# Effect of Statins Therapy on Renal Function and CRP Levels in Chronic Kidney Disease Patients

**Dr. Afraa Zrieki***

**(Received 26 / 10 / 2024. Accepted 26 / 11 / 2024)**

## □ ABSTRACT □

Persistent, low-grade inflammation with increased inflammatory markers, like C-reactive protein (CRP), is now considered a hallmark feature of CKD, being involved in the development of cardiovascular and all-cause mortality of these patients. In this study, we aimed to investigate the possible anti-inflammatory effects of statins and their effect on kidney function in predialysis (stage 3-4) and hemodialysis CKD patients.

Seventy-four CKD patients seen at the department of kidney disease and hemodialysis of Tishreen Hospital in Lattakia, were assigned into two groups (a statin group (N=44), and a control group (N=30)). Patients in statin group received either 40 mg of atorvastatin or 10 mg of rosuvastatin daily for 6 months. Serum levels of C-reactive protein (CRP) and estimated glomerular filtration rate (eGFR) were measured in both groups at baseline and at the end of the follow period. The levels of lipid profile parameters were also measured.

In statin group, mean serum CRP levels decreased significantly in predialysis (from 5.3±1.9 to 4.7±1.6 mg/l, $P$ <0.001) and in hemodialysis patient (from 5.3±1.6 to 4.6±1.5 mg/l, $P$<0.001) after 6 months of treatment with statin. In control group, mean CRP values were not significantly changed at the end of 6 months follow up. Statin therapy prevented the regression of eGFR rate with non-significant change after 6 months follow up in both, predialysis and hemodialysis patient CKD, while in control group eGFR declined significantly, from 37.13±15.6 to 30.63±11.4 mL/min/1.73 $m^2$, $P$=0.046 in predialysed patients and from 6.4±2.6 to 5.2±1.6 mL/min/1.73 $m^2$, $P$=0.039 in hemodialysis patients, at the end of follow up period. The anti-inflammatory and renoprotective effects were independent of lipid-lowering effect observed with statin therapy. In conclusion, in addition to their beneficial effects on lipid levels, administration of statins could present an anti- inflammatory effect, with a consequential renoprotective effect in CKD patients.

**Keywords:** Chronic kidney disease, statin, inflammation, C-reactive protein, eGFR



* **Assistant Professor - Department of Pharmaceutics and Pharmacotechnology, Faculty of Pharmacy, Tishreen University, Lattakia, Syria.**

# تأثير المعالجة بالستاتينات على الوظيفة الكلوية وعلى مستويات البروتين التفاعلي (CRP) لدى مرضى القصور الكلوي المزمن

**د. عفراء زريقي***

**(تاريخ الإيداع 26 / 10 / 2024. قبل للنشر في 26 / 11 / 2024)**

## □ ملخّص □

يعد الالتهاب المزمن منخفض الدرجة، مع زيادة مستويات المشعرات الالتهابية، مثل البروتين التفاعلي C (C-reactive protein: CRP)، سمة مميزة للقصور الكلى المزمن، ويساهم في حدوث الوفيات لأسباب قلبية وعائية ولجميع الأسباب لدى هؤلاء المرضى. هدفت هذه الدراسة إلى تقييم التأثير المحتمل المضادة للالتهابات للستاتينات وتأثيرها على الوظيفة الكلوية لدى مرضى القصور الكلوي في المراحل 3–4 ما قبل التحال ومرض التحال الدموي.

شملت الدراسة 74 مريضاً من مرضى القصور الكلوي المزمن في قسم أمراض الكلى والتحال الدموي في مشفى تشرين الجامعي في اللاذقية، وتم توزيعهم في مجموعتين (مجموعة الستاتين، 44 مريض، ومجموعة الشواهد، 30 مريض).

تلقى المرضى في مجموعة الستاتين إما 40 ملغ من أتورفاستاتين أو 10 ملغ من روسوفاستاتين يوميًا لمدة 6 أشهر. تم قياس المستويات المصلية للبروتين التفاعلي C ومعدل الرشيح الكبيبي المقدر (estimated glomerular filtration rate: eGFR) في كلتا المجموعتين عند بداية الدراسة وفي نهاية فترة المتابعة لـ 6 أشهر، كما تم قياس مستويات معايير الصيغة الليبيدية.

في مجموعة الستاتين، انخفض متوسط مستويات البروتين التفاعلي C بشكل هام إحصائياً في مرضى المراحل ما قبل التحال (من 5.3±1.9 إلى 4.7±1.6 ملغ/مل، P< 0.001)، وفي مرضى التحال الدموي (من 5.3 ± 1.6 إلى 4.6 ± 1.5 ملغ/مل، P < 0.001) بعد 6 أشهر من المعالجة. في مجموعة الشواهد، لم تتغير قيم CRP بشكل هام إحصائياً في نهاية فترة المتابعة.

