Original Article

Effectiveness of Statin Treatment in Reducing Red Cell Distribution Width and Mean Platelet Volume in Patients with Stable Coronary Artery Disease: A Retrospective Study

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Abstract

Objectives: Mean platelet volume (MPV) has been shown to be a predictor of platelet activation and plays a crucial role in the pathogenesis of atherosclerosis. Red cell distribution width (RDW) is a measure of the variability of erythrocyte volumes and might reflect underlying chronic inflammation. Both MPV and RDW are related to increased risk for cardiovascular disease. Since statins have pleiotropic effects, we aim to investigate the effect of statins on this possible hematologic markers of atherosclerotic risk in stable coronary artery disease (CAD). **Materials and Methods:** One hundred and twenty-one statin-naive patients who had undergone coronary angiography for stable CAD between June 2012 and June 2013 were retrospectively enrolled in this study. Patients were treated with atorvastatin or rosuvastatin. The lipid profile and hematological parameters were measured at baseline and after statin treatment. **Results:** One hundred and twenty-one patients were included in the study. The mean age was 60.5 ± 9 years and 38% of patients were women. Out of 121 patients, 106 (87.6%) patients received atorvastatin therapy and 15 (12.4%) patients received rosuvastatin therapy. After a median follow-up period of 36 days, statin treatment markedly reduced low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) levels (P = 0.0001, for all). For hematological parameters, only RDW significantly decreased after statin treatment (P = 0.0001). The Δ RDW were not associated with Δ LDL-C (r = 0.03; P = 0.72), ΔTG (r = 0.06; P = 0.49) and Δ TC levels (r = 0.05; P = 0.55). Statins had no effect on MPV levels (P = 0.32). **Conclusions:** Statin therapy significantly reduces the RDW levels in stable CAD irrespective of cholesterol levels, which might confirm the anti-inflammatory effect of statins. However, the association between decreased RDW levels and prognosis in stable CAD has to be established by multi-center, prospective studies in large populations.

Keywords: Hematological parameters, pleiotropic effects, statins

Introduction

Atherosclerotic cardiovascular diseases (CVD), including coronary artery disease (CAD), cerebrovascular disorders, aortic aneurysm, and peripheral artery disease, are the most important causes of mortality and morbidity worldwide.[1] Increased serum levels of cholesterol, especially low-density lipoprotein cholesterol (LDL-C), is associated with the high risk of atherosclerotic CVD, and LDL-C reduction with statin treatment was linked to reduced risk of all-cause and cardiovascular mortality both for primary and secondary prevention.[2,3] It has been shown that the benefits of statins resulted from both LDL-C lowering effects and pleiotropic effects.[4] Among many pleiotropic effects of statins, two of the most important ones are reducing platelet aggregation and the anti-inflammatory properties. It has been shown

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that there is a well-established positive correlation between hypercholesterolemia and the level of ADP-induced platelet adhesion, and statin therapy resulted in a significant decrease in ADP-induced platelet aggregation.[5] It has also been demonstrated that statin treatment decreases reactive oxygen species generation and reduces the secretion of pro-inflammatory cytokines.[6]

Mean platelet volume (MPV) is a simple estimate of platelet function and activation, and raised levels of MPV are correlated with increased thromboxane and beta-thromboglobulin secretion, procoagulant action, and expression of adhesion molecules.[7]

Red cell distribution width (RDW) is a readily measured marker of the size variability of erythrocytes. The increase in RDW levels was linked to unfavorable serum lipid profile.[8] In addition, RDW is associated with various inflammatory markers[9-11] and it is assumed that chronic inflammation and oxidative stress have a pivotal role in atherosclerosis.[12]

Thus, the aims of this study were to assess the effectiveness of statin treatment on serum lipid profiles, MPV, and RDW levels in statin-naive patients with stable CAD, the relationship between serum lipid sub-fractions and these hematological parameters, and finally, is there a correlation between the change in serum lipid profiles and the change in RDW and MPV levels.

Materials and Methods

Study design and patient population

We retrospectively enrolled 121 consecutive patients who underwent coronary angiography with suspected CAD from June 2012 to June 2013. Patients having one or more major epicardial coronary artery stenosis of ≥50%, by visual estimation, and patients with medically treated stable CAD were included. Statin-naive patients with elevated levels of LDL-C ≥100 mg/dL were included in this study. We excluded patients with acute coronary syndromes, rheumatic valvular heart disease, anemia (Hemoglobin [Hb] <12 mg/dL in women and Hb <13 mg/dL in men), chronic renal disease (GFR <60 mL/min), chronic liver disease, history of iron, Vitamin B12 and folate deficiency, supplementation of iron, folate or Vitamin B12, chronic obstructive pulmonary disease, hypothyroidism or hyperthyroidism, history of malignancy and normal coronary arteries.

