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*by* Maftuchah Rochmanti

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# Anti-Inflammatory and Anti-Oxidative Therapeutic Approach in Chronic Kidney Disease with Statin Consumption

**Maftuchah Rochmanti[1*], Nadira Muthi Tsania[2], Sharifa Audi Salsabila[2], Mochammad Thaha[3,4]**

[1]Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya, Indonesia
[2]Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya, Indonesia
[3]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya, Indonesia
[4]Department of Internal Medicine, Universitas Airlangga Hospital, Jl. Mulyorejo, Surabaya, Indonesia

**Corresponding Author**. Maftuchah Rochmanti
**Email**: maftuchah-r@fk.unair.ac.id

## ABSTRACT

Inflammation and oxidative stress are 2 factors that play an important role in Chronic Kidney Disease (CKD). Controlling these 2 factors is expected to give better kidney functions outcomes. Statins have anti-inflammatory and anti-oxidative stress effects apart from their lipid-lowering effect. In this study, we want to analyze that statin might be one of a renoprotective agent through their pleiotropic effect as an anti-inflammation and anti-oxidative in CKD patients. This is a cross-sectional study that enrolled of 40 patients with CKD: 20 patients consumed statin and 20 patients did not consume statin. We compared HDL; inflammatory markers: high sensitive – C reactive protein (hs-CRP), absolute neutrophil count, absolute leukocyte count, absolute eosinophil count, and neutrophil-lymphocyte ratio (NLR); and oxidative stress marker malondialdehyde (MDA) with kidney functions (GFR, cystatin c, BUN, albumin urine, and creatinine serum) between groups. Then we analyze the correlation between HDL, inflammatory markers, and oxidative marker with kidney functions. The results are HDL and MDA had a correlation with all the kidney function, hs-CRP correlated with GFR, cystatin c, and BUN, and NLR correlated with GFR, cystatin c, BUN, and creatinine serum. Statin group significantly have lower hs-CRP, NLR, and MDA. HDL, absolute neutrophil, leukocyte, and eosinophil count are lower in the statin group but not significantly. All the kidney function markers significantly have a better outcome in the statin group. This study concludes that lowering inflammation and oxidative stress levels using statin could be one of the strategy therapies in CKD to achieve better kidney function outcomes.

**Keywords:** Chronic kidney disease, inflammation, kidney function, oxidative stress, statin

**Correspondence**:
Maftuchah Rochmanti
Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya, Indonesia
**Email:** maftuchah-r@fk.unair.ac.id

## INTRODUCTION

Statins are potent inhibitors of cholesterol biosynthesis through their 3-hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors mechanism. This mechanism does not just affect cholesterol, a study found out that it also affects the reduction of circulating isoprenoid and inactivation of signaling proteins. Those effects later result in statin capability to be an anti-inflammatory, antioxidant, antiproliferative and immunomodulatory, plaque stabilizer, normalizer of sympathetic outflow and prevent platelet aggregation.1 In this study, we want to see statins' role as anti-inflammatory and antioxidant in one of the diseases for which inflammation and oxidative stress have become a crucial role in its progression and complication, this disease is chronic kidney disease (CKD).

A study showed that 86% of CKD patients have proven to have some evidence of inflammation. Subjects with lower levels of kidney functions have higher pro-inflammatory cytokines and acute-phase proteins in their plasma. Furthermore, the level of inflammatory markers related to the magnitude of proteinuria.2 Several studies have shown that oxidative stress is also involved in CKD. Oxidative stress can accelerate the progression of CKD and is also associated with complications.3 In this study, we also analyzed the correlation between kidney functions and risk factors that influence kidney function: inflammatory markers and oxidative markers.

In this study, we also analyze HDL which is a lipid marker that is affected and also indirectly contributed to CKD. In CKD, HDL level is reduced and its protective function is impaired due to decreased apolipoproteins AI and AII, impairment of lecithin–cholesterol acyltransferase, and reduction paraoxonase activity who responsible for antioxidative and anti-inflammatory role of HDL.4 Change in HDL component can be a marker of kidney damage and situate dysfunctional HDL in inflammatory, oxidative, proliferative pathways that are furthermore involved in kidney damage progression and extrarenal complication.5 Different inflammatory markers have different predictive values for CKD. Study shows white blood cell could predict all-cause mortality risk6, hs-CRP was also associated with increased risk of CKD and a suitable marker for risk prediction7, and MDA have been proven as a biomarker of elevated oxidative stress in CKD and related to kidney health8,9. All of those markers are suitable for use in this study.