حافظت المعالجة بالستاتينات على معدل الرشح الكبيبي دون تراجع هام إحصائياً بعد 6 أشهر من المتابعة في كل من مرضى المراحل 3–4 ومرضى التحال الدموي، بينما انخفض معدل الرشح الكبيبي بشكل هام إحصائياً من (37.13±15.6 إلى 30.63±11.4 مل/دقيقة/1.73 م$^2$، $P$=0.046) في مرضى المراحل 3–4، ومن (6.4±2.6 إلى 5.2±1.6 مل/دقيقة/1.73 م$^2$، $P$=0.039) لدى مرضى التحال الدموي في مجموعة الشواهد. كانت التأثيرات المضادة للالتهابات والحافظة للوظيفة الكلوية مستقلة عن التأثير الخافض للشحوم للمعالجة بالستاتينات. في النتيجة، بالإضافة إلى تأثيرها الايجابي على مستويات الشحوم، يمكن للمعالجة بالستاتينات أن تعطي تأثيراً مضاد للالتهابات مترافق مع تأثير حافظ للوظيفة االكلوية لدى مرضى القصور الكلوي المزمن في المراحل ماقبل وخلال التحال الدموي.

**الكلمات المفتاحية:** مرض القصر الكلوي المزمن، الستاتينات، الالتهاب، البروتين التفاعلي C، معدل الرشح الكبيبي المقدر eGFR



* **مدرس – قسم الصيدلانيات والتكنولوجيا الصيدلية، كلية الصيدلة، جامعة تشرين، اللاذقية، سورية.**

**Introduction:**

Chronic kidney disease (CKD) is identified by the presence of abnormalities of the kidney structure or function that persist for more than 3 months [1]. CKD remains a major public health concern, affecting 10–15% of the population, and its prevalence is constantly growing [2]. It is characterized by a progressive and irreversible loss of kidney function [3], which leads to end-stage renal disease (ESRD), where there is a need for dialysis or renal transplantation to maintain life [4].

CKD patients have higher rates of mortality and morbidity compared to general population [5]. Cardiovascular disease (CVD) is considered the main cause of death in patients with CKD [6]. Although the high prevalence of dyslipidemia in CKD patients (45.5% in CKD stage 1 and increased to 67.8% in CKD stage 4) [7], dyslipidemia and other traditional risk factors such as diabetes mellitus (DM), and hypertension (HT), cannot explain this high rate of cardiovascular mortality in CKD patients.

Many trials have proposed that non-traditional risk factors, such as chronic inflammation, anemia, endothelial dysfunction, are more important for the development of atherosclerosis in these patients [8]. Among these, it seems that inflammatory processes play a crucial role in development and progression of CKD and its cardiovascular complications [9].

Persistent inflammation has been recognized as a common and important comorbid condition in patients with CKD, particularly in dialysis patients [10]. In addition, clinical researches have proved that elevated inflammatory markers, C-reactive protein (CRP), and interleukin-6 (IL-6), were associated with many complications of CKD, such as atherosclerosis, heart disease, and enhanced CKD mortality [11].

CRP is the most common marker to reflect the inflammatory state. It is mainly synthesized in the liver, stimulated by inflammatory cytokines such as (IL-6) [12]. With the advancement of technology, a high sensitivity (hs)-CRP assessment method was developed, enabling the measurement of CRP with high precision even at low concentration, or mild elevation such as that seen in chronic inflammation [12].

A significantly higher serum level of CRP was seen in patients with CKD, and it was correlated with serum creatinine level [13]. Moreover, CRP has been demonstrated to be an independent risk factor of cardiovascular events in CKD [14]. It is implicated in facilitating LDL deposition on the atrial wall and promotes atherosclerotic disease progression [15]. Therefore, CRP presents an important target in management of CKD and its complication.

The earlier strategies for CKD management concentrated on reducing cardiovascular risks by hypertension control and dyslipidemia correction. However, the assessment and treatment of all circumstances that provide a risk for cardiovascular disease are now essential for a comprehensive approach. Therefore, inhibiting inflammation in CKD would bring many benefits to these patients, and it is necessary to find an effective therapy for the management of inflammation in CKD.

Statins are a class of lipid-lowing drugs [16], that are the mainstay treatment for hyperlipidemia [17]. Studies have demonstrated that statins are effective in improving dyslipidemia in CKD [18], and thereby reduced cardiovascular mortality in CKD patients [19, 20]. However, it has been established that the benefits of statins in cardiovascular disease can be explained not only by their lipid-lowering potential but also by non-lipid-related mechanisms, the so-called “pleiotropic effects”. Some of these beneficial effects are related to the anti-inflammatory properties [21, 22]. Statins exert an anti-inflammatory effect that might be related to lower cholesterol because cholesterol strongly promotes

inflammation [23]. In addition, statins are associated with reduced activation of immune cells, such as T cells and monocyte [24]. In vivo studies, the results showed that statins improved lung injury due to their anti-inflammatory actions [25]. In CKD patients, although some studies have assessed the anti-inflammatory effects of statins [26, 27], there is lacking conclusive evidence that statins have anti-inflammatory effects in this group of patients. In this study, the possible CRP lowering effect of statins therapy in predialysis (stages 3-4) and hemodialysis CKD patients, and their effect on renal function, were investigated, to draw evidence whether statins could serve as potential drugs for attenuating inflammation in CKD patients.