Data collection

Medical history, medication use, smoking status, and anthropometric data were collected from institutional medical records retrospectively. Body mass index was counted as weight (kg) divided by the square of height (m^2). Systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg or the present use of BP-lowering medication is defined as hypertension. A fasting serum glucose ≥126 mg/dL or the present use of medication for diabetes is defined as diabetes mellitus. We specified 1-vessel, 2-vessel, and 3-vessel disease according to the number of major epicardial coronary artery stenosis of ≥50%. Left ventricular ejection fraction (LVEF) was calculated from the apical 4-and 2-chamber imaging planes using the biplane method of disks using the Vivid 7 Dimension ultrasound system (GE Vingmed Ultra-sound, Horten, Norway).

Hematological and biochemical data were obtained from the results of preprocedural venous blood sample analysis retrospectively. Biochemical data were measured using an automated chemistry analyzer (Abbott Laboratories, Abbott Park, IL). Baseline fasting glucose, serum creatinine, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) values were recorded. Hematological data were measured using EDTA tubes with Coulter LH Series hematology analyzer (Beckman Coulter, Inc., Hialeah, Florida). Since this study is retrospective, the time delay between sampling and data examination could not be rigidly controlled. Baseline hematologic parameters, including red blood cell, white blood cell and platelet count, Hb, RDW, and MPV were also recorded. The time between the coronary angiography and the first outpatient clinic visit is defined as the duration of the statin treatment. Hematological and biochemical data in the first outpatient clinic visit were also recorded for each patient.

Ethical statement

This study was approved by the local medical ethics committee (approval number 311, October 12, 2013) and was performed in accordance with the rights expressed in the Declaration of Helsinki.

Statistical analysis

A standard statistical software program (SPSS version 26; SPSS, Inc., Chicago, IL, USA) was used. The Kolmogorov–Smirnov test and histograms were used to check continuous variables for normality. The categorical variables were represented as numbers and percentages and continuous variables were represented as the means ± standard deviations and median (interquartile range). Pre- and posttreatment levels were compared with Paired *t*-tests and Wilcoxon tests. The correlation between RDW and MPV levels with lipid parameters was determined with Spearman correlation analysis. Linear regression analysis was used to determine the relationships of RDW change (ΔRDW) with changes in other lipid parameters. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

The baseline clinical characteristics of all patients are presented in Table 1. The average age of these patients was 60.5 ± 9 years and consisted of 38% were women. The median duration of statin treatment was 36 days. All patients received statin therapy. In addition, 87.6% of patients received atorvastatin and 12.4% of patients received rosuvastatin therapy. Specifically, 41.3% of patients ($n = 50$) were hypertensive and 26.4% of patients ($n = 32$) had diabetes mellitus. The median LVEF of the patients was 60%.

As presented in Table 2, statin therapy significantly reduced TC (P = 0001), LDL-C (P = 0.0001) and TG (P = 0.0001) levels. Moreover, statin therapy significantly lowered RDW (P = 0.0001), whereas no significant changes were observed for MPV (P = 0.32) and other hematological parameters. We found no correlation between RDW and serum cholesterol levels before (TC: r = 0.15, P = 0.87, LDL-C: r = 0.57, P = 0.53, HDL-C: r = 0.75, P = 0.41, TG: r = −0.10, P = 0.29) and after statin treatment (TC: r = 0.04, P = 0.67, LDL-C: r = 0.01, P = 0.88, HDL-C: r = 0.17, P = 0.07, TG: r = −0.09, P = 0.33) [Table 3]. Furthermore, there was no significant correlation between ΔRDW and the change in each serum lipid parameter in linear regression analysis (ΔTC: r = 0.05, P = 0.55, ΔLDL-C: r = 0.03, P = 0.72, ΔHDL-C: r = 0.03, P = 0.70, ΔTG: r = 0.06, P = 0.49) [Figure 1].

Table 1: Baseline clinical characteristics

	All patients (n=121)
Age* (year)	60.5±9
BMI* (kg/m^2)	27.3±1.8
Women†	46 (38)
Duration of statin treatment (days)**	36 (32-52)
Hypertension†	50 (41.3)
Diabetes mellitus†	32 (26.4)
Medications	
Acetylsalicylic acid†	121 (100)
ACEI†	31 (25.6)
ARB†	19 (15.7)
Beta blocker†	45 (37.2)
Atorvastatin†	106 (87.6)
Rosuvastatin†	15 (12.4)
Incidence of coronary atherosclerosis	
1-vessel disease†	66 (54.5)
2-vessel disease†	44 (36.4)
3-vessel disease†	11 (9.1)
LVEF** (%)	60 (55-60)

