The Anti-Inflammatory Effect of ACE-I/ARBs Drug on hs-CRP and HDL-Cholesterol in CKD Patient

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Abstract

Chronic kidney disease (CKD) is progressive disease that closely related to the chronic inflammatory process. Angiotensin-Converting Enzyme Inhibitor (ACE-I)/Angiotensin Receptor Blockers (ARBs) is the main therapy in the management of CKD, based on the recent sudies stated that this drug have pleiotropic effects as anti-inflammation.The aim of this study is tosee the interaction of hs-CRP and HDL-Cholesterol to prove the role of ACE-I/ARBs as an anti-inflammatory treatment for CKD patient. In this study we compared hs-CRP, HDL Cholesterol and HDL Cholesterol /hs-CRP ratio levels in CKD patients who consumeand do not consumeACE-I/ARBs. Forty eight samples of CKD patients were taken randomly and then separated into two group based on their consumption of ACE-I/ARBs, each group have 24 samples.There were significantly different of mean of hs-CRP, HDL Cholesterol, and HDL Cholesterol/hs-CRP ratio between group, the mean concentration of hs-CRP in the ACE-I/ARBs group was significantly lower than in non-ACE-I/ARBs group (1,48±0,81 vs 4,19±4,02; P= 0.038),the mean of HDL (48,95±13,05vs 41,50±12,31; P= 0,048).There were negative correlation between HDL Cholesterol and hs-CRP, positive correlation between HDL Cholesterol/ hs-CRP ratio and eGFR.This result indicate that hs-CRP and HDL-Cholesterol monitoring very important in CKD patient.

Keywords: *Chronic kidney disease, ACE-I, ARBs, hs-CRP, HDL Cholesterol*

Introduction

Chronic kidney disease is defined as a kidney disorder, both structure and function, that persists more than 3 months with associated health problems[1]. Based on Global Burden Disease (GBD) the incidence of chronic kidney disease continues to increase from year to year, in 2017 it was ranked 6th in the world with a death rate of 34.18 / 100,000 population[2].The incidence of this disease continues to growth with the increasing number of elderly people and the presence of comorbids such as diabetes and hypertension[2].

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The inflammatory process is the main cause of the progression of CKD disease[3]. The inflammatory process that occurs is characterized by an increase in inflammatory markers[4]. hs-CRP is marker of inflammation that can be observed in CKD patients and there is an association between a decrease in GFR and an increase in hs-CRP levels, which indicates the role of inflammation in the progression of CKD[5]. Because of the large role of inflammation in the pathophysiology of CKD, the management of inflammation is one of the main focuses in the treatment of this disease.

Inflammatory conditions in CKD patients are often exacerbated by the presence of comorbid diseases such as dyslipidemia, dyslipidemia conditions in CKD patients arise even at an early stage and will get worse

following the progression of the CKD, the decresease in HDL Cholesterol levels is one of the main symptoms in dyslipidemia patients[6,7], this condition lead to the impairness of HDL Cholesterol function to regulate the immune system to reduce the inflammatory condition[8]. Kidney Health Australia recommends the use of anti-angiotensin drug (Angiotensin Converting Enzym-Inhibitor (ACE-I) or Angiotensin Receptor Blocker (ARB)) as the first choice therapy in patients with chronic kidney disease, these drugs can improve the condition of CKD patients through improving hemodynamic conditions and also act as anti-inflammatory[3].Anti-angiotensin drugs have anti-inflammatory effects by inhibiting the renin-angiotensin-aldosterone system (RAAS), the RAAS system plays a role in the formation of the inflammatory process through activation of Angiotensin-II[9], ACE-I/ARBs also supported the capacity to elicit cholesterol efflux from lipid-loaded macrophage and stabilized HDL cholesterol acceptor function[10].

Based on the information that ACEI / ARBs are related to hs-CRP and HDL cholesterol, it is very important to analyze and observe hs-CRP and HDL cholesterol levels in CKD patients who are taking ACE-I / ARBs. This study aimed to analyzed the effect of ACE-I/ARBS drug as an anti-inflammatory treatment in patients with CKD by comparing the difference of inflammatory marker level of hs-CRP, HDL Cholesterol, and HDL Cholesterol /hs-CRP Ratio between patient that consumed ACE-I / ARBs and patient who did not consume ACE-I / ARBs.

