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Evaluation of Anti-Inflammatory Effect of Pitavastatin with Monocyte Count to HDL Cholesterol Ratio in Patients with Coronary Artery Disease

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ABSTRACT

Objectives: Monocyte count to high-density lipoprotein cholesterol ratio (MHR) was proposed as a novel inflammation marker. Statins have some anti-inflammatory pleiotropic effects as well as lipid-lowering effects. This study aims to examine the effect of lipid-lowering therapy with pitavastatin on MHR in patients with coronary heart disease.

Methods: This was a descriptive study, single-center study. Hospital registries between October 2018 and April 2019 were retrospectively reviewed. Eligible patients were those who had both stable coronary artery disease and hypercholesterolemia of low-density lipoprotein cholesterol (LDL-C) >100 mg/dL and started to take treatment (pitavastatin, 4 mg/day). Pre-and post-treatment complete blood count values and lipid parameters were evaluated, and MHR was calculated.

Results: This study enrolled 150 patients. Pitavastatin (4 mg/day) was administered throughout median 3.0 (1.0-7.0) months. Mean total cholesterol level declined from 235.2±52.3 mg/dl to 186.9±48.8 mg/dl ($p<0.001$). Mean triglyceride level declined from 167.2±75.0 mg/dl to 152.8±66.7 mg/dl and mean LDL-C level declined from 153.9±45.0 mg/dl to 109.0±41.2 mg/dl ($p=0.020$ and $p<0.001$, respectively). Moreover, pre-treatment MHR declined from 1.4 (0.4-4.0) to post-treatment MHR 1.3 (0.5-3.4) ($p=0.263$).

Conclusion: This study concluded that pitavastatin improved serum lipid levels but did not decrease MHR.

Keywords: Pitavastatin, inflammation, lipids, monocyte, high density lipoprotein



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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide.^[1] In addition, inflammation plays a major role in the development of CVDs. Macrophages and monocytes are the main cell types for pro-inflammatory cytokines and may modulate inflammatory cytokines. The inflammation process is not only contributed by the immune cells but also by lipids in the serum.^[2,3]

High-density lipoprotein cholesterol (HDL-C) protects endothelial cells from the harmful effects of low-density lipoprotein cholesterol (LDL-C) and resists oxidation of LDL-C molecules.^[4-5] HDL-C was therefore thought to be both anti-inflammatory and anti-oxidant. Statins block the β -hydroxy β -methylglutaryl-CoA reductase enzyme in the mevalonate pathway and reduce LDL-C levels, thus reducing cardiovascular morbidity and mortality

in hypercholesterolemic patients. Moreover, side effects can vary between different statins. Common side effects are headache, digestive system problems, muscle pain, low blood platelet count, and liver damage. They also have pleiotropic effects beyond the lipid-lowering effects and show anti-inflammatory and anti-oxidant effects.^[6-10] Moreover, pitavastatin lowers LDL-C and increases HDL-C.^[11] Hence, pitavastatin is expected to show an anti-inflammatory effect. Previous studies supported that pitavastatin has anti-inflammatory effects.^[12] Monocyte count to HDL-C ratio (MHR) was proposed as a novel marker to reflect the prognosis of CVDs based on the pro-inflammatory effect of monocyte and the anti-inflammatory effect of HDL-C.^[13]

Thus, this study was designed to examine the effect of lipid-lowering therapy with pitavastatin on MHR in patients with coronary heart disease.

METHOD

This was a descriptive, single-center study. Hospital registries between October 2018 and April 2019 were retrospectively reviewed. Eligible patients were those who were diagnosed as having both stable coronary artery disease and hypercholesterolemia of LDL-C >100 mg/dl and currently not taking medication to lower hypercholesterolemia and started treatment with pitavastatin (4 mg/day). Retrospectively, pre- and post-treatment complete blood count values and lipid parameters were evaluated, and MHR were calculated.

Exclusion criteria were taking lipid-lowering drugs (statins and fibrates) or cyclosporine, having a history of familial

hypercholesterolemia, acute or chronic inflammatory or infectious diseases, moderate or severe hepatic or renal failure, and thyroid disorder.

R software (ver. 3.5.1), Jamovi (Jamovi project 2018, ver. 1.0.5) and JASP Team (2018, ver. 0.10.2) were used for statistical analysis. Normality was tested with Kolmogorov-Smirnov test. Normally distributed data were presented as mean, standard deviation and Paired sample t-test was used for comparison of dependent groups. Non-normal variables were presented with median, minimum and maximum values. Comparisons for non-normal variables were performed with Wilcoxon test. Categorical data were presented with frequency and percentage values. A p value <0.05 was considered to have statistical significance.

