

Original Research Article

Influence of short-term therapy with statins on some inflammatory biomarkers and oxidative stress in hyperlipidemic patients

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Abstract

Purpose: To determine the effect of statins on some inflammatory and oxidative stress biomarkers in hyperlipidemic patients.

Methods: The study was a 3-month randomized clinical trial conducted on 80 participants (52 males and 28 females), comprising 60 hyperlipidemic patients and 20 healthy individuals (controls), at the Cardiac Care Unit of Al-Salam Teaching Hospital. The hyperlipidemic patients were assigned to three groups, each with 20 participants. Group I was made up of hyperlipidemic patients given 20 mg rosuvastatin, while group II patients were hyperlipidaemic patients who were treated with 20 mg atorvastatin. The hyperlipidemic patients in group III received 20 mg simvastatin. Each treatment was given once daily at night for a duration of 4 weeks. The fourth group (group IV) was composed of 20 apparently healthy volunteers who never had any antihyperlipidemic medications, regardless of lipid profiles. Serum levels of malondialdehyde (MDA), total antioxidant capacity (TAC), interleukin-6 (IL-6), C-reactive protein (CRP), total cholesterol (TC), and total triglycerides (TG) were measured in the four groups at the end of 4 weeks of treatment.

Results: Serum levels of MDA, TAC, IL-6, CRP, TC, and TG were significantly higher than the reference ranges in the hyperlipidemic patients, relative to the apparently healthy controls ($p < 0.05$). However, treatment with rosuvastatin, atorvastatin, and simvastatin significantly reduced the serum levels of MDA, IL-6, CRP, TC, and TG, when compared to pre-treatment values ($p < 0.05$), but TAC level was not markedly changed. No gender differences in response to statin therapy were observed in this study.

Conclusion: Rosuvastatin, atorvastatin, and simvastatin may have beneficial effects in mitigating the damage caused by increased oxidative stress and excessive inflammation in hyperlipidemic patients.

Keywords: Statins, Inflammatory biomarkers, Hyperlipidemia, Oxidative stress, C-Reactive Protein

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INTRODUCTION

Statins (e.g. rosuvastatin, atorvastatin, and simvastatin) which were isolated for the first time from fungi [1], are the mainstay and most frequently used cholesterol-lowering therapy for dyslipidemia worldwide. Statins function by

inhibiting the activity of hydroxymethyl glutaryl-CoA reductase (HMGCR), which in turn inhibits the biosynthesis of cholesterol [2]. The inhibition of HMGCR results in overexpression of low-density lipoprotein (LDL) receptor and reduction in hepatic cholesterol production, ultimately leading to an increase in the clearance of plasma

LDL-cholesterol. Additionally, the inhibition of HMG-CoA reductase by statins may block the synthesis of a number of vital isoprenoid metabolites of L-mevalonic acid, such as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) [2,3]. These intermediary lipid metabolites serve as crucial lipid attachments for the post-translational modification of intracellular proteins such as nuclear lamins, Ras, Rho, Rac, and Rap [4]. Therefore, in addition to lowering cholesterol, it is possible that some of the biological effects of statins are caused by the inhibition of these subcellular isoprenoid-modulated transduction proteins.

Statins have varying levels of inhibitory potencies or extra-hepatic HMG-CoA reductase, due to differences in lipophilicity, half-life, and potency. Variations in the rate of metabolism and tissue distribution may cause some statins (e.g., rosuvastatin, atorvastatin, and simvastatin) to exert higher pleiotropic effects, which may also account for some of the reported differences in their peripheral side effects [5].

It has been proposed that the primary factors that delay the progression of thrombus formation are statin-induced decreases in levels of reactive oxygen species (ROS) and pro-inflammatory cytokines such as interleukins and tumor necrosis factor-alpha (TNF- α) [6].

The ancillary pleiotropic effect of statins accounts for their multiple therapeutic benefits, particularly for patients with cardiovascular ailments. These therapeutic benefits comprise enhancement of endothelial function, reduction of inflammation and oxidative stress, enhancement of stability of atherosclerotic plaque, regulation of vascular tone, and inhibition of platelet aggregation and thrombogenic response [7].

Lipophilic statins such as atorvastatin and simvastatin are believed to have greater capacities to passively enter vascular cells than hydrophilic statins such as pravastatin and rosuvastatin, which primarily target the liver. However, the fact that hydrophilic statins exhibit pleiotropic effects that are comparable to those of lipophilic statins raises doubts about whether statins actually produce cholesterol-independent effects. In fact, a well-designed study has revealed that hepatic HMG-CoA reductase inhibition may be the mechanism underlying some of the cholesterol-independent actions of these drugs, which in turn may lower levels of isoprenoids and related intermediates in the circulatory system [8]. This theory may help explain why hydrophilic statins such as

rosuvastatin and pravastatin still exert beneficial effects on the vascular wall without directly entering the cells that comprise the wall. In this context, and in view of the fact that statins exert multiple effects, such as anti-inflammatory, antioxidant, plaque-stabilizing properties, and improved endothelial function, the term *pleiotropic* might not adequately describe how these drugs affect the liver, relative to non-liver tissues. The target of this study was to compare the effects of lipophilic statins, namely simvastatin and atorvastatin, with those of the hydrophilic statin, i.e., rosuvastatin, on several biomarkers of inflammation, oxidative stress, and lipid-lowering potential in hyperlipidemic patients.