This study aimed to evaluate the anti-inflammatory and antioxidant effects of statins in their impact on kidney functions. We compared inflammatory and oxidative stress markers, then we compared kidney functions

between patients that consumed statin and who did not consume statin.

## MATERIALS AND METHODS

*Study design, participant, and data collection*

This cross-sectional analytical study consisted of 40 patients diagnosed with CKD at Airlangga University Hospital, Surabaya, Indonesia from May to August 2017. All patients were agreed and signed informed consent and Universitas Airlangga Hospital Ethics Committee approved this study. We excluded subjects who had systemic disease, infection, malignancy, and who consumed anti-dyslipidemia besides statin. Forty patients were divided into 2 groups based on statin consumption: Group A consisted of 20 patients who took statin and Group B consisted of 20 patients who did not take statin. All data was collected from the Case Report Form.

*Variables*

In this study, there are 4 groups of variables. First is the lipid marker, specifically HDL. Then, the inflammatory markers group consisted of hs-CRP, absolute neutrophil count, absolute leukocyte count, absolute eosinophil count, and neutrophil-lymphocyte ratio. The third is an oxidative stress marker that consisted of MDA. Last is kidney functions that consisted of GFR, cystatin c, BUN, urine albumin, and serum creatinine.

*Laboratory examination*

The laboratory test measured in this study consisted of leukocyte differential count from peripheral blood cell, Malondialdehyde (MDA) which was measured in blood serum and processed by HPLC method using Agilent 1100, High-sensitivity CRP (hs-CRP) was measured by Particle enhanced Turbidimetry (Roche Diagnostic, California, USA). Measurement of kidney function parameters (estimated glomerular filtration rate (eGFR), serum creatinine, and serum cystatin C) were performed using routine laboratory methods. The urine level of albumin was measured with a Hitachi 7600 using a turbidimetric immunoassay and an enzymatic method.

*Statistical analysis*

Data analysis is supported by SPSS Statistics. A normality test was performed using Shapiro-Wilk method. Descriptive analyses were performed in the form mean ± SD. To assess the difference of general characteristics, lipid marker, inflammatory marker, oxidative stress marker, and kidney function between-group, we used independent t-test for data with normal distribution and Mann-Whitney test for data that could not qualify normal distribution assumption, p-value <0.05 defined a significant difference. Correlation between variables and kidney function was calculated using Kendall's tau_b, categorized as having a correlation if p-value <0.05. The interpretation is if correlation coefficient >0.00, we considered as a weak correlation, >0.25 considered as a moderate correlation, strong correlation if >0.5, very strong correlation if >0.75, and perfect if the correlation coefficient 1.

## RESULTS

*General characteristic of study participants*

The study included 40 patients with CKD from stage 1 until stage 5. There are 2 patients in stage 1, 2 patients in stage 2, 9 patients in stage 3, 9 patients at stage 4, and 18 patients at stage 5. We can see the patient's general characteristics in table 1. Patients' age characteristics in groups A and B was not significantly different (p=0.097) and each group's sex ratio was almost the same. BMI between groups A and B was also not significantly different (p=0.77) with a mean only difference of 0.38. Most frequent comorbidities in CKD are hypertension and diabetes mellitus, and in both groups, these comorbidities are equally dominant. We can say that their basic characteristics were not remarkably different, so it could be concluded that patients in group A and B are fair to be compared to each other.

*Lipid marker level each group*

As we can see in table 2, HDL level in statin group was higher than in non-statin group but was not significantly different.

*Inflammatory marker level each group*

From 5 inflammatory markers, all of them were lower in group A. hs-CRP and neutrophil-lymphocyte ratio level between group A and B was significantly different with p-value 0.037 (Table 2)

*Oxidative stress marker level each group*

As shown in table 2, MDA level differences between group A and B was significantly different (p=0.014)

*Kidneys function each group*

All differences in the kidney function between group A and B was significantly different (Table 3). Overall, group A had a better kidney function outcome than group B by comparing the mean levels.