# MATERIALS AND METHODS

## Study population and treatment protocols

This study is a 6 month follow-up study that conducted at the department of kidney disease and hemodialysis of Tishreen Hospital in Lattakia, Syria, between 2021 and 2023. All participants provided their signed consent after receiving full information about the study. Inclusion criteria were CKD patients (stage 3-4) with an estimated glomerular filtration rate (eGFR) in the range less than 60 to 15 ml/min/1.73 $m^2$, and patients on hemodialysis.

Exclusion criteria included patients under the age of 18, pregnant women, those who had a life-threatening illness such as cancer, autoimmune diseases, thyroid dysfunction, chronic liver disease and lung diseases, patients with only one kidney, recent surgery, myopathies, or signs of active inflammation (CRP≥ 10); smokers; and those taking corticosteroid, antioxidants, and any hypolipidemic drugs. Diabetic CKD patients were also excluded to avoid the potential effect of hypoglycemic medications on studied parameters.

Participant's data (age, sex), body mass index (BMI) ($kg/m^2$), and comorbidities were obtained. BMI was calculated using the equation: BMI= weight/ $(height)^2$. The eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [28]. In all, 87 patients were enrolled and divided into two main groups:

**Statins group** (47 patients): included patients who started statins treatment (rosuvastatin 10 mg or atorvastatin 40 mg at the time of inclusion in the study, as they were diagnosed with dyslipidemia, and maintained the same statin regimen during the entire follow-up period (6 months).

**Control group** (40 patients): included patients who did not take any lipid-lowering medication during the study period.

All patients were suffering from CKD associated with hypertension, and most of them were receiving anti-hypertensive agents including renin-angiotensin system blockers, calcium channel blockers (CCB), or beta-blockers (β-blockers). They were controlled hypertensives (BP ≤ 140/90 mmHg), and their dosages were not changed during statins therapy.

Of the 87 CKD patients, 13 passed away during the follow-up period, all of them were on hemodialysis. Among them, three patients received treatment with statins while ten patients in control group, (6.4 %, and 25 % respectively). In all, 74 patients with CKD (44 patients in statin group, and 30 patients in control group) were followed up and completed the study.

## Blood sampling and Laboratory data

From each participant, a peripheral venous blood samples were obtained twice, at the beginning of the study and again 6 months later. Blood samples were taken in the morning

after at least 10-hour fast in order to conduct biochemical test. Blood was drawn before sessions of hemodialysis for CKD patients on hemodialysis. Serum creatinine concentrations, total cholesterol (TC), HDL-C, LDL-C, and serum triglyceride (TG) levels were determined using commercially available kits and the automated biochemical analyzer (Mindray BS-380). The serum levels of CRP were measured with an immunoturbidimetry assay kit (Biosystem®).

**Statistical analysis**

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0 for Windows. All results were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Student's t-test was used to compare means, and Chi-square test for comparing percentage. Person correlation test was used to assess correlation between CRP and lipid parameters levels. Differences were considered significant at $P < 0.05$.

# RESULTS

**Demographic characteristics and biochemical results of study population**

Table (1) presents the demographic and biochemical characteristics of study population at the beginning of the study, in patients who completed the study.

The two groups, statin and control group, were comparable in term of age, sex, BMI, percentage of patient on hemodialysis. According to eGFR, the 44 patients in statin group distributed to 12 participants (27.3%) with stage 3 CKD; 14 (31.8 %) with stage 4 CKD, and 18 patients (40.1%) were on hemodialysis. In control group, there were 8 (26.6%), 9 (30%), and 13 (43.3%) participants in stage 3, 4 CKD and on hemodialysis respectively. No significant difference was observed in the distribution of patients according to CKD stages between the two groups ($P$=0.79).

Baseline levels of inflammatory marker (CRP) also showed no statistically significant difference between statin and control group, neither in predialysis CKD patients, (5.3±1.9 mg/l vs 5.5±1.8 mg/l, P=0.81, respectively), nor in patients on hemodialysis (5.5±1.6 vs 5.8±1.7, $P$=0.72, respectively).

The mean eGFR calculated by CKD-EPI formula was also comparable between the two groups in CKD patients with stage (3-4) (35.7±17.7 mL/min/1.73 $m^2$ in statin group vs 37.13±15.6 mL/min/1.73 $m^2$ in control group, $P$=0.71), and in patients on hemodialysis (6.3± 2.2 vs 6.4±2.6 mL/min/1.73 $m^2$, $P$= 0.92 respectively).

Comparing the baseline lipid profile parameters, the statin group had a significantly increased total as well as LDL cholesterol and triglycerides but similar HDL cholesterol levels compared to control group.

By monitoring blood pressure in all individuals during 6-monthes follow-up, we found that all patients had controlled hypertension in statins and control group, and the distribution of antihypertensive drugs was comparable between the two groups.

