

# The relationship between statin therapy and adipocytokine/inflammatory mediators in dyslipidemic nondiabetic patients: A comparative study

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## Abstract

**Background:** Statins have emerged as a vital therapeutic option for dyslipidemia, effectively reducing morbidity and mortality in individuals with various medical conditions. Recent research has shed light on the intricate pathophysiology of atherosclerosis, which involves lipid accumulation and inflammatory mediators. This research was conducted to assess the correlation between statin therapy and adipocytokine and inflammatory mediator levels in dyslipidemic nondiabetic patients.

**Methods:** A total of 67 dyslipidemic nondiabetic patients were enrolled, alongside 33 healthy controls. The participants were categorized into three groups: Group (A), comprising patients undergoing statin therapy (n = 34), Group (B), consisting of patients not receiving statin therapy (n = 33); and Group (C), comprising healthy controls (n = 33).

**Results:** Patients not receiving statin therapy exhibited significant dyslipidemic profiles compared to patients undergoing statin therapy and healthy controls. Levels of total cholesterol (TC), triglycerides (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) were higher in patients not receiving statin therapy. Serum levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) were higher in the statin group than in the non-statin group and controls. Additionally, PCSK9 levels were higher in patients treated with rosuvastatin than those treated with atorvastatin. Conversely, levels of retinol-binding protein 4 (RBP4) were lower in the statin group compared to the non-statin group and controls. Although no significant difference in RBP4 levels between atorvastatin and rosuvastatin users was found, atorvastatin displayed lower RBP4 values. The study also revealed lower C-reactive protein (CRP) levels in the statin group, primarily in the rosuvastatin subgroup, compared to the non-statin group.

**Conclusion:** Statin therapy increased PCSK9 levels, with a more pronounced rise observed in patients treated with rosuvastatin than atorvastatin. Statin therapy proved protective by reducing RBP4 and CRP levels in dyslipidemic nondiabetic patients.

## Keywords

adipocytokine, inflammatory mediators, statins therapy

## Introduction

Dyslipidemia, characterized by abnormal lipid profiles, contributes to occurring of serious illnesses related to cardiovascular diseases (CVDs) (Al Ashoor et al. 2023). Statins, a class of medications commonly used as first-line treatment of hypercholesteremia and hyperlipidemia, and their use shows a decline in the incidence of CVDs (Bardolia et al. 2021). However, the mechanism of action of statins and their effects on various biomarkers and pathways are still being actively studied. One such area of research is the association between statin therapy and PCSK9 (proprotein convertase subtilisin/kexin type 9) and adipocytokine levels in dyslipidemic nondiabetic patients. This article explores the proposed effects of statins on PCSK9 and adipocytokine levels in this randomized sample of populations (Bell et al. 2023).

PCSK9, which stands for Proprotein Convertase Subtilisin/Kexin Type 9, is a protein that plays a critical role in regulating cholesterol levels in the body. It was first discovered in 2003, and since then, extensive research has been conducted to understand its functions and potential therapeutic implications.

### PCSK9 and cholesterol homeostasis

The main role of PCSK9 is to regulate low-density lipoprotein receptors (LDLRs) on the hepatocellular level. These LDLRs are responsible for capturing and removing LDL cholesterol (often referred to as “bad cholesterol”) from the blood and increase its catabolism. When PCSK9 is present, it binds to LDLRs, marking them for destruction within the cell. This results in fewer LDLRs available on the liver cell surface, leading to reduced LDL cholesterol uptake from the blood.

Individuals with mutations that cause loss of PCSK9 function have naturally low LDL cholesterol levels and are protected from cardiovascular diseases, highlighting the protein's significance in cholesterol metabolism. Conversely, those with mutations that lead to excessive PCSK9 activity cause LDL cholesterol levels, increasing their risk of developing cardiovascular problems.