METHODS

The study was primarily focused on evaluating the potential protective effects of statins against inflammation and oxidative stress-induced damage. Since the damage is directly connected to oxidative stress, the study was specifically planned to accomplish analysis of the effects of statins on biochemical parameters of oxidative stress and inflammation in hyperlipidemic patients.

Drugs

The inhibitors of HMG-CoA reductase used in this study (simvastatin, atorvastatin, and rosuvastatin) were acquired from Bristol Myers-Squibb (Munich, Germany), Parke Davis (Karlsruhe, Germany), and HEXAL AG (Holzkirchen, Germany), respectively.

Ethical approval

Ethical approval for this study was obtained from the Nineveh Health Directorate on September 9, 2024 (ethical approval number = 58928). The study was conducted at the Cardiac Care Unit of Al-Salam Teaching Hospital, Mosul City (<https://maps.app.goo.gl/znMKs6oA59D1h7d86>) using the International Council for Harmonization-Good Clinical Practice (ICH-GCP) guidelines.

Sixty patients diagnosed with hyperlipidemia, in addition to twenty apparently healthy individuals (weighing between 60 - 85 kg) participated in the study.

Inclusion and exclusion criteria

The patients included in the study were those who had mild hyperlipidemia without any other diseases and who were eligible for treatment with statins, based on laboratory findings. Patients

with hyperlipidemia coexisting with other cardiovascular diseases or lipid profile-altering diseases such as thyroid diseases, and those taking medications that cause hyperlipidemia, such as β -adrenoceptors blockers or thiazide diuretics, were excluded from the study. This study was carried out from September 2024 to December 2024, i.e., for 3 months.

The hyperlipidemic patients were randomly allocated to three groups, each with twenty patients ($n = 20$). Group I patients were placed on 20 mg rosuvastatin once daily at night for 4 weeks. Patients in group II received 20 mg atorvastatin once daily at night for 4 weeks, while group III patients were administered 20 mg simvastatin once daily at night for 4 weeks. Group IV comprised 20 apparently healthy volunteers who had never taken any lipid-lowering medications. A specialist physician took the full history of all participants (medical history, statin therapy history, and personal history). In addition, the physician carried out general physical examination on the participants. The data obtained were reported in a structured case form.

Measurement of biochemical parameters

The biochemical indices were measured by expert laboratory staff in the Al-Salam Teaching Hospital laboratory. Fasting venous blood sample (5 mL) was taken from each participant under sterile conditions. Serum was obtained after centrifuging the blood for 15 min at 3,000 rpm. The serum samples were preserved at -80°C prior to analysis. A portion of each serum sample was screened for total cholesterol (TC) and triglycerides (TG), while another portion was tested for levels of interleukin-6 (IL-6) and C-reactive protein (CRP). The lipid profile parameters were estimated using Roche Diagnostics' COBAS Integra 400 plus automated analyzer and colorimetric enzymatic assay [9,10]. In addition, CRP level was measured using particle-enhanced immunonephelometry [11] and an image analyzer (Dade Behring, IL, USA). Serum level of IL-6 was determined using commercially available kits and enzyme-linked immunosorbent assay (ELISA) (eBioscience, CA, USA) kits, in line with the guidelines provided by the kit suppliers [12]. Serum level of MDA was determined using commercially available ELISA kits (Cell Biolabs, San Diego, CA, USA) [13], in line with the manufacturer's instructions. Total antioxidant capacity (TAC), which reflects the overall antioxidant status inside the body, was measured with Elabscience Company kit [14] according to the instructions specified in the kit. All the aforementioned parameters (MDA, TAC,

IL-6, CRP, TC, and TG) were estimated in the 4 groups of participants at the onset of the study (baseline) before administration of medications, and after 4 weeks of treatment (post-treatment).

Statistical analysis

The data obtained from assays of the biochemical parameters are expressed as mean $\pm$ standard error of the mean (SEM). The GraphPad Prism 7.0 software was used to perform a two-way analysis of variance (ANOVA), followed by Dunnett's or Bonferroni multiple comparison test, as appropriate. Differences were assumed statistically significant at $p < 0.05$.

