ORIGINAL ARTICLE

Correlation between Serum High-Sensitivity C-Reactive Protein Level and Severity of Albuminuria Measured by Urine Albumin-to-Creatinine Ratio in Type 2 Diabetic Patients

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ABSTRACT

Introduction: One of complications in type 2 diabetes mellitus (DM) that require high treatment cost is diabetic kidney disease (DKD), which is characterized by the presence of albuminuria, decrease in glomerular filtration rate, or both. Researches show a positive correlation between type 2 DM and serum high-sensitivity C-reactive protein (hs-CRP) level, a sensitive marker of subclinical inflammation. This study aimed to analyze the correlation between serum hs-CRP level and severity of albuminuria measured by urine albumin-to-creatinine ratio (ACR).

Methods: The study was conducted at the Endocrinology Outpatient Clinic of Dr. Soetomo General Academic Hospital, Surabaya, on June-July 2020.

Results: The study included 50 patients with type 2 DM, consisting of 25 (50%) men and 25 (50%) women, with median age of 58.0 (42-68) years and mean body mass index (BMI) of 21.91 ± 1.310 kg/m^2. Median duration of DM was 12.0 (6-22) years, median HbA1c level was 7.20% **(5.7%-12.3%)**, mean serum creatinine level was 0.83 ± 0.180 mg/dL, and median estimated glomerular filtration rate (eGFR) value was 92.85 (61.6-121.2) mL/minute/1.73 m^2. Median serum hs-CRP level was 1.20 (0.1-4.0) mg/L and median urine ACR value was 49.570 (7.78-426.00) mg/g. Normoalbuminuria was detected in 28% of subjects, microalbuminuria in 66% of subjects, and macroalbuminuria in 6% of subjects. This study showed positive and significant correlation between serum hs-CRP level and severity of albuminuria (r = 0.701; p = <0.001).

Conclusion: There was positive and significant correlation betweeen serum hs-CRP level and severity of albuminuria in type 2 diabetic patients.

Keywords: Serum hs-CRP level; albuminuria; urine ACR; type 2 diabetes mellitus

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INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (DM) have grown significantly throughout the world. One of the most common complications in DM patients is diabetic kidney disease (DKD) (Tuttle et al., 2014). DKD is characterized by the presence of albuminuria, decrease in glomerular filtration rate (GFR), or both. However, currently it is well known that kidney damage in the course of type 2 DM may occur without increased albuminuria. Moreover, the decrease in GFR is not an early indicator of diabetic renal damage (Zylka et al., 2018). There is a need for early detection of albuminuria as a means of evaluating disease progression and target treatment of DKD (Alicic et al., 2017).

Researches showed a positive correlation between type 2 DM and increase in serum high-sensitivity C-reactive protein (hs-CRP) level, a sensitive marker of subclinical inflammation (Jiang et al., 2013; Gupta et al., 2015). Most researches showed that increase in serum hs-CRP level has significant positive correlation with severity of albuminuria (Sabanayagam et al., 2009; Wang et al., 2013), some others showed weak positive correlation (Pojskic et al., 2018), while some others showed no correlation (Jiang et al., 2013). Therefore, this controversy is an issue that still needs to be resolved with research. However, patients with persistent microalbuminuria often develop persistent macroalbuminuria and progress to ESRD (Persson & Rossing, 2018). Early detection of albuminuria is expected to be followed up with earlier intervention so that it can reduce incidence of ESRD in DM.

Some studies have shown correlation between serum hs-CRP and various complications of type 2 DM through chronic low-grade inflammation, insulin resistance, and endothelial dysfunction (Tutuncu et al., 2016; Aryan et al., 2018; Wan et al., 2019). In this study, subclinical inflammation was measured by serum hs-CRP level, while the severity of albuminuria was measured by urine albumin-to-creatinine (ACR) value. This study aimed to analyze the correlation between serum hs-CRP level and severity of albuminuria measured by urine ACR.

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METHODS

This cross-sectional analytic observational study included type 2 diabetic patients who came to The Endocrinology, Metabolism, and Diabetes Outpatient Clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during the period of June to July 2020. Patients of both gender, diagnosed with type 2 DM for more than 5 years, aged less than 70 years, had the results of renal function tests (blood urea nitrogen [BUN] and serum creatinine) of the last 3 months, were included in this study. Patients with current infection status, chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m^2, chronic liver disease, smoking history, alcohol consumption history, obesity, pregnancy, menstruation, malignancy, and current consumption of medicines that affect albuminuria and serum hs-CRP, were excluded from this study. In this study, patients with serum hs-CRP level of >10 mg/L were excluded from analysis because such a high hs-CRP level indicates clinical inflammation, whereas this research studied subclinical inflammation. Patients who found anemia (hemoglobin [Hb] level of <10 g/dL) from complete blood count were excluded because anemia is one of the signs of chronicity of kidney disease which could lead to a bias with the severity of the albuminuria being studied. Besides, in those with anemia the HbA1c examination as one of the clinical profiles of study subjects became inaccurate.