*Mean±SD, †n (%), **Median (IQR). SD: Standard deviation, IQR: Interquartile range, ACEI: Angiotensin converting enzyme inhibitör, ARB: Angiotensin receptor blocker, LVEF: Left ventricular ejection fraction, BMI: Body mass index

Table 2: Effects of statin treatment on laboratory data in all patients

	Baseline (n=121)	After treatment (n=121)	P
Serum glucose** (mg/dL)	103 (92-124)	105 (94-124)	0.12
BUN* (mg/dL)	37.1±10.8	36.1±11.1	0.22
Serum creatinine* (mg/dL)	0.89±0.18	0.92±0.19	0.08
TC* (mg/dL)	221±36	154±34	0.0001
HDL-C* (mg/dL)	46.5±14.4	44±11.5	0.027
LDL-C** (mg/dL)	141 (121-162)	78 (66-95)	0.0001
TG** (mg/dL)	141 (103-190)	116 (81-165)	0.0001
Red blood cell* (×10^3/mL)	5±0.4	5±0.3	0.92
White blood cell* (×10^3/mL)	7.7±1.8	7.8±2	0.21
Platelet** (×10^3/mL)	255 (227-305)	250 (215-307)	0.14
Hemoglobin** (g/L)	14.8 (13.7-15.7)	14.3 (13.3-15.3)	0.07
RDW** (%)	14 (13.6-14.5)	13.6 (13.2-14)	0.0001
MPV** (fL)	8.6 (8.3-9.2)	8.8 (8.3-9.2)	0.32

*Mean±SD, **Median (IQR). BUN: Blood urea nitrogen, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, RDW: Red cell distribution width, MPV: Mean platelet volume, TC: Total cholesterol, TG: Triglyceride, SD: Standard deviation, IQR: Interquartile range

Discussion

Our study demonstrates that statin treatment significantly reduces serum lipid profile and RDW. Statin treatment had no effect on MPV levels. RDW levels are not correlated with serum lipid profiles at baseline and after treatment. Importantly, the magnitude of RDW decline is not associated with the change in serum lipid profiles.

The pleiotropic effects, including the anti-inflammatory effects of statin treatment, were demonstrated in many large randomized controlled trials. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin was a primary prophylaxis trial between rosuvastatin and placebo. Rosuvastatin decreased LDL-C levels by 50%, high-sensitivity C-reactive protein (hs-CRP) levels by 37%, and the primary endpoint of acute myocardial infarction, ischemic stroke, arterial revascularization, hospitalization for unstable angina or mortality from cardiovascular causes by 44%.[13] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering was a secondary prophylaxis trial between atorvastatin 80 mg and placebo.[14] Atorvastatin 80 mg/d reduced ischemic outcomes and significantly decreased hs-CRP levels by 83%.[15] However, as there is a strong relationship between elevated serum lipid levels and CVD, it is particularly difficult to distinguish the LDL-C-lowering effect of statin treatment from their pleiotropic effects.[16] As RDW serves as a useful parameter of chronic inflammation and oxidative stress, the effect of statin treatment on RDW levels might potentially explain the role of anti-inflammatory effects of statins in CAD population. In this study, we have noticed a significant reduction in RDW levels after statin treatment in stable CAD patients. This result of the present study is in accordance with a previous study that demonstrated a statistically significant association between decreasing RDW and statin use in a population with decompensated heart failure.[17] In contrast to our findings, a few reports had showed no effect on RDW levels after atorvastatin treatment.[18,19] This difference might be explained by the percentage of CAD patients in these studies. Kucera *et al*.[18] recruited only %15 CAD patients, and Akın *et al*.[19] conducted a primary prophylaxis trial. Since atherosclerosis is a low-grade inflammatory process[12] and RDW is a well-documented marker of chronic inflammation, the magnitude of the decline in RDW levels in our study might have reached statistical significance. A further work with atorvastatin 10 mg/d in patients with hyperlipidemia and chronic cerebrovascular disease revealed a significant decrease in erythrocyte deformability in the treatment group, which also supports our findings.[20]