RESULTS

Table 1 shows the comprehensive characteristics of participants in the 4 groups studied. There were no statistically significant differences in age, weight and body mass index (BMI) between the hyperlipidemic patients and the healthy volunteers ($p > 0.05$). In addition, graphical presentation of the results (Figure 1) shows no differences in the concentrations of inflammatory parameters and blood lipids among patients with hyperlipidemia, prior to treatment with statins ($p > 0.05$). However, apart from TAC, the levels of all parameters were significantly reduced following 4 weeks of treatment with rosuvastatin ($p < 0.0001$), atorvastatin ($p < 0.01 - p < 0.0001$), and simvastatin ($p < 0.01 - p < 0.0001$). The responses to rosuvastatin, atorvastatin and simvastatin were comparable. However, rosuvastatin induced a significantly greater IL6-lowering effect than atorvastatin and simvastatin ($p < 0.0001$ for rosuvastatin, versus $p < 0.01$ for atorvastatin and simvastatin).

Effects of statins on inflammatory parameters, total cholesterol and triglycerides in male patients ($n = 52$)

The blood concentrations of the tested inflammatory parameters and MDA showed similar patterns in both male and female subgroups before commencement of the statin therapy. These data are presented in Figures 2 and 3. However, in male patients, rosuvastatin significantly ($p < 0.05 - p < 0.0001$) reduced the levels all inflammatory parameters. In contrast, TAC level strangely showed a slight elevation following rosuvastatin therapy. Treatment with atorvastatin and simvastatin resulted in marked reductions in the levels of CRP and MDA ($p < 0.001$) but not in IL-6 levels. Expectedly, the levels of TC and triglycerides were decreased

following treatment with rosuvastatin, atorvastatin or simvastatin ($p < 0.01$ - $p < 0.001$; Figure 2).

Effects of statins on inflammatory parameters, total cholesterol and triglycerides in female patients (n = 28)

In female patients, rosuvastatin significantly reduced the levels of all inflammatory parameters apart from TAC ($p < 0.05$ - $p < 0.001$). Simvastatin significantly decreased the serum concentrations of CRP, MDA, and IL-6 ($p < 0.05$ - $p < 0.001$), while atorvastatin induced significant reductions in levels of CRP and MDA, but not in levels of IL-6. Total cholesterol level was significantly decreased ($p < 0.05$ - $p < 0.001$) following treatment with rosuvastatin, atorvastatin or simvastatin. However, neither atorvastatin nor simvastatin led to significant reductions in the levels of triglycerides. These results are shown in Figure 3.

Effects of statins on inflammatory parameters, total cholesterol and triglycerides

The levels of MDA, TAC, IL6, CRP, TC and TG in the hyperlipidemic male and female patients differed significantly from the corresponding levels in the apparently healthy controls ($p < 0.05$). However, no significant differences were observed in the baseline values of inflammatory parameters between male and female hyperlipidemic patients, as shown in AI, BI, CI, DI, EI and FI (Figure 4 and Figure 5). Rosuvastatin, atorvastatin and simvastatin markedly reduced the levels of IL-6 and TC in both male and female patients ($p < 0.05$), when compared to the corresponding controls (CII, EII). However, the three statins did not elicit any significant reductions in levels of MDA, TAC, CRP, and TG after treatment, as shown in AII, BII, DII, and FII (Figures 4 and 5).