**Table 1: Baseline demographic and biochemical characteristics study population.**

| Characteristic | Statins group N=44 | Control group N=30 | *P* value |
|---|---|---|---|
| **Male, number (%)** | 24 (54.54) | 17 (56.66) | 0.88 |
| **Age (years)** | 58.12±13.14 | 49±15.17 | 0.51 |
| **BMI (kg/m$^2$ )** | 24.38±3.28 | 22.38±3.78 | 0.54 |
| **CKD stage at baseline (N, %)** | | | |
| **Stage 3** | 12 (27.3%) | 8 (26.6%) | 0.79 |
| **Stage 4** | 14 (31.8%) | 9 (30%) | |
| **Hemodialysis** | 18 (40.1%) | 13 (43.3%) | |
| **CRP (mg/l) (mean ±SD)** | | | |
| **All CKD patients** | 5.3± 1.7 | 5.6±1.6 | 0.71 |
| **Predialysis patients** | 5.3± 1.9 | 5.5±1.8 | 0.81 |
| **Dialysis patients** | 5.5±1.6 | 5.8±1.7 | 0.72 |
| **eGFR (mL/min/1.73 m$^2$) (mean ±SD)** | | | |
| **Predialysis patients** | 35.7±17.7 | 37.13±15.6 | 0.71 |
| **Dialysis patients** | 6.3± 2.2 | 6.4±2.6 | 0.92 |
| **Lipid parameters ( mg/dl)** | | | |
| **Total cholesterol** | 251.86±42.44 | 173.76±34.32 | **<0.001** |
| **LDL cholesterol** | 154.36±26.3 | 83.44±13.50 | **<0.001** |
| **HDL cholesterol** | 46.91±13.24 | 47.23±12.86 | 0.54 |
| **Triglycerides** | 173.35±47.50 | 135.02±61.45 | **<0.001** |
| **24-hour Ambulatory BP, mmHg for 6 months follow-up** | | | |
| **Systolic BP** | 132.82±8.05 | 131.71±12.59 | 0.92 |
| **Diastolic BP** | 83.51±5.26 | 79.27±9.05 | 0.81 |
| **Antihypertention medications (N)** | | | |
| **ARBs** | 10 | 8 | 0.83 |
| **ACEI** | 9 | 7 | |
| **CCBs** | 11 | 8 | |
| **β-blockers** | 10 | 7 | |

Data are presented as total (%), mean±SD. BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. ARBs: Angiotensin II receptor blockers, ACI: Angiotensin II converting enzyme inhibitors, CCBs: Calcium channel blockers,

**Effects of statins therapy on lipid parameters and renal function in CKD patients**

Table (2) shows the effect of statins treatments on lipid profile and eGFR among the study population after 6-month follow-up.

The comparison of mean serum lipid levels between the baseline and the 6 month endpoint showed the expected effects in CKD patients received statin therapy. A significant reduction was obtained in serum levels of total cholesterol, LDL cholesterol, triglycerides, with a significant increase in HDL levels. In contrast, no significant variations in lipid parameters levels were noticed in control patients.

In addition to lipid-profile improving effects of statins, renal protective effects appeared in statins group. Statins treatment maintained eGFR over 6 months of treatment, in predialysis patients and patients on hemodialysis, while a regression of renal function was

observed in control group, where eGFR decreased significantly in this group of patients at the end of follow up period in both predialysis CKD patients and patients on hemodialysis.

**Table 2: Lipid profile and eGFR changes over 6 months of treatment with statins in CKD patients**

| Parameter | | Statin group (Mean±SD) | | | | Control group (Mean±SD) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Baseline | After 6 months | *P* value | N | Baseline | After 6 months | *P* value |
| TC (mg/dl) | | 44 | 251.86±42.44 | 184.52±27.03 | **<0.001** | 30 | 173.76±34.32 | 176.65±32.12 | 0.79 |
| LDL-C (mg/dl) | | 44 | 154.36±26.3 | 100.2±21.00 | **<0.001** | 30 | 83.44±13.50 | 85.23±12.47 | 0.91 |
| HDL-C (mg/dl) | | 44 | 42.91±13.24 | 55.06±12.45 | **0.042** | 30 | 47.23±12.86 | 45.33±16.83 | 0.83 |
| Triglycerides (mg/dl) | | 44 | 173.35±47.50 | 145.18±60.65 | **0.024** | 30 | 135.02±61.45 | 130.02±67.23 | 0.68 |
| eGFR | Predialysis patients | 26 | 35.7±17.7 | 36.4±15.5 | 0.812 | 17 | 37.13±15.6 | 30.63±11.4 | **0.046** |
| | Dialysis patients | 18 | 6.3± 2.2 | 6.4±1.8 | 0.923 | 13 | 6.4±2.6 | 5.2 ±1.6 | **0.039** |

**Effects of statins therapy on CRP levels in CKD patients**

In parallel with the lipid-lowering effects and eGFR maintenance, statin therapy showed a significant reduction in CRP concentrations. Serum CRP levels decreased significantly from 5.3± 1.7 to 4.5± 1.7 in all statin treated patients. This effected was always maintained when patients were divided into the two subgroups, predialysis patients (from 5.3±1.9 to 4.5±1.5 mg/l, ($P$<0.001), and patients on hemodialysis (from 5.3±1.6 to 4.6±1.5 ($P$<0.001). However, CRP levels remained stable in the control two subgroups, predialysis and dialysis patients during the 6 months follow up period (Table 3).