RESULTS

A total of 150 patients were enrolled in the study. The mean age was 62.5±11.0 years, and 87 (58.0%) patients were males. Pitavastatin (4 mg/day) was administered throughout median 3.0 (1.0-7.0) months. Pre and post-treatment values of complete blood count and lipid parameters are shown in Table 1.

DISCUSSION

Inflammation and lipid accumulation are cornerstones of atherosclerosis.^[14] According to numerous studies, statins affect not only serum lipid levels but also macrophage functions.^[15] In this study, it was found that the treatment with pitavastatin did not statistically change MHR in patients with stable coronary artery disease and hyperlipidemia.

Table 1. Pre and post-treatment values of complete blood count and lipid parameters

	Pre-treatment (n=150)	Post-treatment (n=150)	p
LDL-C (mg/dl)	153.9±45.0	109.0±41.2	<0.001*
HDL-C (mg/dl)	48.2±11.0	48.0±11.4	0.592*
TG (mg/dl)	167.2±75.0	152.8±66.7	0.020*
TC (mg/dl)	235.2±52.3	186.9±48.8	<0.001*
WBC (10 ³ /mm ³)	7.7±1.9	7.9±2.0	0.155*
Platelets (10 ³ /mm ³)	242.9±62.3	236.7±58.8	0.113*
Monocytes (10 ³ /UI)	65.4±20.2	66.9±20.5	0.305*
Lymphocytes (10 ³ /UI)	245.2±73.2	240.3±69.8	0.302*
Neutrophils (10 ³ /UI)	435.3±146.1	455.8±169.1	0.078*
RDW (10 ³ /UI)	13.4±1.4	13.2±1.4	0.195*
MHR	1.4 (0.4-4.0)	1.3 (0.5-3.4)	0.263 [†]

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol, MHR: Monocyte count to high density lipoprotein cholesterol ratio; RDW: Red cell distribution width; TC: Total cholesterol; TG: Triglyceride; WBC: White blood cell count.

Data is presented as mean±SD and median (minimum-maximum).

*Paired samples t test, [†]Wilcoxon test.

Although several studies showed that statins lower total cholesterol, LDL-C, and triglyceride levels, statins are often prescribed not only in patients with dyslipidemia but also in patients with coronary artery disease, acute coronary syndromes, stroke, and diabetes mellitus irrespective of serum cholesterol levels to take advantage of the atheromatous plaque-stabilizing, anti-inflammatory, and antioxidant effects.^[16,17]

Macrophages secrete matrix metalloproteinase (MMP) and degrade the extracellular matrix predisposing an atheromatous plaque to rupture. Fluvastatin and simvastatin inhibit MMP-9 (gelatinase B) activity by macrophages.^[18] Previously, Jialal et al. showed that statins decreased levels of high-sensitivity C-reactive protein. These data support the anti-inflammatory effect of these drugs.^[19] Pitavastatin has pleiotropic and anti-inflammatory effects on vascular cells.^[20,21] However, simvastatin reduces macrophage superoxide formation. Fluvastatin and lovastatin bind to LDL-C and do not allow the diffusion in to the atheromatous plaque. Atorvastatin and fluvastatin have direct antioxidant effects.^[22-25] Pravastatin changes the composition of atheromatous plaque independent of its cholesterol-lowering effect.^[26]

Monocytes are pro-inflammatory and HDL-C suppresses monocyte activation and proliferation-differentiation of monocyte progenitor cells. Previous studies have shown that low HDL-C levels and high monocyte count may be relevant to inflammation.^[27-29] Hence, the MHR may be a useful marker for inflammation.

The results of this study demonstrated that pitavastatin improved serum lipid levels and conformed to those of previous studies. Consequently, pitavastatin did not diminish MHR. There was no significant increase in HDL-C levels in this study, which may be the reason for the non-significant decrease in MHR levels although pitavastatin has been shown to increase HDL-C in previous studies.^[12]

There were some limitations to this study. Firstly, follow-up period was short and the sample size was small. Also, no other inflammatory markers were studied to compare with MHR.

CONCLUSION

Physicians prefer statins which act as anti-inflammatory besides lipid-lowering because inflammation plays an important role in atherosclerosis and CVDs pathogenesis. Parameters of complete blood count and lipid panel are widely accessible and inexpensive. Thus, MHR can be simply calculated. Further studies are needed to investigate the usefulness of MHR for evaluating anti-inflammatory effects of statins in clinical practice.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Ethics Committee Approval: The study was performed in compliance with the Declaration of Helsinki (as revised in Brasil, 2013) and ethics approval was obtained from the local ethics committee of Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Approval date: Jan 06, 2020 and Approval number:2019/528).

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