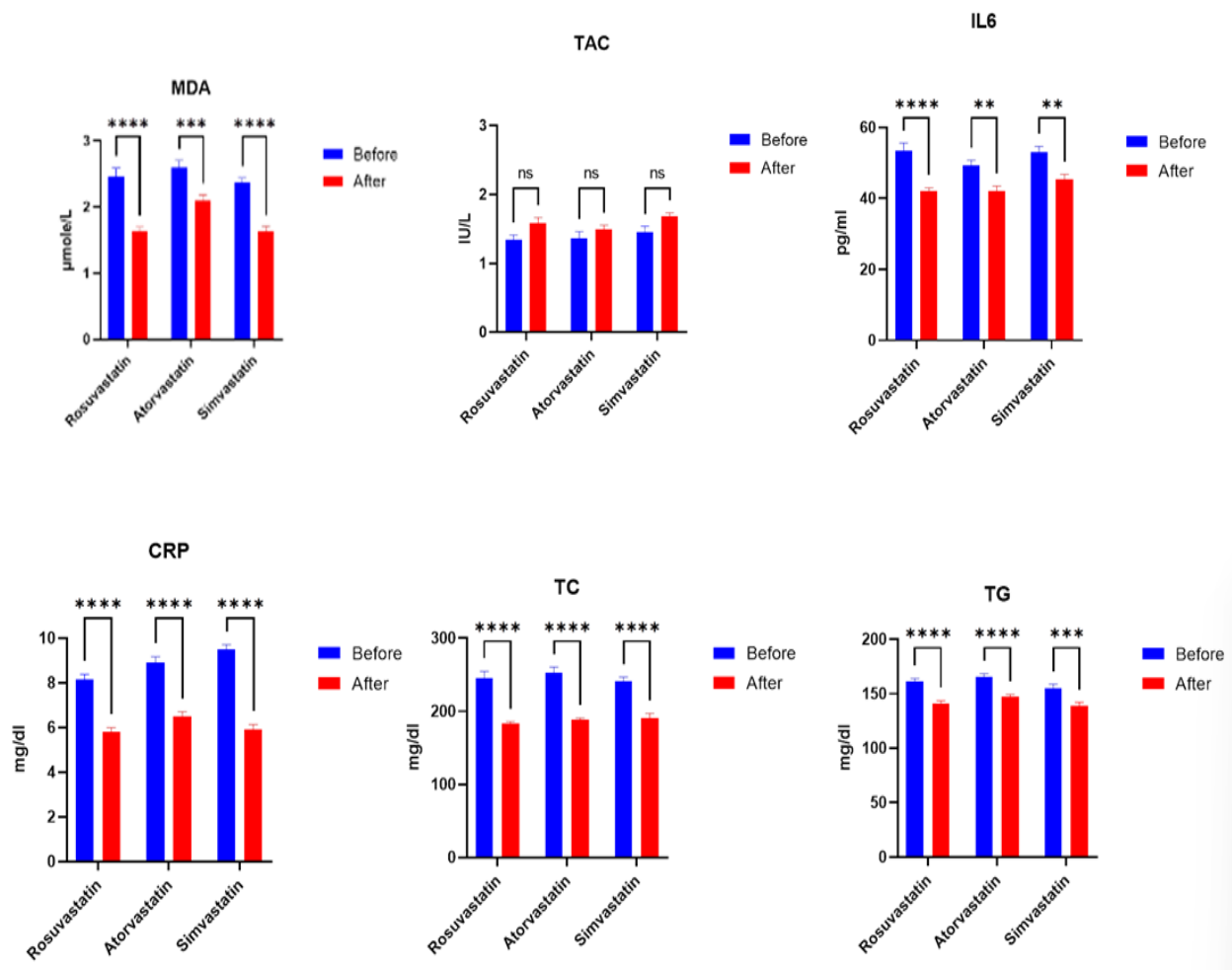


Figure 1: Representative graphs showing the effects of statins on inflammatory parameters, total cholesterol, and triglycerides in the hyperlipidemic patients. Data were pooled from 60 participants (n=60) and presented as mean $\pm$ S.E.M. Statistical significance was determined using two-way ANOVA. ns: non-significant; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, with Sidak post hoc correction)

Table 1: Demographic characteristics of the participants

Parameter	Rosuvastatin		Atorvastatin		Simvastatin		Controls		All	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No. of Participants	13	7	14	6	12	8	13	7	52	28
Age range (years)	35-58	41-60	38-57	45-60	39-58	45-60	43-56	39-60	35-58	38-60
Average age (years)	48.2±5.5	50.1±6.2	49.3±5.7	50.5±5.8	47.5±6.3	51.3±6.1	49.5±5.4	51.1±4.9	48.6±5.85	50.7±5.6
Weight (kg)	86±8.2	78±7.5	83±6.9	87±8.1	84±7.65	89±7.9	86±8.3	82±6.9	84.8±7.3	84±7.7
BMI (kg/m ²)	29.6±3.5	31.5±4.1	28±3.7	28.7±3.8	29.1±4.2	29±4	28.4±3.6	28.7±3.85	28.8±4.25	29.5±3.79