**Table3. Effect of statins on CRP levels in CKD patients**

| Parameter | | statins group | | | *P* value | control group | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Baseline | After 6 months | | N | Baseline | After 6 months | |
| CRP (mg/l) (mean ±SD) | All CKD patients | 44 | 5.3± 1.7 | 4.5± 1.7 | **<0.001** | 30 | 5.1±1.9 | 5.2± 1.2 | 0.791 |
| | Predialysis patients | 26 | 5.3± 1.9 | 4.7±1.6 | **<0.001** | 17 | 5.7±1.8 | 5.4± 1.5 | 0.891 |
| | Dialysis patients | 18 | 5.3±1.6 | 4.6±1.5 | **<0.001** | 13 | 5.8±1.7 | 5.9±1.4 | 0.874 |

**Correlation between CRP and lipid parameters levels in statin treated CKD patients**

To clarify whether the reducing of CRP level achieved by statin therapy is related or no to their lipid lowering effect, we assessed the correlation between CRP level and lipid parameters levels in statin group. No correlation was found between the relative decrease in CRP levels and the relative decrease in LDL cholesterol levels after 6 months of treatment with statin, neither in predialysis patients ($R^2$= 0.020, $P$ = 0.492), nor in patients on hemodialysis ($R^2$= 0.086, P = 0.238), (Figure 1). Similarly, no correlation was found between other changes in the lipid profile and CRP levels (data not presented).

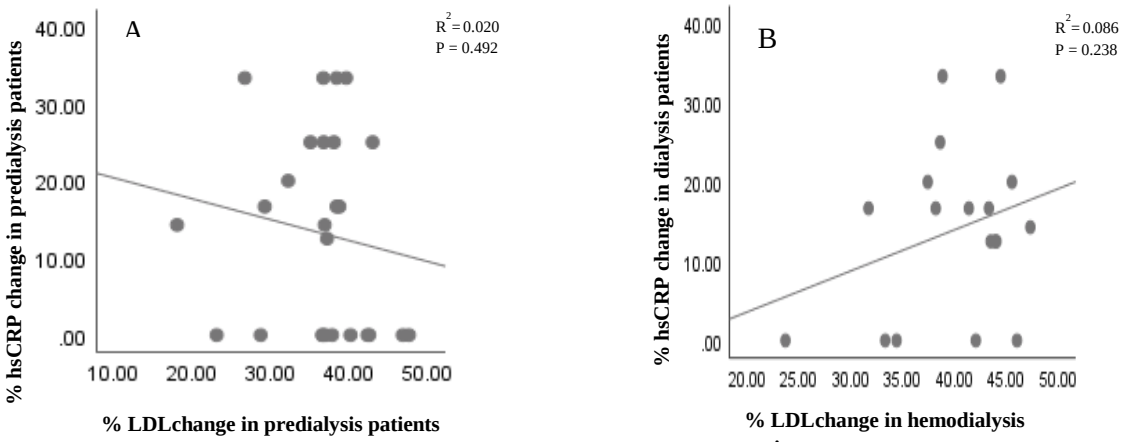


**Fig 1: Correlation between relative change in CRP and LDL cholesterol levels in predialysis CKD patients (A), N=26, and dialysis CKD patients (B), N=18, in statin group.**

## Discussion:

The present study aimed to assess the anti-inflammatory effects of statins, presented by their effect on CRP level, in CKD patients with moderate to advanced stage including patients on hemodialysis. To the best of our knowledge, this study is the first one to explore this topic in Syrian predialysis and hemodialysis CKD patients.

Our study showed that, in addition to lipid profile improvement, statins treatment achieved a significant decrease in CPR levels. This effect was associated with renal function protection presented by the prevention of eGFR regression. This finding provides clear evidence that statins therapy may have an important clinical significance in the management of CKD by inhibiting inflammation.

Many factors contribute to the chronic inflammatory state in CKD, including the increased production of pro-inflammatory cytokines, oxidative stress and acidosis, chronic and recurrent infection [29, 30]. Our finding demonstrated that statins therapy inhibited inflammatory state evidenced by reducing CRP levels which might be one of the mechanisms that contribute to their beneficial effects in CKD. This effect was always maintained when performing Subgroup analysis, in both predialysis and dialysis CKD patients. Consistent with our results, in previous studies, that focused on CKD stages 3 and 4, statins therapy also proved the lipid-lowering and anti-inflammatory effect [31-33]. Panichi et al. found that simvastatin therapy with a daily dose of 40 mg in stages 3 and 4 CKD caused a significant decrease of serum inflammatory markers CRP after 6 months of follow-up [34]. Similarly, in the study of Goicoechea et al., 6 months of atorvastatin administration at the dose of 20 mg/day, less than in our study, led to a significant decrease of CRP, and TNF-α level [31]. In contrast, some studies have failed to demonstrate a decrease in CRP levels in CKD patients using statins. Zagajewska et al. showed only a tendency of serum inflammatory markers such as CRP and IL-6 to decrease after statin therapy, but this effect was not significant in comparison with changes of these parameters after placebo therapy [35]. Furthermore, in hemodialysis CKD patients, controversial results were also observed. In line with our results, the results of Hussein et al. study revealed that atorvastatin therapy in hemodialysis CKD patients caused a statistically significant decrease in levels of CRP after 6 months of therapy [36]. Similarly, The results published by Vernaglione et al., despite the lower dose used, compared to our study, where

