

Atorvastatin effectively lowers lipid profiles in ASCVD, and TG/HDL-C ratio shows higher sensitivity but lower specificity, while LDL-C (the current lipid intervention target), shows the highest specificity. Therefore, combined assessment of lipid indicators and inflammatory factors such as PLA2 and YKL40 accurately predicts high-risk individuals for ASCVD, enabling early intervention to reduce disease incidence and mortality rates. Further larger-scale, long-term studies are needed to validate the effectiveness of combining lipid and inflammatory biomarkers for ASCVD risk prediction and management.

DECLARATIONS

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None.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Cuijun Hao and Tianhua Hou contributed equally to this study.

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