Values are Mean ± SEM

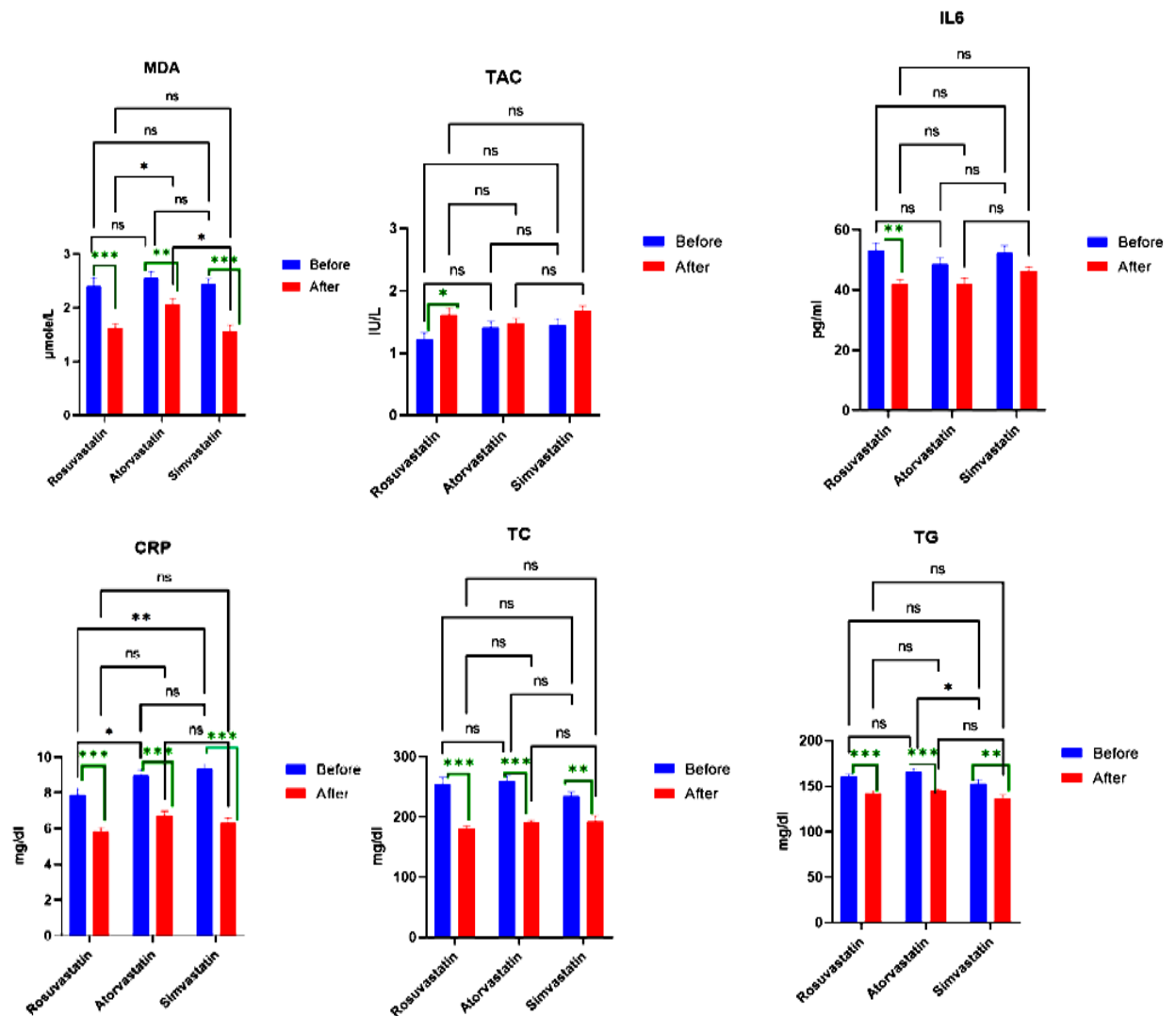


Figure 2: Representative graphs showing the effects of 4 weeks of treatment with statins on inflammatory parameters, total cholesterol, and triglycerides in male hyperlipidemic patients. Data were pooled from 52 participants (n=52) and presented as mean $\pm$ S.E.M. Statistical significance was determined using two-way ANOVA. ns: non-significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, with Sidak post hoc correction)