10 mg of atorvastatin was administered to hemodialysis patients for 6 months, showed a significant decrease in levels of CRP [37]. Our results also agree to those by Tian et al., where two groups of hemodialysis patients received either 20 mg of atorvastatin or 10 mg of rosuvastatin daily for 12 weeks. Both drugs significantly reduced the concentrations of CRP; however, this effect was more pronounced in the atorvastatin group [38]. In the study by Kirmizis et al., a daily dose of 10 mg of simvastatin for 6 months caused a significant decrease in levels of CRP along with a significant decrease in levels of IL-6 in hemodialysis patients [39]. A higher dose of simvastatin was evaluated in the studies by Chang et al. [40] and Shahbazian et al. [41]. In both trials, a daily dose of 20 mg of simvastatin was given to a group of hemodialysis patients, for a period of 8 weeks and 12 weeks, respectively. In accordance with our results, in both studies, levels of CRP showed a significant decrease at the end of the study period. These similarities in the effect on levels of CRP come despite the shorter duration of statin administration in both studies compared to our study (8 weeks and 12 weeks versus 24 weeks in our study). However, in disagreement with our results, Tsirpanlis et al. evaluated the effect of a statin on levels of inflammatory makers for shorter duration, where a daily dose of 40 mg of fluvastatin was administered for a period of 4 weeks only. Levels of IL-6 decreased significantly at the end of the study period, while CRP levels did not change [42]. Similarly, the results published by Dornbrook-Lavender et al., where 10 mg of atorvastatin was administered to hemodialysis patients for 5 months, showed an insignificant decrease in levels of CRP [43].

The studies cited above suggest that the anti-inflammatory effect exerted by statins can be affected by the duration of treatment but also by the dose or type of statin. In our study, we did not conduct additional subgroup analysis based on dose or types of statins due to the limited number of included patients. Therefore, more clinical studies are needed to explore the potential factors affecting the anti-inflammatory effect of statins.

Regarding the effect of statins used in our study (Atorvastatin and rosuvastatin) on different parameters of lipid profile, as expected our results revealed that the both drugs caused a statistically significant decrease in levels of total cholesterol, LDL cholesterol, and serum triglycerides with a significant increase in levels of HDL cholesterol. These results fully agree with the results reported by previous studies in ckd patients with or without hemodialysis [35, 36, 38, 42].

The notable point in our study is the lack of correlation between CRP levels and lipid parameters levels after 6 months of Statin therapy. This was in line with the results demonstrated by Hussein et al. [36], and Vernaglione et al. [37], where CRP levels did not correlate with levels of lipid parameters after 6 months of atorvastatin intake. In contrast, this finding was partially in disagreement with the results by Kirmizis et al. [39], which demonstrated a positive correlation between the decrease in levels of CRP and the relative decrease in levels of total as well as LDL cholesterol. However, in the same study, no similar correlation was found between changes in CRP and the levels of other lipid parameters.

The lack of correlation observed in our study suggest that the decrease in serum CRP levels would be attributed to an effect of statin on CRP, independent from the reduction in serum lipid parameters levels, pointing to a different mechanism of action of statins on inflammatory markers.

The mechanisms by which statins could exert their inhibition of CRP might be explained by the following pathways. First, some evidence suggest that the pathogenesis of chronic

inflammation in CKD is associated with NF-κB activation [44]. Activation of NF-κB promotes the production of inflammatory cytokines in CKD like IL-6, where IL-6 gene transcription is NF-κB dependent [45] . IL-6, in its turn, stimulates the production of CRP [12]. Statins have been shown to inhibit the nuclear accumulation of NF-κB and further block the activation of its downstream targets, including inflammatory cytokines [44, 45].
Preventing or slowing the progression of CKD by lipid-lowering agents could indirectly lead to reduction in CVD in these patients. The hypolipidimic and anti-inflammatory effect observed in our study was associated with protective effect on renal function, shown by preserving eGFR in statin group compared with control group. We postulated that the protective effect of statin on renal function might be mediated by its anti-inflammatory properties. The effect of statins on the progression of CKD was discussed by previous studies. Two reports indicated that rosuvastatin treatment tended to preserve GFR in patients with CKD [46, 47]. In the study of Sawara et al., eGFR was significantly increased in CKD (2-4 stages) patients treated with rosuvastatin for 12 months, while no significant changes was observed in non-treated patients [32]. However, in the study of Kendrick et al. lovastatin did not have any renoprotective effects in CKD patients, except those with known CVD [48]. Furthermore, Anna Masajtis-Zagajewska et al. observed a significant deterioration in eGFR during administration of atorvastatin but also during administration of placebo in CKD stage 3-4 patients [35]. The effect may be however dependent on the dose of statin. One metaanalysis showed that high-dose statin therapy slightly slowed the decline in eGFR in patients with CKD compared with control, but moderate and low dose statins, did not [49]. Additionally, the lack of efficacy may be related to delay in initiating hypolipidimic therapy in patients who already have an atypically severe form of atherosclerosis, as this protective effect on renal function was not replicated in more advanced (stages 4-5) CKD patients [50].

