A Potential Combination of HDL-Cholesterol and HS-CRP for Inflammation Monitoring in CKD Patient with Statin Therapy

by Nadira Muthi Tsania

Submission date: 28-Jul-2021 12:50PM (UTC+0800)
Submission ID: 1624945669
File name: r_Inflammation_Monitoring_in_CKD_Patient_with_Statin_Therapy.pdf (177.4K)
Word count: 4029
Character count: 22491

Sapporo Medical Journal
Volume 54, Issue 10, October 2020

A POTENTIAL COMBINATION OF HDL-CHOLESTEROL AND HS-CRP FOR INFLAMMATION MONITORING IN CKD PATIENT WITH STATIN THERAPY

NadiraMuthi Tsania[1], Maftuchah Rochmanti[2]*, Lukman Hakim[3], Mochammad Thaha[4,5]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Urology, Universitas Airlangga/Dr.Soetomo Teaching Hospital, Surabaya, Indonesia
[4]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[5]Department of Internal Medicine, Universitas Airlangga Hospital, Surabaya, Indonesia

Abstract— Reducing inflammation can be one of the therapeutic targets in in Chronic Kidney Disease (CKD) patients. Many studies have shown that statins have pleiotropic effects as anti-inflammation. In this study we will be seen interaction of HDL-Cholesterol and hs-CRP to prove the role of statins as an anti-inflammatory and dyslipidemia treatment simultaneously. We compared hs-CRP and HDL Cholesterol/hs-CRP ratio levels in CKD patients who took statins and who did not take statins. Forty samples of CKD patients were taken randomly and then grouped based on their consumption of statin: taking statins (20) and not taking statins (20). There were negative correlation between HDL Cholesterol and hs-CRP (R=-0.374; P= 0.017), positive correlation between HDL Cholesterol/hs-CRP ratio and eGFR (R= 0.421; P= 0.007). The median concentration of hs-CRP in the statin group was significantly lower than in non-statin group (1.80 (1.20 – 5.30) vs 3.60 (1.90 – 11.60); P= 0.038), meanwhile there were not significantly different of median of HDL Cholesterol and HDL Cholesterol/hs-CRP Ratio between group. CKD subjects that consumed statin have a lower hs-CRP compared to subject that did not consume statin. But there was no difference of HDL-Cholesterol/hs-CRP ratio between CKD subjects that consume statin compared to did not consume statin but had a good correlation with eGFR. This result mean that HDL-Cholesterol and hs-CRP monitoring very important in CKD patient with statin treatment.

Keyword—chronic kidney disease, statin, hs-CRP, HDL Cholesterol

1. Introduction

Chronic kidney disease (CKD) is a determination for abnormalities of kidney structure or function that present for more than 3 months, with health implications.[1]In 2015 Global Burden Disease (GBD) estimated 1.2 million people died from kidney failure, 19 million disability-adjusted life years (DALYs), and 18 million years of life lost from cardiovascular disease were directly correlated to reduced glomerular filtration rates (GFR). Kidney disease is one of disease that spends many costs in the health care system globally.[2]A complication can happen at any stage.[1]So early detection and slow down the progression is important.

Inflammation has an immense contribution to the pathophysiology of CKD. Inflammation is one of the mediators responsible for progressivity and complications.[3] This is supported by evidence that patients with CKD have elevated inflammatory markers.[4] One of the inflammatory markers that elevated in patients with CKD is high sensitivity C-Reactive Protein (hs-CRP). It is proven that there is a correlation between hs-CRP and GFR.[5] Controlling inflammation has become one of the alternative strategy therapy in CKD. This strategy can be through overcoming the source of inflammation (cardiovascular, gastrointestinal, periodontal disease), healthy lifestyle, pharmacological approaches that have pleiotropic effects, or with anti-cytokine interventions.[3]

Dyslipidemia is a common condition in a patient with CKD. This lipid abnormality can happen at an early stage or as a manifestation of end-stage renal disease (ESRD) that can further lead to complications such as atherosclerosis.[6] Dyslipidemia also contributes to the inflammatory state in CKD. This happens because in

dyslipidemia, there is a decline of HDL that responsible for increasing inflammation. Paraoxonase, an enzyme in HDL, also decreased and it causes impaired HDL function as anti-oxidative and anti-inflammation.[7]Statin has become the first line for dyslipidemia treatment.[8] KDIGO recommends the use of statin for patient > 50 years old with GFR < 60 ml/min/1,73 m2 without a history of transplantation and for patient 18-49 years old with a risk of cardiovascular disease.[1]Recent study mention that statin has pleiotropic effects as anti-inflammation.[9] This effect of drug occur through mevalonate pathway and also through response innate and adaptive immune mechanism simultaneously. Statin slows down inflammation response to endothelial and T cell through stimulating Kruppel-like transcription factor. [10],[11] Based on brief theory of pleiotropic effect of statin above, it is very useful to analyze HDL-Cholesterol and hs-CRP interaction in CKD patient during statin treatment to monitor the beneficial effect simultaneously in daily practice.