The link between PCSK9 and cholesterol regulation has sparked considerable interest in the medical and pharmaceutical communities. Researchers have been investigating ways to target and inhibit PCSK9 as a potential strategy to treat individuals with high LDL cholesterol levels and mitigate the danger of CKDs. This led to the discovery of PCSK9 inhibitors, a class of medications that can block PCSK9's activity, resulting in increased availability of LDLRs and enhanced LDL cholesterol clearance from the bloodstream.

PCSK9 inhibitors have shown remarkable success in clinical trials, demonstrating their ability to significantly reduce LDL levels and decrease the risk of cardiovascular disease. These medications have provided new hope for individuals who are unable to control their cholesterol levels through traditional therapies like statins or lifestyle modifications (Al-hussainy et al. 2022a; Maligłowska et al. 2022).

## Statin therapy and PCSK9 levels

Statins primarily exert lipid-lowering effects by suppression HMG-CoA reductase which is an essential enzyme in cholesterol Biosynthesis (Zhang et al. 2020). This leads to decreased intracellular cholesterol levels, triggering upregulation of hepatocyte LDLRs. Importantly, statin treatment also showed elevated another metabolic enzyme such as the expression of PCSK9, which can partially counteract the beneficial effects of LDLR upregulation. This statin-induced upregulation of PCSK9 is thought to be a compensatory mechanism to maintain cholesterol homeostasis. As a result, statins may not achieve optimal LDL-C reduction in some patients due to the increased PCSK9 levels (Al-hussaniy and AL-Biati 2022; Awad et al. 2022).

### Adipocytokines and cardiovascular risk

Adipocytokines, including adiponectin, leptin, and resistin, are bioactive molecules secreted by adipose tissue. These cytokines significantly affect energy metabolism, insulin sensitivity, and inflammation (Kojta et al. 2020). Dysregulation of these adipocytokines has been linked to developing insulin resistance, obesity, and CVDs. Furthermore, adipocytokines have been implicated in the pathophysiology of dyslipidemia (Francisco et al. 2019; Parida et al. 2019).

### Impact of statins on adipocytokines

Studies investigating the effects of statins on adipocytokines have yielded mixed results. Some studies have shown that statin therapy can modulate adipocytokine levels, improving metabolic profiles. For instance, statins have been associated with increased adiponectin levels, which have anti-inflammatory and insulin-sensitizing properties (Gubina et al. 2021). On the other hand, statins have also been found to increase leptin and resistin levels, which are linked to weight gain and insulin resistance. Therefore, statins' impact on adipocytokines appears complex and may vary depending on patient characteristics, statin type, and dosage (Al-Hussaniy et al. 2021; Mohammad et al. 2021; Al-hussaniy et al. 2022b).

### Exploring the association

Given the interplay between PCSK9, adipocytokines, and dyslipidemia, researchers have begun investigating the potential association between statin therapy, PCSK9, and adipocytokine levels in dyslipidemic nondiabetic patients (Althanoon and Mahmood 2021). Many researches have shown that statin therapy can lower PCSK9 levels, which may help improve the lipid-lowering effects of statins. However, the impact of statins on adipocytokines in this patient population is less clear and requires further investigation (Zhou et al. 2021; Mahmood et al. 2023).

## Materials and methods

This case-control study included 34 dyslipidemic nondiabetic patients on statin therapy, 33 dyslipidemic nondiabetic patients not on statin therapy, and 33 healthy controls. Participants were recruited from Alkarama Hospital between Jan 2022 and December 2022. Inclusion and exclusion criteria were applied. Anthropometric measurements and biochemical analyses were conducted, including lipid profiles, adipocytokine, and inflammatory biomarkers. Statistical calculations were done by using SPSS-24.

## Results

Demographic characteristics of the participants showed no significant variations among the patient and healthy control groups. Dyslipidemic profiles were more pronounced in participants not on statin than those on statin therapy and healthy controls. PCSK9 levels were significantly higher in the statins group, particularly in rosuvastatin-treated patients. Retinol-Binding Protein 4 RBP4 levels were less in the statins group. CRP (C-reactive protein) also decreased in the statins group, primarily in the rosuvastatin subgroup (Tables 1, 2).