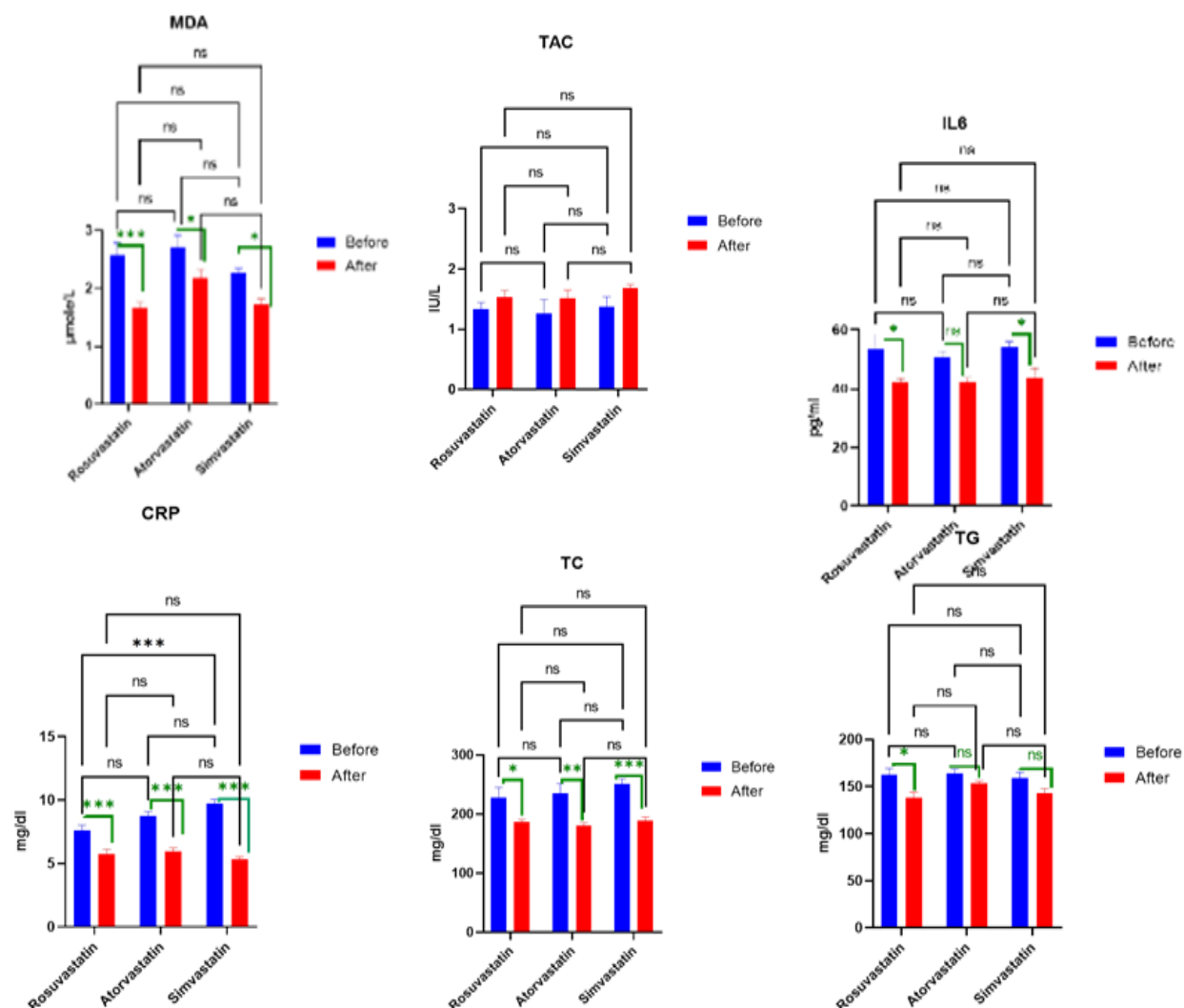


Figure 3: Representative graphs showing the effects of 4 weeks of treatment with statins on inflammatory parameters, total cholesterol, and triglycerides in female hyperlipidemic patients. Data were pooled from 28 participants ($n=28$) and presented as mean $\pm$ S.E.M. Statistical significance was determined using two-way ANOVA. ns: non-significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, with Sidak post hoc correction)