**Study Limitations:**
Limitations of this study include the relatively small number of participants, and the short duration of follow up. However, many other related studies included the same number of patients or less, with a similar period of treatment [32-34]. A further limitation of this study is that we didn't conduct subgroup analysis depending on the type or dose of statin because of the small number of study population, and didn't investigate the safety of used statins concerning the liver and muscle functions. However, none of the patient in statin group suffered any clinical side effects that could be related to drug intake. Furthermore, the statins used in our study (atorvastatin, rosuvastatin) are considered generally safe in CKD since they have negligible renal elimination [51]. Finally, we were unable to determine the duration of kidney disease, however the cause of CKD in all patients was hypertension and the distribution of the used antihypertensive drugs was comparable between the two groups which gave some homogeneity of the study groups and could eliminate or at least minimize the interference of these co-medicaments on the results.

## Conclusion:

In conclusion, this study demonstrates that, in addition to their favorable effect on lipid profile parameters, statins therapy exert an anti-inflammatory effect in CKD patients with moderate to advanced stages including patients on hemodialysis. This anti-inflammatory effect is independent of lipid lowering effect and clinically important in slowing progression of CKD. This pose the question to knew whether statins can reduce

inflammation in CKD patients with normal serum lipid, and so whether stains could be prescribed for aiming to inhibit inflammation in CKD patients without dyslipidemia. The comprehension of the role of inflammation in the setting of CKD could permit the development of therapeutic strategies in order to treat and even prevent the underlying inflammation, thus improving CKD outcomes. This question is the topic of further investigation.

**Acknowledgement**
We would like to thanks, Dr. Hussein Said, professor at the department of internal medicine in the faculty of medicine at Tishreen University, for his exceptional support and assistance in monitoring and evaluating the patients throughout this study**.**

## References:

**1.** KETTELER, M., et al., *Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters.* Kidney Int, 2017. 92(1): p. 26-36.
**2.** LEVIN, A., et al., *Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy.* Lancet, 2017. 390(10105): p. 1888-1917.
**3.** GO, A.S., et al., Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med, 2004. 351(13): p. 1296-305.
**4.** MENON, V. and M.J. SARNAK, The epidemiology of chronic kidney disease stages 1 to 4 and cardiovascular disease: a high-risk combination. Am J Kidney Dis, 2005. 45(1): p. 223-32.
**5.** CORESH, J., et al., Prevalence of chronic kidney disease in the United States. JAMA, 2007. 298(17): p. 2038-47.
**6.** KEITH, D.S., et al., Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med, 2004. 164(6): p. 659-63.
**7.** KIM, K.M., et al., Impact of chronic kidney disease on mortality: A nationwide cohort study. Kidney Res Clin Pract, 2019. 38(3): p. 382-390.
**8.** STENVINKEL, P., et al., Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol, 2008. 3(2): p. 505-21.
**9.** DUNGEY, M., et al., Inflammatory factors and exercise in chronic kidney disease. Int J Endocrinol, 2013. 2013: p. 569831.
**10.** AKCHURIN, O.M. and F. KASKEL, Update on inflammation in chronic kidney disease. Blood Purif, 2015. 39(1-3): p. 84-92.
**11.** STENVINKEL, P., et al., Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int, 1999. 55(5): p. 1899-911.
**12.** SEO, Y.H. and H.Y. Shin, Relationship between hs-CRP and HbA1c in Diabetes Mellitus Patients: 2015-2017 Korean National Health and Nutrition Examination Survey. Chonnam Med J, 2021. 57(1): p. 62-67.
**13.** ABRAHAM, G., et al., C-Reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis Transpl, 2009. 20(5): p. 811-5.
**14.** BAZELEY, J., et al., C-reactive protein and prediction of 1-year mortality in prevalent hemodialysis patients. Clin J Am Soc Nephrol, 2011. 6(10): p. 2452-61.

**15.** ZWAKA, T.P., V. HOMBACH, and J. Torzewski, C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. Circulation, 2001. 103(9): p. 1194-7.

**16.** ISTVAN, E.S. and J. DEISENHOFER, Structural mechanism for statin inhibition of HMG-CoA reductase. Science, 2001. 292(5519): p. 1160-4.

**17.** KARR, S., Epidemiology and management of hyperlipidemia. Am J Manag Care, 2017. 23(9 Suppl): p. S139-S148.

**18.** SCARPIONI, R., et al., Treatment of dyslipidemia in chronic kidney disease: Effectiveness and safety of statins. World J Nephrol, 2012. 1(6): p. 184-94.

**19.** ESMEIJER, K., et al., Effect of different types of statins on kidney function decline and proteinuria: a network meta-analysis. Sci Rep, 2019. 9(1): p. 16632.

**20.** SUNG, F.C., et al., Statin Therapy for Hyperlipidemic Patients With Chronic Kidney Disease and End-Stage Renal Disease: A Retrospective Cohort Study Based on 925,418 Adults in Taiwan. Front Pharmacol, 2022. 13: p. 815882.