*Correlation with Kidney Function*

In this study, to achieve our hypothesis, we ensure that lipid marker, inflammation, and oxidative stress correlate with kidney function itself. We analyze all of the kidney function markers with HDL levels, hs-CRP, neutrophil-lymphocyte ratio, and MDA (Figure 1-5). For correlation with HDL, all of the kidney function markers correlated. GFR had a weak positive correlation, cystatin c and urine albumin had a weak negative correlation, and BUN and serum creatinine had a moderate negative correlation. Results in this study showed that hs-CRP only correlated with GFR (moderate negative correlation), cystatin c (weak moderate correlation), and BUN (weak positive correlation. We found the neutrophil-lymphocyte ratio which is another inflammatory marker had a moderate negative correlation with GFR and with cystatin c, BUN, and serum creatinine had a positive moderate correlation. In this study, we found that MDA and GFR had a strong negative correlation and with the rest kidney function markers had a moderate positive correlation.

## DISCUSSION

Statin has been proven to have several mechanisms in reducing inflammation. The first common mechanism is through their mevalonate pathway that statins could inhibit isoprenoid synthesis which is required for modification and function of small GTPases that are involved in signal transduction pathways. Statins can reduce innate and adaptive immune responses and further reduce inflammation. Through inducing Kruppel-like-transcription factors, statin block inflammatory responses of endothelial cells and T cells. Statins also could induce the synthesis of lipoxins, which could reduce acute inflammation.10 Many inflammatory markers have been analyzed to support the theory that statin anti-inflammatory effect is independent from lipid-lowering mechanism. In this study, Hs-CRP and white blood cells that consist of leukocyte, neutrophil, eosinophil, and neutrophil-lymphocyte ratio are lower in statin group than in non-statin group.

The antioxidant effect of statin could occur through several mechanisms. Statin could inhibit oxidant enzyme activity, up regulate anti-oxidant activity, reduce circulating markers of oxidation such as F2-isoprostane and nitrotyrosine, reduce circulating oxidized low-density lipoprotein, and inhibit their uptake by macrophages.11 In this study, we used MDA as an oxidative stress marker and the result is MDA significantly lower in statin group compared to non-statin group.

Inflammation in CKD is multifactorial and has been proven to impact clinical outcomes.12,13 The result in this study showed that hs-CRP and NLR as an inflammatory marker correlate with most of the kidney functions. Via several signaling pathways hs-CRP lead to hyperglycemia-mediated augment in oxidative stress. There is a vicious cycle where increasing oxidative stress will also amplify inflammation through activation of the nuclear transcription factor-kB which contributes to the activation and recruitment of immune cells. These inflammatory cytokines associated with oxidative stress further promote renal tissue injury by apoptosis, necrosis, and fibrosis.8 NLR in CKD is associated with hs-CRP and endothelial dysfunction. High levels of neutrophils reflect oxidative stress and low levels of lymphocytes indicate worsening of nutritional status. Oxidative stress and malnutrition are associated with kidney disease progression and adverse renal outcomes.14

The same thing with oxidative stress is the imbalance between antioxidant defense and free radical further contributing to the renal injury progression. Oxidative stress involved in renal function decline, glomerular filtration barrier damage, and fibrosis.15 Besides glomerular damage and renal ischemia, oxidative stress indirectly contributes to the CKD progression through inflammation, hypertension, and endothelial dysfunction. Oxidants interactions with the nucleic acid of a cell resulting in the death of these cells, oxidants inactivated mitochondrial enzymes and directly damage the DNA, DNA repair enzymes, and transcription factors.16 There is a positive correlation between increased oxidative stress and the advancing stage of CKD. 8 In this study, we found out that MDA has a significant correlation with all kidney functions that consist of GFR, cystatin c, BUN, albumin urine, and creatinine serum. GFR and serum creatinine are a marker to estimate a decline in kidney function. Oxidative stress contributes to the occurrence of proteinuria which is a sign of glomerular damage through asymmetric dimethylarginine (ADMA) activity, leading to co endothelial dysfunction, then cardiovascular disease, and to the progression of CKD.16 Other studies also proved that an increasing level of MDA is also accompanied by an increasing level of kidney dysfunction. This condition is also supported by a decreasing anti-oxidant level, but in this study, we did not research any anti-oxidant level.17

In this study, we analyze HDL levels between groups and their correlation to kidney functions. HDL has an important role in CKD. Systemic inflammatory and oxidative stress in CKD change HDL into a pro-oxidant and pro-inflammatory direction that leads to HDL's decreasing capability to prevent oxidation of LDL reduced monocyte chemotactic activity, and impairment in the reverse cholesterol transport.18 There is study found that inflammatory HDL in CKD leads to poor outcomes.19 In our study group, statin has a higher HDL level and is followed by better kidney functions. We also found that HDL correlates with all of the kidney function markers in this study.