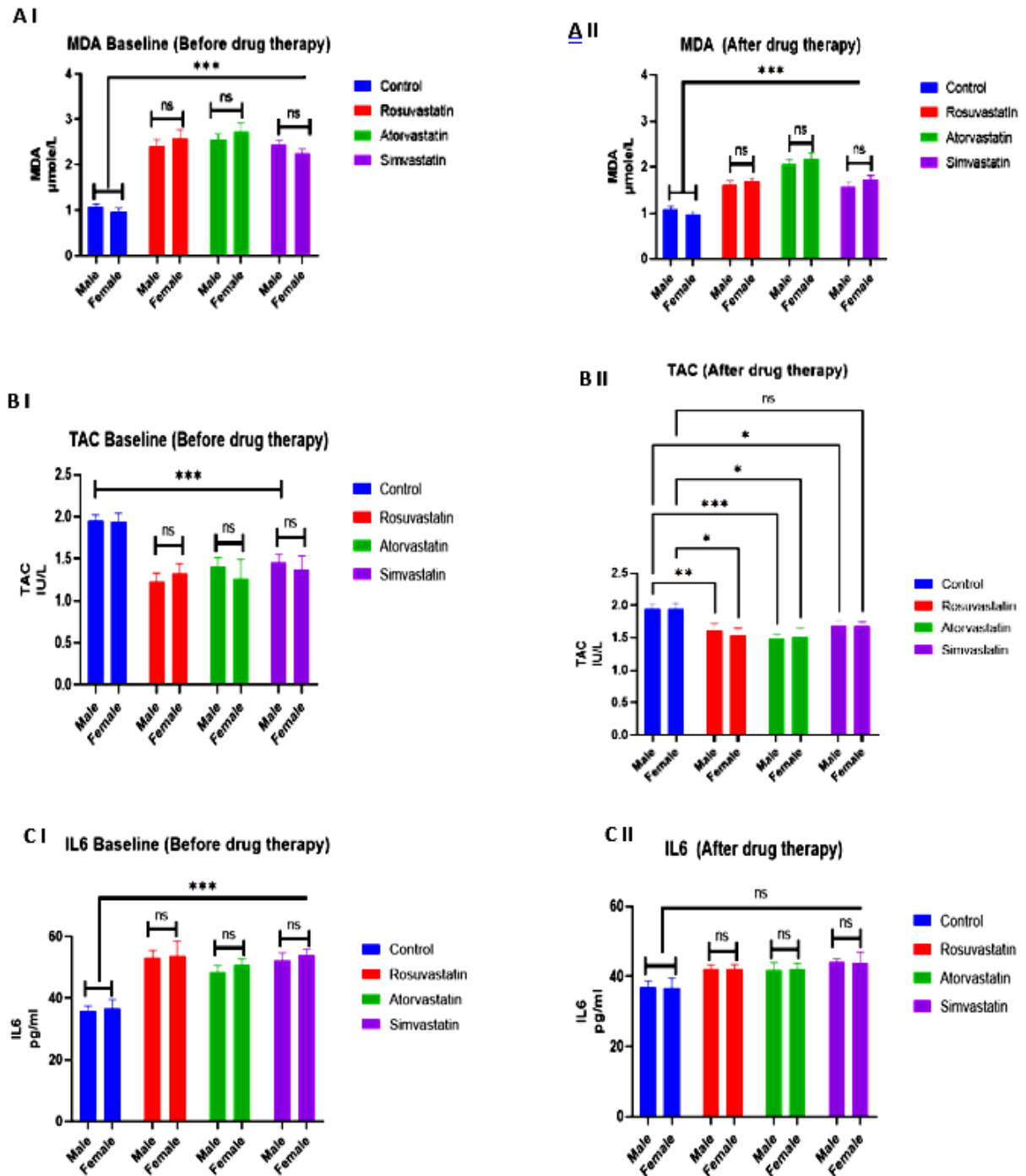


Figure 4: Comparison of male and female responses to rosuvastatin, atorvastatin, and simvastatin in terms of lipid-lowering and anti-inflammatory effects. Data were presented as mean $\pm$ S.E.M. Statistical significance was determined using two-way ANOVA. ns: non-significant. * $P < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, with Sidak post hoc correction)

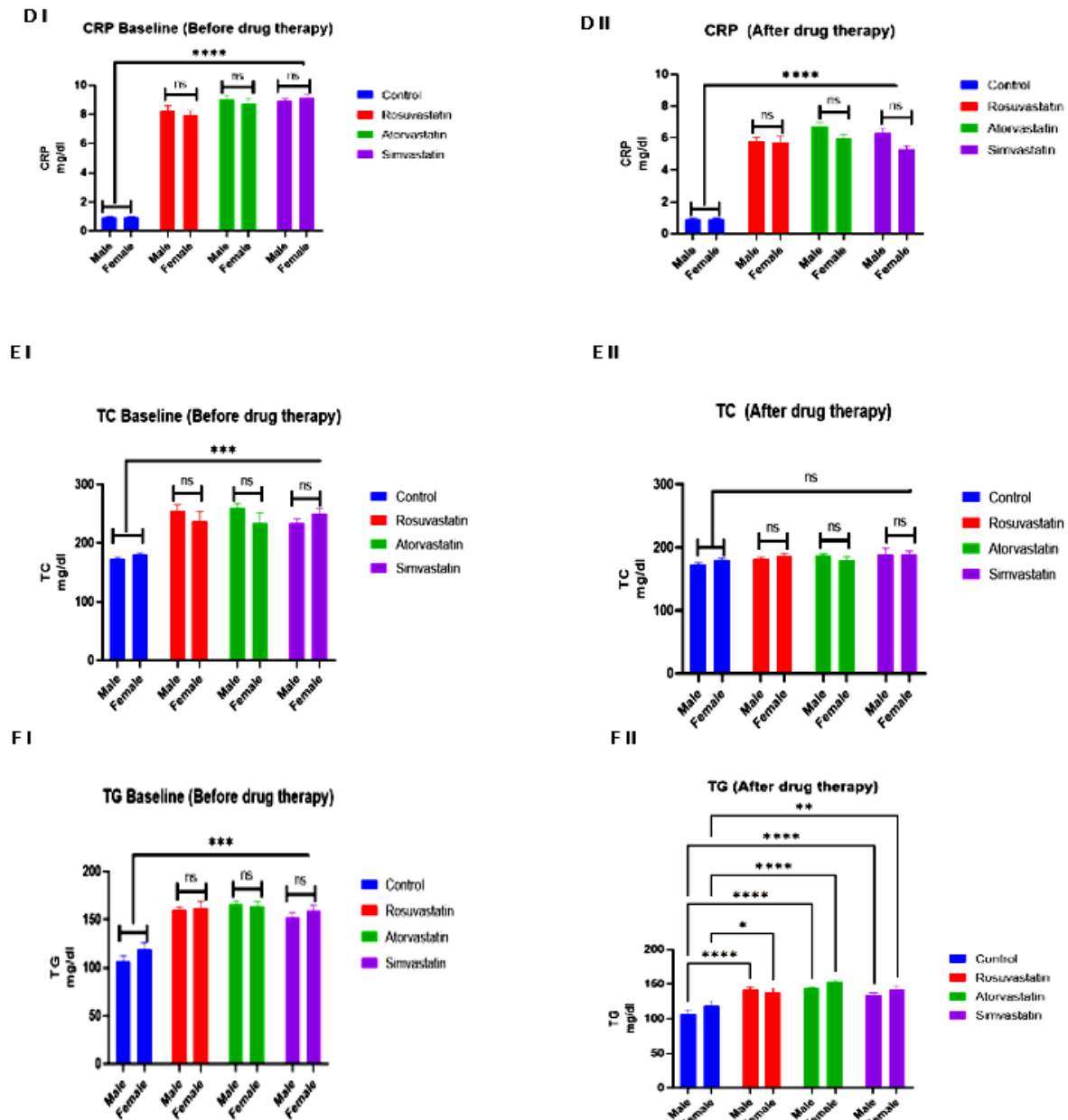


Figure 5: Comparison of male and female responses to rosuvastatin, atorvastatin, and simvastatin in terms of lipid-lowering and anti-inflammatory effects (*continued*). Data were presented as mean $\pm$ SEM. Statistical significance was determined using two-way ANOVA. ns: non-significant. * $P < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, with Sidak post hoc correction)