Materials and Methods

Study design and participant

This study is an analytical study with a cross-sectional design. With a minimum 13 CKD patients based on previously described calculation[11], this research was approved by UniversitasAirlangga Hospital Ethic Committee (Approval Number: 116/KEH/2019). The subjects of this study were patients were diagnosed with CKD in University Airlangga Hospitalfrom May to August 2017, all the subjects were agreed and signed the informed consent. There are forty eight subjects recruited by both the inclusion and exclusion criterion.

The participant was divided based on ACE-I/ARB consumption: a group with patients that consumed ACE-I/ARB(Group A) and group with patients who did not consume ACE-I/ARB (Group B). Each group consisted of 24 patients. Most of the patients.Most of the patients were also receiving other antihypertensive agents such as β_1-blocker (BB), calcium-channel blocker (CCB), statin, diuretics, and antioxidant agents.

Laboratory examination

The laboratory test measured in this study consisted of Hs-CRP. Hs-CRP measured in blood serum and process using particle enhanced turbidimetry (Roche Diagnostic, CA, USA).EstimatedGlomerular Filtration Rate (eGFR) was calculated from serum Creatinine concentration using CKD-EPI formula.

Statistical Analysis

Data analysis is supported by SPSS Statistics version 25. All quantitative data were performed to normality test usingSaphiro-Wilk method.Correlation was calculated using Spearman's Rho test. The difference of hs-CR, HDL Cholesterol, and HDL Cholesterol/hs-CRP ratio between group that consumed ACE-I/ARBs and group did not consume ACE-I/ARBs 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.

Result

Characteristic of study participants

Forty eight patients were evaluated in this study. The mean ages of participants were 58. Eighteen (37,5%) were on hemodialysis. nineteen (39,5%)patient was on stage 5; stage 4 had ten (20,9%) patient, stage 3 had fourrteen (29%) patients, stage 2had three (6,25%) patients and stage 1had two(4%)patient .Most of the subjecthas hypertension as a commorbid disease with total of 43 patients (89,5%).

Table 1. Characteristic of study participants

No	Characteristic	Group A (n=24)	Group B (n=24)
1	Age>50, n (%)	20 (83)	23 (95)
2	Sex ratio (M/F)	15/9	16/8
3	Body Mass Index ≥25, n (%)	13 (54)	17 (70)
4	Systolic Blood Pressure ≥ 130 mmHg, n (%)	18 (75)	13 (54)
5	Diastolic Blood Pressure ≥ 80 mmHg, n (%)	11 (45)	10 (41)
6	Hemodialysis	8 (33)	10 (42)
7	Hypertension, n (%)	22 (91)	21 (86)
8	Diabetes Mellitus, n (%)	18 (75)	19 (79)
9	Chronic Heart Failure, n (%)	7 (29)	16 (67)
10	Coronary heart disease, n (%)	1 (4)	5 (20)
11	Smoking, n (%)	4 (16)	8 (33)
12	BB	11	7
13	CCB	19	18
14	Diuretics	1	3
15	Statin	7	6
16	Antioxidant	13	10

Kidney function profile of study participant

Kidney function of subject were analyzed based on reference value category both in ACE-I/ARBs group and non-ACE-I/ARBs group.