The previous study said that reducing inflammation can prevent renal function decline.20. It also said that anti-oxidant supplements and controlling exogenous oxidants via diet and lifestyle modification might protect the kidney.21 It means that controlling inflammation and oxidative stress could be beneficial and could be an alternative therapeutic strategy in CKD. In this study, we found group that consumed statin significantly have better kidney functions. As mentioned above, this group also has a lower inflammatory and oxidative stress level. All of these results lead us to the theories about statin as a renoprotective drug. Study said that statin's pleiotropic effect is a key importance in how statin could affect renal dysfunction, not their plasma lipid-lowering effect. This pleiotropic effect refers to anti-inflammatory and anti-oxidative effects. One of the mechanisms that statin can do to prevent the production of free radicals is by increasing nitric oxide (NO) availability. NO increasing renal blood flow and GFR then mediates endothelial-derived vasodilation and promotes natriuresis and diuresis.22 Another study found that statin induced an increase in creatinine clearance, significantly decreasing albumin creatinine ratio and cystatin c.23 There is a study in rats confirmed that statins protect renal functions through anti-oxidant and anti-inflammatory actions by showing that statins improve renal function, urinary osmolarity, reduced urinary peroxide excretion, and macrophage infiltration.24 Statin ability to improve endothelial dysfunction later on will reduce abnormal permeability to plasma proteins. Statin improves endothelial and cardiac function also will benefit CKD because of an increase in renal perfusion.25

There are several studies discussing statin's renoprotective effect in non-CKD patients. Study said that in patients with acute coronary syndrome undergoing PCI, statin could increase NO synthase, reduce oxidative stress, reduce renal vascular permeability and tubular hypoxic injury.22

Statin renoprotective effects may be dependent on doses, duration, and kidney disease stage.26 High doses of statin improve the decline in GFR and low doses of statin does not affect renal progression.25 There is a meta-analysis study said that the longer the duration of therapy, the better the trend is, especially for serum creatinine, creatinine clearance, and GFR up to 3 years. Statin effect in decreasing albuminuria also depends on baseline levels. 20 Within the statin class itself, each type has a different effect. Study has shown that atorvastatin has anti-inflammatory effects stronger than simvastatin.22 Another study found that atorvastatin was also more effective in preventing an increase in cystatin c than pravastatin. This effect is considered as a result of the pleiotropic effect independently of its cholesterol-lowering effect because in another study atorvastatin compared to rosuvastatin which had more potent cholesterol-lowering effects, atorvastatin showed renoprotective effect stronger that rosuvastatin.23

This study's strength is that we analyze more than 1 marker and kidney functions and that could describe this study more comprehensive. This study showed that there is a correlation between inflammatory and oxidative stress markers with kidney functions and through anti-inflammation and anti-oxidative therapeutic approaches

that statin bring could make better kidney functions in CKD patients.

## CONCLUSION

In this study, HDL, hs-CRP, NLR, and MDA were significantly related to most of the kidney functions. This result indicated that inflammatory and oxidative stress play an important role in renal dysfunction. Statin pleiotropic effects as anti-inflammatory and antioxidative are considered to be the reason why the statin group has a lower inflammatory and oxidative marker and significantly has a better kidney function than the non-statin group. These results lead to the conclusion that anti-inflammatory and anti-oxidative effects from statin might be beneficial for study approach in CKD.