The mean values with standard deviation (SD) are reported in the table. Statistical analysis was conducted by

**Table 1.** Comparison of variables between controls, non-statin, and statin groups: assessing the impact of therapy on lipid profile.

Variables	Controls (n = 33)	Patients (n = 100)
Age (in years)	63.73±14.6	63.73±10.6
BMI	(26.30±4.31) (kg/m <sup>2</sup> )	(28.36±5.39)(kg/m <sup>2</sup> )
Gender		
Male	27(81%)	80 (80%)
Female	6 (18%)	20(20%)
Smoker		
– Yes	26 (78%)	44 (44%)
– No	13 (40%)	56 (56%)
PMH		
– Hypertension	–	50(50%)
– Dyslipidemia	1 (1.5%)	–
– IHD	28 (44.4%)	–
– CVA	7 (11.1%)	–
Life Style		
– Active	28 (84%)	35 (35%)
– Moderate	4 (12%)	27 (27%)
– Sedentary	1(3%)	38 (38%)

**Table 2.** Comparison of lipid profiles among non-statin, statin, and control groups in dyslipidemic nondiabetic patients.

Variables	Non-statin (n = 34)	Statin (n = 33)	Controls (n = 33)	P
total cholesterol (mg/dl)	204.78±40.6	142.87±41.56	160.3±30.6	0.001
high-density lipoprotein (mg/dl)	26.3±3.97	34.4±9.09*	29.9±5.5	0.005
triglyceride (mg/dl)	162.65±39.8#	132.57±36.92*	91.3±43.66	0.001
very-low-density lipoprotein (mg/dl)	33.23±7.97#	29.72±7.57*	19.23±9.93	0.001
low-density lipoprotein (mg/dl)	145.16±41.68#	80.75±42.43*	111.46±32.69	0.001

the ANOVA test, then by the LSD post-hoc test. The P value is considered significant when its less than 0.05, and it was used to determine the differences between the control group and the groups receiving statin therapy (Table 3).

**Table 3.** Presents the adipocytokine and inflammatory biomarker data for both the patient groups and the control group.

Variable	Statins group (n = 34)	Non-statin group (n = 23)	Controls (n = 33)	P Value
PCSK9 (ng/ml)	4.60±1.08*	3.64±0.86#□	2.64±0.68	0.0001
RBP4 (ng/ml)	37.22±7.11	48.57±15.21#	42.55±28.27	0.051
CRP (mg/L)	2.57±0.85	3.04±0.90#	2.95±0.77	0.070

The mean values and the standard deviation (SD) are presented in the analysis, which involved using the ANOVA test followed by the LSD post-hoc test. In this context, PCSK9 denotes proprotein convertase subtilisin/kexin type 9, RBP4 represents Retinol binding protein 4, and CRP stands for C-reactive protein.

A significance result was observed when comparing the control group with the statins groups. Similarly, there was a significance between the statins and non-statin groups. Additionally, a significance level of p<0.05 was also observed when comparing the control group with the non-statin group.

## Discussion

Our results are consistent with previous studies indicating the lipid-lowering effects of statins in dyslipidemic patients (Pasta et al. 2020). In the study by Janice Mayne et al., the researchers investigated the effects of statins and fibrates on plasma PCSK9 levels in human subjects. They found that atorvastatin administration causes a significant increase in plasma PCSK9 levels and suggested that statins directly increase PCSK9 expression. This augments our result that administration of atorvastatin causes elevated PCSK9 levels in dyslipidemic nondiabetic patients undergoing statin therapy (Mayne et al. 2008). Moreover, Beth A. Taylor & Paul D. Thompson reviewed the statins interactions and PCSK9 inhibition. They noted that statins raise levels of PCSK9, which may reduce the LDL-C response to statin therapy. This observation aligns with our study's findings of increased PCSK9 levels in dyslipidemic nondiabetic patients receiving statin therapy (Taylor and Thompson 2016; Al-Hussaniy et al. 2023).