Table 2. Kidney function profile of study participant

No	Characteristic	Category	n (%)	Mean ± SD	
				Group A	Group B
1	eGFR	> 60 mL/min/1,73 m²	8 (17%)	32,88 ±30,37	29 ±27,64
		< 60 mL/min/1,73 m²	40 (83%)		
2	BUN	≥ 20 mg/dl	37 (77%)	50,50 ±39,44	46,20 ±30,90
		< 20 mg/dl	11 (23%)		
3	Cystatin C	19-49 years ≥ 0.92 mg/L ≥ 50 years ≥ 1.02 mg/L	5(10,6%) 41(85,1%)	3,57 ±2,41	3,95 ±2,72
		19-49 years < 0.92 mg/L ≥ 50 years < 1.02 mg/L	0 (0%) 2 (4,3%)		
4	Serum Albumin	≤ 3.5 g/dl	5 (10,4%)	4,29 ± 0,41	4,18 ± 0,53
		> 3.5 g/dl	43 (89,6%)		
5	Urine Albumin	≥ 1.9 mg/dl	29 (60,5%)	95,66 ±92,04	141,03 ±179,33
		< 1.9 mg/dl	19 (39,5%)		
6	Serum Creatinine	≥ 1.2 mg/dl	40 (83,4%)	6,31 ±6,67	6,14 ±5,37
		< 1.2 mg/dl	8 (16,6%)		
7	Urine Creatinine	≤ 37 mg/dl women ≤ 40 mg/dl men	2 (4,1%) 2 (4,1%)	95,65 ±71,67	105,01 ±63,38
		> 37 mg/dl women > 40 mg/dl men	15 (31,2%) 29 (60,6%)		
8	ACR	≥ 30 mg/g	27 (56,3%)	1.670,29 ±2091,20	1565,79 ±1796,01
		< 30 mg/g	21(43,7%)		
9	HDL-C	≤ 50 mg/dl women ≤ 40 mg/dl men	9 (18,75%) 11 (23%)	48,96 ±13,05	41,5 ± 12,31
		>50 mg/dl women > 40 mg/dl men	20 (41,5%) 8 (17%)		

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

The data showed that there were positive correlation between HDL-Cholesterol and eGFR ,positive correlation between HDL-Cholesterol/hs-CRP ratio and eGFR,positive correlation between HDL-Cholesterol and HDL-Cholesterol/hs-CRP Ratio,negative correlation between HDL-Cholesterol and hs-CRP, and negative correlation between hs-CRP and eGFR.

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

Correlation	R	P
HDL-Cholesterol and hs-CRP	-0,234	0,110
HDL-Cholesterol and eGFR	0,200	0,172
hs-CRP and eGFR	-0,137	0,353
HDL-Cholesterol/hs-CRP Ratio and eGFR	0,202	0,168
HDL-Cholesterol and HDL-Cholesterol/hs-CRP Ratio	0,465	0,001

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

There was a statistically lower of hs-CRP concentration in ACE-I/ARBs group compared to non- ACE-I/ARBs group (1,48±0,81 vs 4,19±4,02; P= 0.038), for HDL-Cholesterol and HDL-Cholesterol/hs-CRP ratio it found that the mean in ACE-I/ARBs group was higher compared to non- ACE-I/ARBs group with statistically significant (48,95±13,05vs 41,50±12,31; P= 0,048) and (45,41±31,75vs 21,88±18,83; P= 0,002).

Table 4. Comparison of HDL-Cholesterol, hs-CRP, and HDL-Cholesterol/hs-CRP ratio between group

Parameters	Group 1	Group 2	P Value
hs-CRP (mg/L)	1,48±0,81	4,19±4,02	0,010
HDL-Cholesterol (mg/dL)	48,95±13,05	41,50±12,31	0,048
HDL-Cholesterol/hs-CRP	45,41±31,75	21,88±18,83	0,002

Discussion

In this study, it was found that the mean age of the subjects was more than 50 years old which indicated a tendency for kidney disease at the age of more than 50 years. physiological decline of renal function in terms of the number of nephrons and LFG[12]. From allsubjects, it was found that CKD patients were dominated by men with a ratio of 3:2 indicating that men had more chronic kidney disease than women, this was due to physiological differences between men and women, women had the sex hormone estrogen. which is protective while testosterone as the main sex hormone in males is destructive[13]. A total of 48 (89,5%) patients in this study had a history of hypertension and 37 patients (77%) had a history of diabetes mellitus. hypertension and diabetes can lead to CKD disease[14], hypertension can cause CKD because chronically high blood pressure in hypertensive patients will affect the intrarenal adaptation mechanism which will exacerbate the glomerular hyperfiltration process that occurs in CKD patients [15,16] and diabetes will cause a hyperglycemia state that triggers hyperfiltration and injury to the kidneys coupled with the presence of advanced glycosylation products and activation of cytokines which will exacerbate the damage experienced by the kidneys[16].

Inflammation causes various conditions in CKD patients such as decreased GFR and an increased risk of developing end-stage kidney disease[17], in The Chronic Renal Insufficiency Cohort (CRIC) study found that an increase in inflammatory indicators such as IL-1β, IL-1RA, IL-6, TNF-α, hs-CRP, and fibrinogen would further reduce kidney function in CKD patients[18].