**21.** HALCOX, J.P. and J.E. DEANFIELD, Beyond the laboratory: clinical implications for statin pleiotropy. Circulation, 2004. 109(21 Suppl 1): p. II42-8.

**22.** WU, N.Q., et al., Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers. Lipids Health Dis, 2018. 17(1): p. 265.

**23.** KIM, S.W., et al., Statins and Inflammation: New Therapeutic Opportunities in Psychiatry. Front Psychiatry, 2019. 10: p. 103.

**24.** QUIST-PAULSEN, P., Statins and inflammation: an update. Curr Opin Cardiol, 2010. 25(4): p. 399-405.

**25.** SPARROW, C.P., et al., Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol, 2001. 21(1): p. 115-21.

**26.** ALMQUIST, T., et al., Lipid-lowering treatment and inflammatory mediators in diabetes and chronic kidney disease. Eur J Clin Invest, 2014. 44(3): p. 276-84.

**27.** DUMMER, C.D., et al., Acute effect of simvastatin on inflammation and oxidative stress in chronic kidney disease. J Nephrol, 2008. 21(6): p. 900-8.

**28.** LEVEY, A.S. and L.A. Stevens, Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis, 2010. 55(4): p. 622-7.

**29.** MIHAI, S., et al., Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. J Immunol Res, 2018. 2018: p. 2180373.

**30.** RAPA, S.F., et al., Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites. Int J Mol Sci, 2019. 21(1).

**31.** GOICOECHEA, M., et al., Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. J Am Soc Nephrol, 2006. 17(12 Suppl 3): p. S231-5.

**32.** SAWARA, Y., et al., Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease. Intern Med, 2008. 47(17): p. 1505-10.

**33.** VERMA, A., et al., Effect of rosuvastatin on C-reactive protein and renal function in patients with chronic kidney disease. Am J Cardiol, 2005. 96(9): p. 1290-2.

**34.** PANICHI, V., et al., In vivo and in vitro effects of simvastatin on inflammatory markers in pre-dialysis patients. Nephrol Dial Transplant, 2006. 21(2): p. 337-44.
**35.** MASAJTIS-ZAGAJEWSKA, A. and M. NOWICKI, Effect of atorvastatin on iron metabolism regulation in patients with chronic kidney disease - a randomized double blind crossover study. Ren Fail, 2018. 40(1): p. 700-709.
**36.** HUSSEIN . S. Effect of atorvastatin on inflammatory markers in hemodialysis patients. The Egyptian Journal of Internal Medicine 2020. 32. p. 6-13
**37.** VERNAGLIONE, L., et al., Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis? Am J Kidney Dis, 2004. 43(3): p. 471-8.
**38.** TIAN, J., et al., Efficacy comparison of atorvastatin versus rosuvastatin on blood lipid and microinflammatory state in maintenance hemodialysis patients. Ren Fail, 2017. 39(1): p. 153-158.
**39.** KIRMIZIS, D., et al., Effects of simvastatin on markers of inflammation, oxidative stress and endothelial cell apoptosis in patients on chronic hemodialysis. J Atheroscler Thromb, 2010. 17(12): p. 1256-65.
**40.** CHANG, J.W., et al., Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. Am J Kidney Dis, 2002. 39(6): p. 1213-7.
**41.** SHAHBAZIAN, H., et al., Anti-inflammatory effect of simvastatin in hemodialysis patients. Jundishapur J Nat Pharm Prod, 2015. 10(1): p. e17962.
**42.** TSIRPANLIS, G., et al., Treatment with fluvastatin rapidly modulates, via different pathways, and in dependence on the baseline level, inflammation in hemodialysis patients. Blood Purif, 2004. 22(6): p. 518-24.
**43.** DORNBROOK-LAVENDER, K.A., et al., Effects of atorvastatin on low-density lipoprotein cholesterol phenotype and C-reactive protein levels in patients undergoing long-term dialysis. Pharmacotherapy, 2005. 25(3): p. 335-44.
**44.** ZHANG, H. and S.C. SUN, NF-kappaB in inflammation and renal diseases. Cell Biosci, 2015. 5: p. 63.
**45.** SANZ, A.B., et al., NF-kappaB in renal inflammation. J Am Soc Nephrol, 2010. 21(8): p. 1254-62.
**46.** VIDT, D.G., et al., Rosuvastatin-induced arrest in progression of renal disease. Cardiology, 2004. 102(1): p. 52-60.
**47.** VIDT, D.G., et al., Effect of short-term rosuvastatin treatment on estimated glomerular filtration rate. Am J Cardiol, 2006. 97(11): p. 1602-6.
**48.** KENDRICK, J., et al., Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. Am J Kidney Dis, 2010. 55(1): p. 42-9.
**49.** SANGUANKEO, A., et al., Effects of Statins on Renal Outcome in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis. PLoS One, 2015. 10(7): p. e0132970.
**50.** ATHYROS, V.G., et al., The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol, 2004. 57(7): p. 728-34.
**51.** KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE (K/DOQI) Group, K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease, in Am J Kidney Dis. 2003. p. S1–S91