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**TABLES AND/OR FIGURES**

Table 1 : General characteristic of study participants

| Characteristic | Group A (n=20) | Group B (n=20) | P |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD | 60 ± 5.5 | 56 ± 9.3 | 0.097 |
| Range | 48 - 68 | 45 - 79 | |
| Sex | | | |
| Male | 12 | 11 | |
| Female | 8 | 9 | |
| Body Mass Index (kg/m²) | | | |
| Mean ± SD | 26.55 ± 3.46 | 26.17 ± 4.70 | 0.77 |
| Underweight | 0 | 1 | |
| Normal | 7 | 5 | |
| Pre obesity | 10 | 11 | |
| Obesity | 3 | 3 | |
| Hypertension, n (%) | | | |
| Yes | 19 (95) | 18 (90) | |
| No. | 1 (5) | 2 (10) | |
| Diabetes Mellitus, n (%) | | | |
| Yes | 18 (90) | 11 (55) | |
| No. | 2 (10) | 9 (45) | |

Group A: consumed statin; Group B: did not consume statin

Table 2 : Inflammatory and Oxidative Stress Markers Level Between Groups

| | Group A | Group B | P |
|---|---|---|---|
| **Lipid Marker** | | | |
| HDL (mg/dL) | 43.95 ± 16.30 | 39.15 ± 13.77 | 0.32 |
| **Inflammatory Marker** | | | |
| Hs-CRP (mg/L) | 4.2 ± 4.63 | 7.47 ± 8.83 | 0.037* |
| Leukocyte | 8530 ± 2396.07 | 8680 ± 2846.53 | 0.93 |
| Neutrophil | 5302.91 ± 5302.91 | 5836.16 ± 2536.93 | 0.64 |
| Eosinophil | 367.04 ± 394.75 | 391.28 ± 311.78 | 0.49 |
| NLR | 2.58 ± 1.03 | 3.79 ± 1.85 | 0.037* |
| **Oxidative Stress Marker** | | | |
| MDA (mmol/L) | 2.59 ± 0.61 | 3.19 ± 1.17 | 0.014* |

Group A: consumed statin; Group B: did not consume statin
*p<0.05 (significant difference)

Table 3 : Kidney Function Level Between Groups

| | Group A | Group B | P |
|---|---|---|---|
| **Kidney Functions** | | | |
| GFR (ml/minute/1.73 m²) | 36.35 ± 28.4 | 14.45 ± 18.98 | 0.002* |
| Cystatin C (mg/L) | 2.52 ± 1.69 | 5.51 ± 2.48 | 0.001* |
| BUN (mg/dL) | 37.45 ± 36.16 | 74.95 ± 37.36 | 0.001* |
| Urine albumin (mg/dL) | 95.31 ± 180.9 | 156.70 ± 130.91 | 0.017* |
| Serum creatinine (mg/L) | 3.77 ± 4.8 | 10.27 ± 6.50 | 0.004* |

Group A: consumed statin; Group B: did not consume statin
*p<0.05 (significant difference)