One of the inflammation markers that play a role in CKD progression is hs-CRP.Studies regarding the role of hs-CRP in heart and blood vessel disease explain that CRP has a role in facilitating monocyte adhesion and transmigration to the walls of blood vessels which is a crucial step in the formation of atherosclerotic plaques[19]. The increase in serum hs-CRP levels is significantly related to the severity of aherosclerosis of the blood vessels, especially the coronary arteries[20], hs-CRP has a role through several signaling pathways leading to hyperglycemia-mediated increases in oxidative stress than activated the nuclear transcription factor κB (NF-κB), which contributes to the activation and recruitment of immune cells causing apoptosis, necrosis, fibrosis, and maybe the major mechanisms in the pathogenesis and development of CKD[21,22].

This study showed that the group of the patient that consumed ACE-I/ARBs has a lower hs-CRP compared to the other group and the difference of hs-CRP level between each group is significant P= 0.038. This result prove therole of ACE-I/ARBs drug in lowering hs-CRP in CKD patients. ACE-I / ARB. ACE-I / ARB drugs have an anti-inflammatory mechanism through inhibition of the Renin-Angiostensin-Aldosterone System (RAAS) espescially Angiotensin II, that modulates vascular inflammation by regulating the expression of adhesion molecules, chemokines, and cytokines, such as TNF-α, IL-6, as well as growth factors and cyclooxygenase-2 within the arterial wall[10,23]. There was a negative correlation between hs-CRP and eGFR (R=-0,137; P=0,353). these results are in accordance with previous studiesthat stated high level of hs-CRP associated with eGFR<60 mL/min/1.73 m2, proteinuria, and CKD[24], based on the table 2 we can see that eGFR is higher in the group that consume ACE-I/ARBs compare with the other group.

The result showed that there is a signifficant different of HDL-Cholesterol and HDL-Cholesterol/ hs-CRP ratio between group and higher mean value in ACE-I/ARB group compare to the other group, we know that HDL-Cholesterol is one of lipoprotein molecule that have a protective function in vascular disease[26], the result showed that ACE-I/ARBs drug have ability to improve the HDL-Cholesterol level in CKD patient trough the support capacity to elicit cholesterol efflux from lipid-loaded macrophage and stabilized HDL cholesterol acceptor function[10]. There is negative correlationbetween HDL-Cholesterol and hs-CRP (R= -0,234; P= 0,110) it means that an increase in hs-CRP levels will be lowering HDL-Cholesterol levelsand increase the risk factor for cardiovascular disease as a complication of CKD[25]. The ratio of HDL-Cholesterol/ hs-CRP showed a positive correlation with eGFR (R= 0,202; P= 0,168). This ratio expressed the combination and interaction between inflammation and improvement of HDL -Cholesterol concentrationat the same time when CKD patients who ACE-I/ARBs drug.

with a brief explanation of the role of ACE-I / ARBs against hs-CRP and HDL-Cholesterol stated before, it is very clear the importance of monitoring the level of inflammation which is the main source of problems for CKD patients through these indicators accompanied by a combination of monitoring hs-CRP / HDL-Cholesterol ratio. ACE-I / ARBs have potential as anti-inflammatory drugs in CKD patients and their use should be considered as a reference for clinical therapy for CKD patients in the future.There are some limitations in this study. In this study, we just used one inflammation marker along with lipid profile and eGFR, using more inflammation markers would better reflect the true state of inflammation in CKD patients, and increasing the number of participants in the study would also make the study better.

Conclusion

This study shown that hs-CRP,HDL-Cholesterol and HDL-Cholesterol/hs-CRP ratiohave significant differences between group, the subjects that consumed ACE-I / ARBs have a lower hs-CRP compared to subject that did not consume ACE-I / ARBs but higher HDL-Cholesterol and HDL-Cholesterol/hs-CRP ratio. For HDL-Cholesterol and HDL-CHolesterol/hs-CRP ratio had a positive correlation with eGFR. This resultmean that HDL-Cholesterol and hs-CRP monitoring very important in CKD patient with ACE-I / ARBs treatment.

Ethical Clearance: This experimental study protocol had been approved by the UniversitasAirlangga Hospital Ethic Committee (Approval Number: 116/

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Conflict of Interest: The authors declare that they have no conflict of interest.

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