This study aimed to investigate the effect of statin as an anti-inflammatory and dyslipidemia treatment in patients with CKD. In this study, we investigate the difference of inflammatory marker level specifically hs-CRP and also HDL Cholesterol/hs-CRP Ratio between patient that consumed statin and patient who did not consume statin.

2. Methods

2.1 Study design and participant

This research is an analytical cross-sectional study with a minimum number of patients is 26 based on the previous calculation. [12] Total number of subjects recruited in this research were 40 subjects.

The subjects of this study were patients who diagnosed with CKD at Airlangga University Hospital, Surabaya, Indonesia from May to August 2017. All of the subjects were agreed and signed informed consent for this study. The subject who consumed anti-dyslipidemia besides statin, had an infection, and malignancy or other systemic diseases were excluded. The study was approved by UniversitasAirlangga Hospital Ethic Committee (Approval number: 116/KEH/2019)

In this study, the participant was divided based on statin consumption: a group with patients that consumed statin and group with patients who did not consume statin. Each group consisted of 20 patients. Most of the patients were receiving antihypertensive agents.

2.2 Laboratory tests

The laboratory test measured in this study consisted of hs-CRP. Particle enhanced turbidimetry (Roche Diagnostic, CA, USA) was used to process serum hs-CRP that measured in blood serum.Estimated Glomerular Filtration Rate (eGFR) was calculated from serum Creatinine concentration using CKD-EPI formula.

2.3 Statistical analysis

To test normality of the distribution, all data were using Shapiro-Wilk method. Correlation was calculated using Spearman's Rho test. The difference of hs-CRP, HDL Cholesterol, and HDL Cholesterol/hs-CRP ratiobetween-group consumed statin and group did not consume statin was calculated using Mann-Whitney test. All comparison test utilized in this study used two-tailed 95% Confidence Interval. A significant difference was defined if the p-value<0.05. Data analysis is supported by SPSS Statistics.

3. Result

3.1 Characteristic of subjects

Forty subjects were evaluated in this study. The mean ages of all subjects were 57.7±7.9 years old. Sixteen subjects (40%) were on hemodialysis. Eighteen subjects (45%) was on stage 5; stage 4 and 3 had 9 subjects each (22.5%); stage 2 and stage 1 had 2 patients each (5%). Subjects also known for diabetes and hypertension status. 72,5% of subjects had diabetes mellitus, 92,5% of subjects in this study also had

hypertension, and 65% had both diabetes mellitus and hypertension Distribution of basic characteristics and drugs used between both group listed in table 1.

3.2 HDL-Cholesterol profile of subjects

HDL-Cholesterol of subject were analyzed based on reference value category both in statin group and non-statin group as shown in table 2.

3.3 Correlation of HDL-Cholesterol, hs-CRP, HDL-Cholesterol/hs-CRP Ratio, and eGFR

The data showed that there were negative correlation between HDL-Cholesterol and hs-CRP, positive correlation between HDL-Cholesterol and eGFR, negative correlation between hs-CRP and eGFR, and positive correlation between HDL-Cholesterol/hs-CRP ratio and eGFR as listed in table 3.

3.4 Comparison of HDL-Cholesterol, hs-CRP, and HDL-Cholesterol/hs-CRP ratio between group

There was a higher trend of HDL-Cholesterol and HDL-Cholesterol/hs-CRP ratio median in statin group compared to non-statin group although not statistically significant (43 (37-56) vs 40 (35-44) mg/dL; P= 0.301) and (24.23 (5.37-49.17) vs 12.60 (5.43-18.42); P= 0.102). There was a statistically lower hs-CRP concentration median in statin group compared to non-statin group (1.80 (1.20-5.30) vs 3.60 (1.90-11.60) mg/L; P= 0.037) as listed in table 4.

4. Discussion

Inflammation can lead to impaired endothelium, thrombosis, and decreased kidney function.[10] There are many theories about how inflammation increased in CKD. The theories are it happened because of its pathophysiology, accumulation of oxidative stress, low level of albumin, pre-albumin, and transferrin, pro-inflammatory cell excretion, nitric oxide activities, and CRP filtration decreased, and risk factor such as hypertension, obesity, and diabetes also contributed.[13],[14]