DISCUSSION

The primary risk factor for coronary heart disease is the formation of atherosclerotic clots due to ongoing increases in levels of blood lipids (most notably cholesterol), which elicit an inflammatory reaction in the affected blood vessels [15]. Studies have shown that lowering the blood levels of lipoprotein-C and other atherogenic lipoproteins may mitigate and indeed reverse the progression of atherosclerotic cardiovascular diseases [16,17]. Several inflammatory biomarkers of vascular and non-vascular origins

have been reported to modulate various aspects of atherosclerotic inflammation. Examples of these pro-inflammatory mediators are serum amyloid A, C-reactive protein (CRP), fibrinogen, interleukins-1 (IL-1), IL-6, and IL-10, intercellular adhesion molecule-1 (ICAM-1), and pentraxin3 (PTX3) [18]. In the previous decades, statins, as lipid-lowering medications, were often employed in clinical practice as effective therapies for hyperlipidemia, and also for the prevention of cardiovascular ailments [19]. It has been shown that statins produce beneficial effects in patients with cardiovascular illness, and that these effects

may or may not be facilitated merely by the capacity of statins to lower lipid levels [20].

The molecular targets of reactive oxygen species (ROS) are proteins, lipids, and DNA. These targets were also used to highlight differences in oxidative stress in the peripheral blood. By measuring the level of malondialdehyde (MDA), this study concentrated on lipids, which are the primary target of statins. It was observed that some statins such as rosuvastatin, atorvastatin, and simvastatin significantly reduced serum levels of some oxidative stress biomarkers and inflammatory mediators (CRP, MDA, and IL-6) in the hyperlipidemic patients, in addition to their effects on TC and TG. However, the statins had no effect on total antioxidant capacity (TAC). In this study, the slight gender differences in responses to the statins tested may be attributed to the limitation arising from the small number of patients used, particularly female patients. However, the general pattern of responses in males and females was consistent with the overall responses demonstrated.

When compared to the pre-treatment values, the levels of oxidative stress parameters and inflammatory biomarkers were significantly reduced after four weeks of treatment with rosuvastatin, atorvastatin, or simvastatin. However, none of these statins restored the levels of these parameters to those of healthy controls. Thus, it is important to look into how long-term statin treatment affects oxidative stress metrics and inflammatory biomarkers.

The traditional CRP, with a reference range of 10–1000 mg/L, is typically used to identify systemic inflammation or infection. The suppression of IL-6, and the reductions in levels of CRP and activity MDA by these statins will be beneficial for hyperlipidemic patients by arresting the development of atherosclerotic lesions.

This study has shown that treatment with hydrophilic statins, e.g., rosuvastatin, or lipophilic statins such as simvastatin or atorvastatin, elicits comparable anti-inflammatory action in patients, which is consistent with the results seen in previous studies [21,22]. The study has established that short-term statin therapy is definitely beneficial in reducing oxidative stress and inflammation in hyperlipidemic patients. Therefore, prophylactic statins may be beneficial in lowering oxidative damage, inflammation, and the resultant risk of cardiovascular events [23], particularly in high-risk patients with higher serum levels of MDA, TAC, IL-6, and CRP than the reference values.

Limitations of this study

In addition to the impact of statins on inflammatory markers, it may be necessary to measure the levels of these markers in people who are at risk for circulatory diseases [6]. Therefore, one limitation in the study is sample size. Thus, the results of many sub-group comparisons such as effects of statin types on marker levels, were not consistent. Additionally, only patients with mild hyperlipidemia were included in the study group: a comparison control group with an equal number of patients should have been created.

CONCLUSION

Simvastatin, atorvastatin, and rosuvastatin are approved drugs that lower cholesterol and slow down the progression of cardiovascular diseases. Additionally, they might be beneficial in mitigating the damage caused by elevated oxidative stress and excessive inflammatory disease. This advantage might be secondary to the pleiotropic effects of statins rather than just lowering cholesterol. For now, it is advised that statins should be prescribed for hyperlipidemic patients as well as those with cardiovascular diseases, even though the available data on their effect on the overall oxidative status in these patients is inconclusive. Future research on immunomodulating and anti-inflammatory properties of statins will also be beneficial.

DECLARATIONS

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Ethical approval

This study received ethical approval and permission from the Nineveh Health Directorate on September 9, 2024, with approval no. 58928, and it was conducted in Al-Salam Hospital, Mosul City.

Availability of data and materials

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

Conflict of interest

No conflict of interest is associated with this work.

Contributions 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. All authors made significant contributions to the work reported, whether in the area of conception, study design, execution, data acquisition, data analysis, or interpretation. In addition, all authors participated in drafting, revising and critically reviewing the manuscript. All authors gave approval for the final draft to be published, and also agreed to be accountable for all aspects of the work.

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