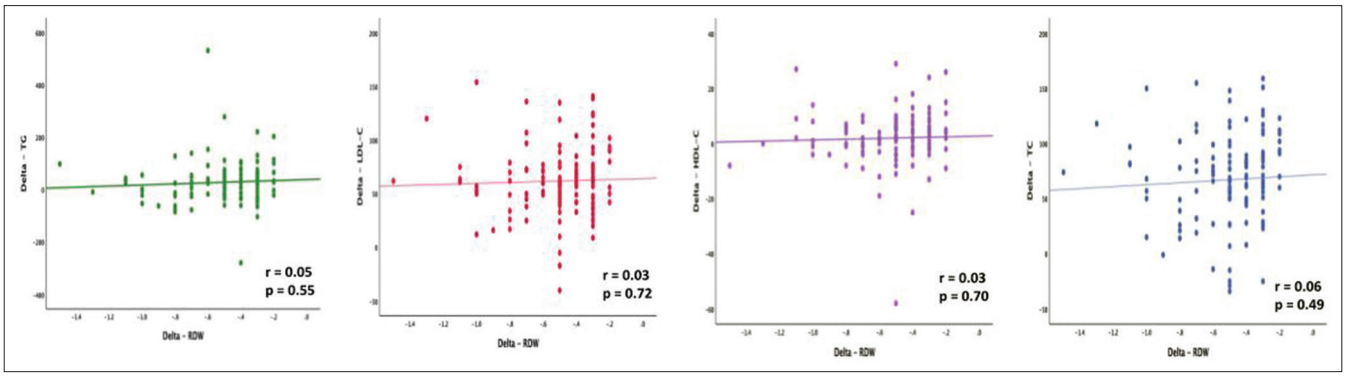

Figure 1: Correlations between Delta – RDW with Delta – total cholesterol, Delta – LDL-C, Delta HDL-C and Delta – triglyceride levels

Table 3: Correlation between plasma lipids and hematological parameters at baseline and after treatment

	Baseline				After treatment			
	RDW		MPV		RDW		MPV	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
TC	0.15	0.87	−0.04	0.65	0.04	0.67	−0.12	0.19
LDL-C	0.57	0.53	−0.16	0.86	0.01	0.88	−0.07	0.46
HDL-C	0.75	0.41	0.03	0.72	0.17	0.07	−0.09	0.33
TG	−0.10	0.29	−0.09	0.34	−0.09	0.33	0.02	0.84

TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride

MPV reflects the size of the thrombocytes and is an easily measured marker of thrombocyte activity. Shattil *et al*.[21] showed that in *ex vivo* enrichment of thrombocytes with cholesterol resulted in increased platelet activity. Up to date, numerous studies have described the potential effects of statin treatment on MPV levels; however, the results of these studies are controversial. Of these 10 studies, eight studies linked statin treatment to lower MPV, while two studies found no link.[22] It is demonstrated that the type of anticoagulant used for the analysis of the components of blood, including thrombocytes, might affect the platelet count and MPV. McShine *et al*.[23] showed that there was a substantial increase of MPV in the EDTA samples compared with citrated samples. In addition, it is demonstrated that MPV can be analyzed correctly by both EDTA and citrate if analysis be conducted within 1 h of sampling.[24] In the present study, we used EDTA samples for blood count analysis. Although most studies that have shown the decrease in MPV levels after statin treatment do not clearly specify the time period of blood sample collection and examination, the hemogram analysis of the blood samples used in our research was conducted more than an hour after the blood sampling, which may have resulted in higher MPV values.

In this study, both MPV and RDW levels were analyzed in relation to the serum lipid profile at baseline and after statin treatment. The primary finding is neither MPV nor RDW correlated with plasma lipids. This finding is in contrast to that reported by Kucera *et al*.[18] who showed a significant relationship between the hematological parameters and plasma cholesterol levels, including HDL-C, TG, and small dense LDL-C. In their cohort, isolated hypercholesterolemia was found 52.5% of patients and combined hyperlipidemia in 47.5% of the patients. In addition, 15% of patients had CAD, and there were no diabetic patients. The imbalance between studied groups in baseline variables might influence the RDW and MPV levels which may explain discordant results.

To our knowledge, this is the first preliminary study suggesting that the decline in RDW levels after statin treatment is not associated with the change in serum lipid profiles. Further research is required to define the underlying pathophysiology and the association between RDW and statin treatment.

Study limitations

Our study has a few limitations. First, this is a retrospective study that reflects a single-center experience with a relatively small number of patients and a short median duration of statin treatment. Thus, large-scale and long follow-up studies are required to make further conclusions on the effect of statin treatment on RDW levels. Second, the time delay between blood sampling and data analysis for MPV might have affected our results. Furthermore, a major limitation of this study is that we did not have data on other inflammatory markers, such as hs-CRP, which might further support the anti-inflammatory effects of statin treatment. Finally, the statin dose was not determined in this study population.

Conclusions

Besides lipid-lowering effects, statin treatment significantly reduces RDW levels independent of serum cholesterol levels. The perception of the pleiotropic effects of statin treatment has provided a probability to examine and target other signaling pathways that may alter cardiovascular outcomes. Our study may serve as additional demonstrable evidence for the anti-inflammatory effects of statins. Further studies are required to clarify whether this decline is associated with better cardiovascular outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Declaration of patient consent

Written informed consent about the coronary angiography was obtained from all patients enrolled in this study.

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