In this study, 72.5% of patients have diabetes mellitus. Diabetic patients showed a significantly higher level of hs-CRP. This high level of hs-CRP might be caused by the induction of cytokines, increased oxidative stress, and activation of macrophages.[15],[16]92.5% of patients in this study also have hypertension. A previous study said that patients with hypertension have a higher level of hs-CRP.[17] Twenty-six patients (65%) have both diabetes mellitus and hypertension. Study showed that hypertensive patients with diabetes mellitus had higher levels of hs-CRP.[18]hs-CRP can be a good predictor of diabetes mellitus and cardiovascular disease.[19]Twenty-seven patients (67.5%) have BMI >25. Overweight and obesity have a significant correlation with hs-CRP. [16] According to Thaha, M. *et al*., 2018 study in CKD patients, *body fat percentage* has a significant correlation with hs-CRP.[20] Sixteen patients are in hemodialysis (40%). Study said that hemodialysis increases hs-CRP level significantly and associated with mortality.[21]

Lipid profiles correlate with inflammation marker including hs-CRP. HDL is known as anti-inflammatory and anti-oxidative. In CKD patients, low level of HDL-Cholesterol is a common thing.[7] Also, in CKD patients due to uremia, HDL does not indicate anti-inflammatory and anti-oxidative. LDL also affected by uremia, it has structural and functional changes causing cell dysfunction and tissue damage.[13] This study showed that 60% of patients have a lower HDL-Cholesterol based on reference value. But in this study, when HDL-Cholesterol concentration compared in statin and non-statin group there was no significant difference although it showed a higher trend in statin group (Table 3). HDL is one of the cholesterol transporter and protective lipoprotein. We know that cholesterol is a risk factor for cardiovascular disease.[22] There is study showed that HDL-Cholesterol and hs-CRP have a negative correlation (R= -0.374; P= 0.017) that in-line with the result of current study. The negative correlation between HDL and hs-CRP means that raised hs-CRP is a risk factor for cardiovascular disease as a complication of CKD.[22] The ratio of HDL-Cholesterol/hs-CRP showed a positive correlation with eGFR (Table 3). This ratio expressed the combination and interaction between inflammation and improvement of HDL-Cholesterol concentration

at the same time when CKD patients who took statin.

hs-CRP plays a role in the pathogenesis and progression of CKD. The mechanism to damage renal tissue is associated with oxidative stress by apoptosis, necrosis, and fibrosis. The roles via several signaling pathways which lead to hyperglycemia-mediated augment in oxidative stress. Other factors also appear to be involved such as uremic toxins, renin-angiotensin system, hypertension, underlying diseases like diabetes, infection, iron overload, and anti-oxidant deficiency.[23]

This study showed there was a negative correlation between hs-CRP and eGFR (Table 3). This result was in line with previous study that stated high level of hs-CRP associated with proteinuria, eGFR<60 mL/min/1.73 m2, and CKD.[5],[24] Besides hs-CRP other studies found PTX3, TNF-α, CRP, IL-8, IL-10, IL-1β, IL-1RA, IL-6, and fibrinogen also increased in CKD. Fibrinogen and TNF-α level serum increased can be indicators for progressivity in CKD. IL-1β/IL-18 beside plays a role in the progressivity of CKD, they also accelerating complications such as vascular calcification, fibrosis, and sepsis.[4],[25] Elevated hs-CRP is a predictor for cardiovascular events and mortality.[26]

This study showed that the group of the patient that consumed statin has a lower hs-CRP compared to the group that did not consume statin. The difference serum hs-CRP level between each group is significant P= 0.038. This result showed that there is a role of statin in lowering hs-CRP in CKD patients. Controlling hs-CRP remains low can reduce the risk of further kidney damage.[24]Statin also can be lowering other inflammatory markers such as CRP, IL-6, TNF-α, IL-1β.[10][27]–[29] Meanwhile, this study also showed that there is no significant difference of HDL-Cholesterol/hs-CRP ratio between statin group and non-statin group. On the other hand, there was a higher trend of ratio that assumed increase of HDL-Cholesterol and decrease of hs-CRP after statin consumption. This ratio would be very potential as a new combination marker in daily practice to monitor CKD patients.

Statin can up-regulate synthesis nitric oxide, decreased neutrophils and macrophage infiltration, inhibit cell proliferation, anti-fibrosis, anti-oxidant, and downregulate cytokines. Statin has the ability to reduce lipid contribution to the occurrence of glomerulosclerosis and fixing blood vessels calcification.[30]

In diabetic non-CKD patients, a study showed that statin could be employed to lower hs-CRP levels.[31]Study about statin in diabetic nephropathy population showed that statin decrease albuminuria and urinary albumin excretion rates significantly.[32] In diabetic patients undergoing hemodialysis, statin can reduce atherosclerotic coronary events by 32% and lowered stroke incidence.[33]

There is study said that statin had been shown to lower CRP and reduce cardiovascular events independent of their lipid-lowering actions in subject with and without metabolic syndrome and hypertension. Statin can be reducing oxidative stress, increasing the bioavailability of nitric oxide (NO), and inhibit inflammatory further this effect beneficial to vascular endothelium.[34]