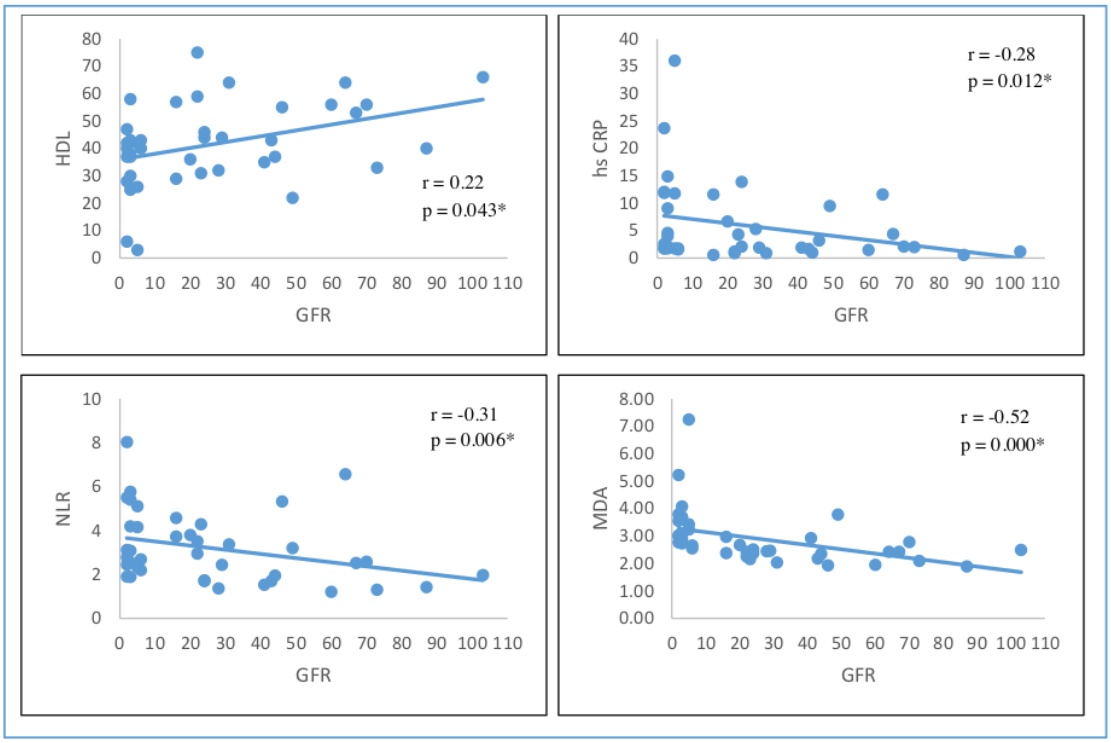


Figure 1 : GFR correlation with HDL, inflammation, and oxidative stress marker **p<0.05 (significantly correlated)*

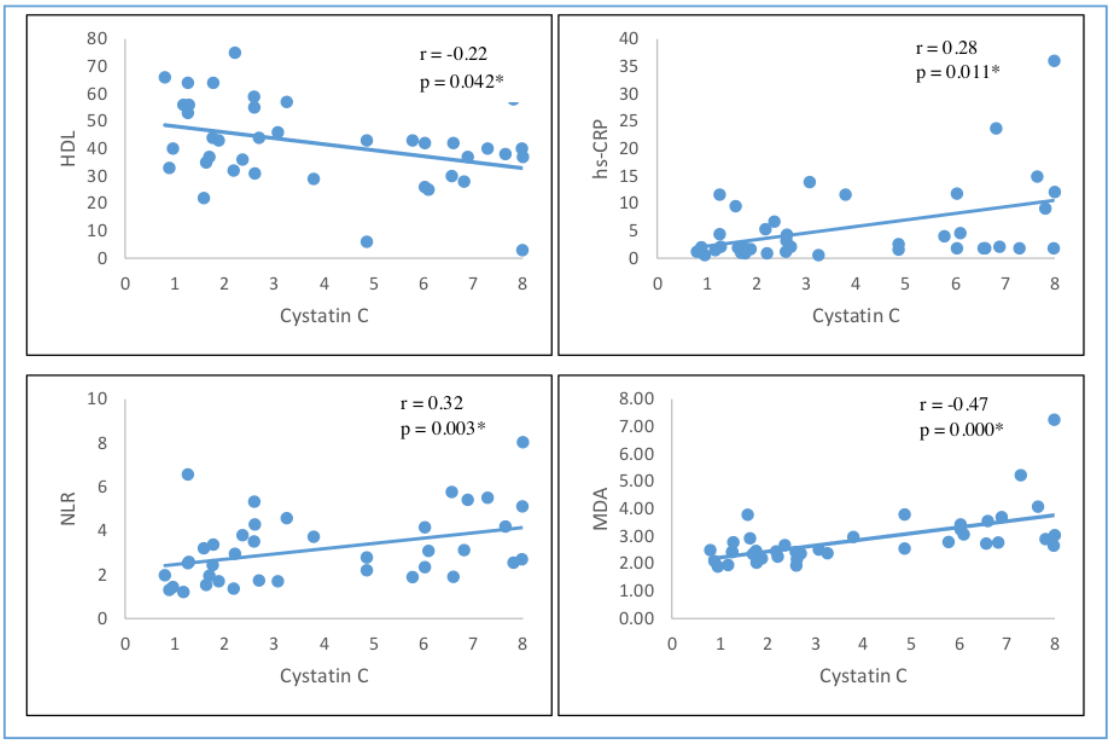


Figure 2 : Cystatin c correlation with HDL, inflammation, and oxidative stress marker

*p<0.05 (significantly correlated)