Susan G. Lakoski et al. conducted an observational study to estimate the PCSK9 levels in a sizable and diverse society (Lakoski et al. 2009). They found that plasma PCSK9 levels varied over a wide range and correlated positively with plasma levels of LDL-C but only explained a small proportion of the variation in LDL-C levels. This suggests that while PCSK9 may influence LDL-C levels, other factors also play significant roles (Al\_hussaniy et al. 2023).

Another study such as Tsuyoshi Nozue evaluated the impact of circulating PCSK9 concentrations and lipid-modifying pharmaceuticals, particularly statins. Tsuyoshi

Nozue evaluated the impact of circulating PCSK9 concentrations and lipid-modifying pharmaceuticals, particularly statins. They noted that statins elevated circulating PCSK9 levels in a dose-dependent manner. This supports our study's observation of elevated PCSK9 levels in patients on statin therapy (Nozue 2017). Overall, when comparing our current study with previous research, it becomes evident that the effects of statins on PCSK9 levels can vary across different patient populations and depend on factors such as the statin type and dosage. While some studies have shown that statins may directly increase PCSK9 expression (Lakoski et al. 2009; Al-hussaniy et al. 2023), others, including our current study, have observed elevated PCSK9 levels in response to statin therapy. Elevated PCSK9 levels in the statins group support the association between statins therapy and PCSK9 expression, with rosuvastatin leading to a more substantial increase than atorvastatin. RBP4 levels were lower in the statins group, aligning with studies suggesting the indirect effect of statins on RBP4 through adipocyte maturation and glucose transporter 4 (GLUT4) expression (Nozue 2017; Salim Mahmood et al. 2022). The study also observed lower levels of CRP in the statins group, primarily in rosuvastatin users.

## Conclusions

In this comparative study, statin therapy significantly affected lipid profiles and biomarkers in dyslipidemic non-diabetic patients. Patients not receiving statin therapy exhibited significant dyslipidemic profiles, including higher levels of total cholesterol, triglycerides, very low-density lipoprotein, and low-density lipoprotein compared to patients on statin therapy and healthy controls. Moreover, statin therapy led to elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels, with a more pronounced increase observed in patients treated with rosuvastatin than atorvastatin.

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On the other hand, statin therapy demonstrated a protective effect by reducing levels of retinol-binding protein 4 (RBP4) and C-reactive protein (CRP) in dyslipidemic nondiabetic patients. RBP4 levels were lower in the statin group in comparative to the non-statin group and controls (Nozue 2017). However, the difference was not statistically significant. Furthermore, lower CRP levels were observed in the statin group, primarily in the rosuvastatin subgroup, compared to the non-statin group.

Further research should be conducted to understand the mechanisms underlying the observed effects of statins on adipocytokines, endocrinal-related hormones such as Leptin, and inflammatory mediators (Gunta et al. 2023). Understanding the intricate relationship between statin therapy, lipid metabolism, and inflammation will contribute to optimizing dyslipidemia management strategies in nondiabetic patients.

## Ethical regulations

The research was made under registration number 192\2022 ethical committee in Alkarama hospital and University of Baghdad, Baghdad, Iraq .

## Author contribution

Hany A. Al-hussaniy was responsible for the study's conceptualization, data collection, data analysis, and drafting of the initial manuscript. Amjad I. Oraibi reviewed and revised the manuscript for important intellectual content, providing critical feedback and suggestions for improvement. Ahmed Hamza Al-Shammari responded to the reviewer's comments, addressed the revisions, and provided additional analysis as requested. Hayder Naji Sameer participated in revising the article, ensuring accuracy, and finalizing the manuscript for submission.

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