There is still controversy about the benefit of statin in the hemodialysis population. There is a study said that statin potentially accelerates vascular calcifications through their effects. Statin affecting vitamin K metabolism, they inhibit the synthesis of vitamin K2 who is responsible for activation protein inhibit of vascular calcification, and statin also stimulates vascular smooth muscle apoptosis. Frequently patients in hemodialysis have vitamin K deficiency and it said that vitamin K is a key player and modifiable for preventing vascular calcification.[35] Other studies also said that the benefit of statin therapy on cardiovascular outcomes is less certain.[36]Despite the controversy, some studies said that statin is effective to reduce inflammatory markers including hs-CRP.[10],[30] Statin is independently associated with a 30-50% mortality reduction in patients with dialysis.[37]KDIGO recommendation is statin can be continued in patients already consume them at the time of dialysis start, but not be initiated in patients on dialysis.[1]

hs-CRP also can promote atherosclerosis, predict, and common risk for cardiovascular events which is one of the most common complications in CKD patients.[26]hs-CRP also plays a role in the pathogenesis and progress of CKD.[23] Inflammation has a crucial role in CKD so controlling it can be beneficial to the

patients. Combination of HDL-Cholesterol and hs-CRP in ratio, showed a potential application in clinical practice to monitor inflammation and HDL-Cholesterol improvement in statin therapy. Statin has a potential anti-inflammatory effect and its use as an anti-inflammatory therapy strategy needs to be considered in line with further research.

There are some limitations in this study. In this study, we just used one inflammation marker along with lipid profile and eGFR, investigate more inflammatory markers can describe the inflammatory process more wholly. Also, the number of samples that should be increased. However, the significant differences showed in this study might indicate a potential benefit of statin to lowering hs-CRP levels and HDL-Cholesterol improvement in CKD patients.

5. Conclusion

This study shown that CKD subjects that consumed statin have a lower hs-CRP compared to subject that did not consume statin. But there was no difference of HDL-Cholesterol/hs-CRP ratio between CKD subjects that consume statin compared to did not consume statin but had a good correlation with eGFR. This result mean that HDL-Cholesterol and hs-CRP monitoring very important in CKD patient with statin treatment.

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7. Acknowledgement

We thank to Prof Thaha and team who collected the data and allowed us to use some of the data for this study.

8. Figures and Tables

Table 1. Basic Characteristics of study participants

Characteristic	Group A (n=20)	Group B (n=20)
Age (Years)	59.8±5.6	55.6±9.4
Sex ratio (M/F)	12/8	11/9
Body Mass Index >25, n (%)	13 (65)	14 (70)
Hypertension, n (%)	19 (95)	18 (90)
Diabetes Mellitus, n (%)	18 (90)	11 (55)
Smoking, n (%)	8 (40)	3 (15)
Coronary heart disease, n (%)	5 (25)	1 (5)
Hemodialysis	2 (10)	14 (70)

CCB	14	16
ARB	9	10
β1-blocker	6	10
ACEi	2	0
Diuretics	3	1
Anti-oxidant	12	7

Group A (consumsed statin) and group B (did not consume statin) ; CCB= Calcium Channel Blocker ; ARB= Angiotensin Receptor Blocker ; ACEi= Angiotensin Converting Enzyme inhibitor

Table 2. HDL-Cholesterol profile of study participants

	Category (mg/dL)	n (%)	Median (95% LL-UL)	
			Group A	Group B
HDL-C	<130	27 (67.5)	43 (37-56)	40 (35-44)
	≤ 50 woman	12 (70.5)		
	≤ 40 man	13 (56.5)		
	> 50 woman	5 (29.4)		
	> 40 man	10 (43.4)		

Group A (consumsed statin) and group B (did not consume statin) ; HDL-C= High Density Lipoprotein Cholesterol

Table 3. Correlation HDL-Cholesterol, hs-CRP, and eGFR

Correlation	R	P
HDL-Cholesterol and hs-CRP	-0.374	0.017
HDL-Cholesterol and eGFR	0.349	0.027
hs-CRP and eGFR	-0.336	0.034
HDL-Cholesterol/hs-CRP Ratio and eGFR	0.421	0.007

Analyzed using Spearman's Rho Test

Table 4. Comparison of HDL-Cholesterol, hs-CRP, and HDL-Cholesterol/hs-CRP Ratio between both groups

Parameters	Group A	Group B	P Value
HDL-Cholesterol (mg/dL)	43 (37-56)	40 (35-44)	0.301
hs-CRP (mg/L)	1.80 (1.20-5.30)	3.60 (1.90-11.60)	0.037
HDL-Cholesterol/hs-CRP Ratio	24.23 (5.37-49.17)	12.60 (5.43-18.42)	0.102

Median (95% Lower CL – 95% Upper CL)
Analyzed using Mann-Whitney U Test

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