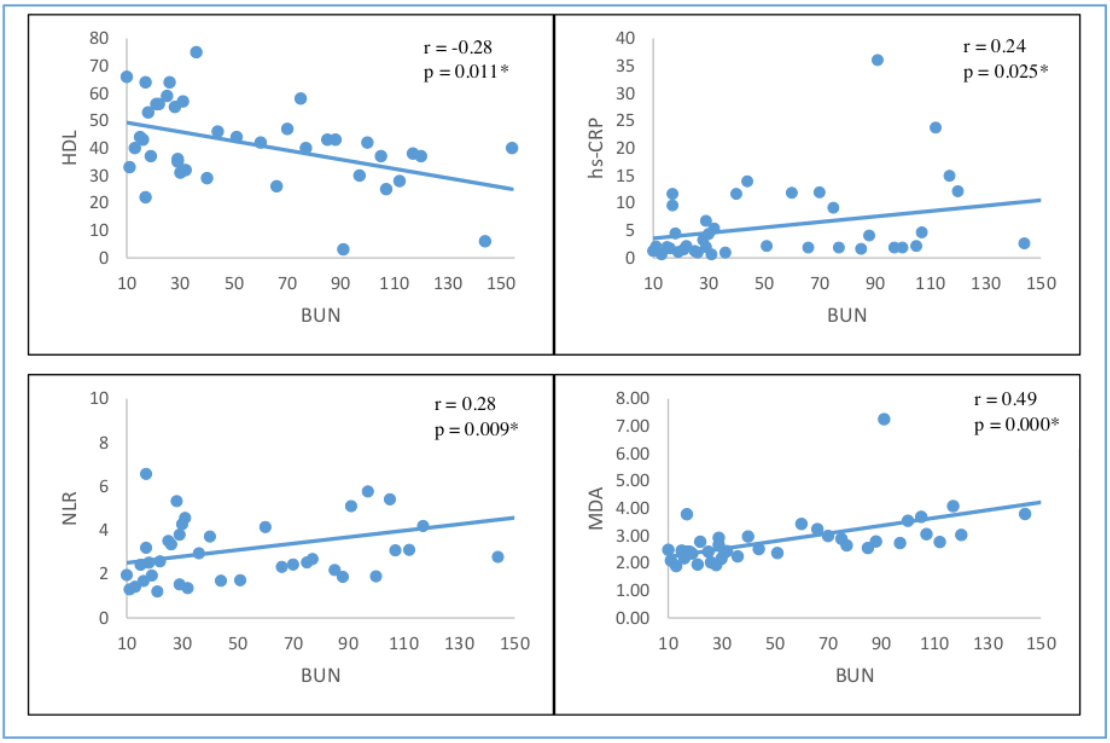


Figure 3 : BUN correlation with HDL, inflammation, and oxidative stress marker
*p<0.05 (significantly correlated)

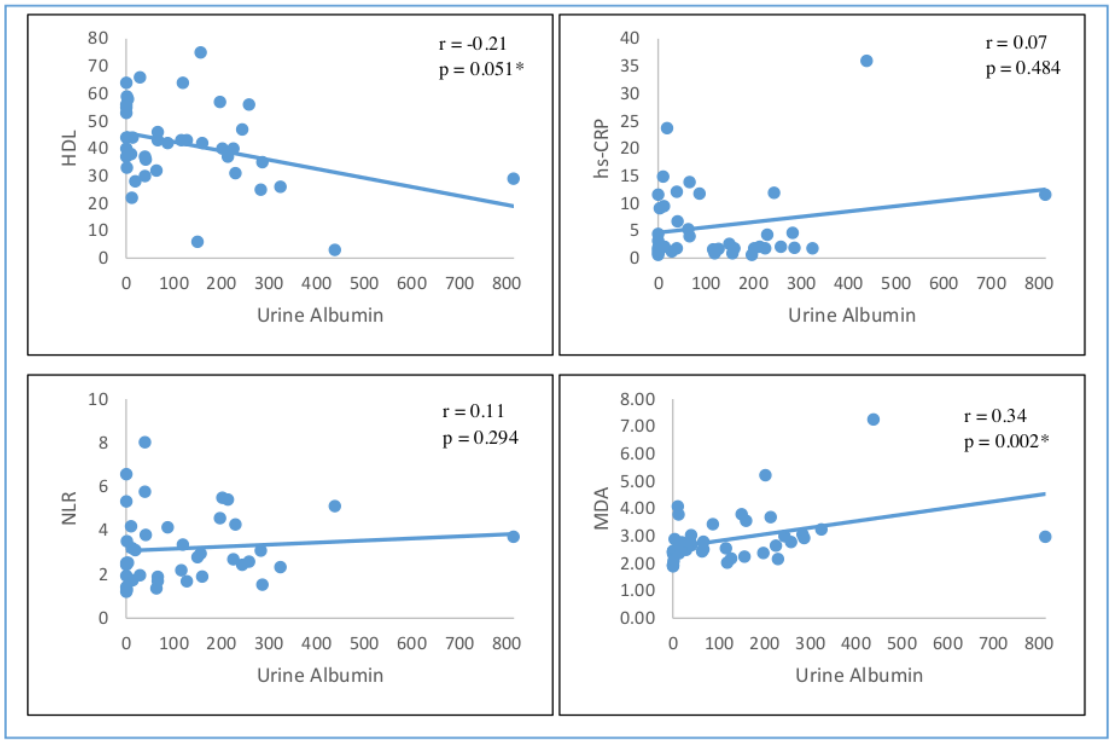


Figure 4 : Urine albumin correlation with HDL, inflammation, and oxidative stress marker
*p<0.05 (significantly correlated)

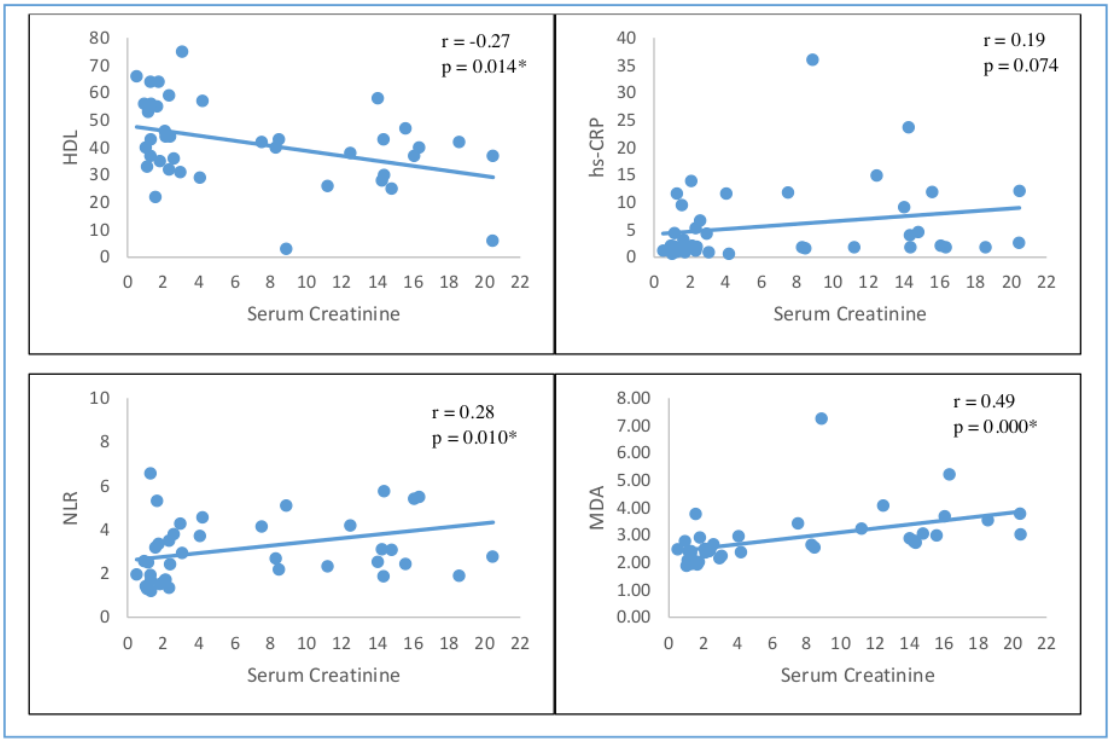


Figure 5 : Serum creatinine correlation with HDL, inflammation, and oxidative stress marker
*p<0.05 (significantly correlated)

# Anti-Inflammatory and Anti-Oxidative Therapeutic Approach in Chronic Kidney Disease with Statin Consumption

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