The infection status was obtained from the history and physical examination, namely the presence of fever accompanied by dyspnea, cough and cold, swallowing pain, nausea, vomiting, jaundice, painful urination, or diarrhea. The eGFR calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (KDIGO, 2012). Data of chronic liver disease were obtained from the history and physical examination, namely the presence of jaundice, spider nevi, gynecomastia, axillary hair loss, ascites, palmar erythema, splenomegaly, caput medusa, and history of hematemesis and melena (Miroliaee et al., 2010; Volker et al., 2019). Smoking history was defined as the activity of smoking at least 1 cigarette for at least 1 year or quitting smoking for less than 20 years. Alcohol consumption history was defined as activity of consuming alcohol in the last 12 months. Obesity was defined as body mass index (BMI) of >25 kg/m^2 (Harbuwono et al., 2018; Uemura et al., 2017). Data of malignancy were obtained from anamnesis and physical examination, consisting of malignancy, history of surgery related to malignancy, or history of undergoing chemotherapy.

Medicines that affect albuminuria and serum hs-CRP are angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), statins, fibrates, niacin, vitamin D analogues, and hormonal therapies of estrogen/progesterone (Heerspink et al., 2015; Pearson et al., 2003; Yorulmaz et al., 2006; Sproston et al., 2018). The patients would be excluded if they were taking these medicines for at least 1 month or stopped less than 2 weeks prior to enrollment in this study. The patients receiving statins medication or antihypertensive drugs other than ACE inhibitors and ARBs were not excluded.

Patients who fulfilled eligibility criteria were then interviewed for current symptoms and past medical history. Laboratory examination data of the last 3 months were collected from medical record, which included the data of complete blood count (hemoglobin [Hb], white blood cell, platelet), glycated hemoglobin (HbA1c), fasting blood glucose, 2-hour postprandial blood glucose, lipid profile (total cholesterol, trigelyceride, low-density-lipoprotein [LDL], high-density-lipoprotein [HDL]), aspartate transaminase (AST), alanine transaminase (ALT), serum albumin, BUN, serum creatinine, and urinalysis. After history taking, physical examination was performed to collect data of body weight, body height, BMI, blood pressure, heart rate, respiratory rate, and temperature.

The patients were then asked to collect a sample of 10 mL of mid-stream urine in the container. The patients had 5 mL of venous blood sample taken from the median cubital vein or the basilic vein. Urine and blood samples were then sent to Balai Besar Laboratorium Kesehatan Surabaya, a health-laboratory belonging to the Ministry of Health of the Republic of Indonesia in Surabaya. Blood samples were analyzed using Prestige Nefleton 24-I® Specific Protein Analyzer with enzymatic method to obtain data of serum hs-CRP level. Patients with serum hs-CRP level >10 mg/L were excluded from analysis. Urine samples were analyzed using Roche/Hitachi® Cobas C 501 Analyzer with immunoturbidimetry method to obtain data of urine ACR. Data of urine ACR were used to categorized severity of albuminuria into 3 categories: normoalbuminuria (urine ACR of <30 mg/g), microalbuminuria (urine ACR of 30-300 mg/g), and macroalbuminuria (urine ACR of >300 mg/g).

All data collected were then analyzed using SPSS 23.0® Demographic and clinical characteristics were presented descriptively. Normality test for numeric data was performed with Saphiro-Wilk test. Categorical data were expressed as frequency and percentage. Normally distributed numerical data were expressed as mean and standard deviation, while non-normally distributed numerical data were expressed as median and range. Correlation between serum hs-CRP and severity of albuminuria was analyzed using Spearman's rank correlation test. Significance level of $p<0.05$ and confidence interval of 95% were used.

RESULTS

Based on inclusion and exclusion criteria, a total of 51 subjects were selected to participate in this study. One subject with serum hs-CRP level of >10 mg/L was excluded from the analysis, so that the data analysis was performed on 50 subjects.

Study subjects were 25 (50%) males and 25 (50%) females. The median age of the patients was 58.0 years old, with an age range of 42-68 years old. There were 27 (54%) subjects who received insulin therapy or a combination of insulin and oral anti-diabetes drug, while the rest only received oral anti-diabetes drugs. Of the 50 subjects, 28 (56%) subjects had hypertension, either without drugs or with drugs other than ACE inhibitors or ARBs. The mean BMI of study subjects was 21.91 kg/m^2, with a standard deviation of 1.310 kg/ m^2. Based on the Mann-Whitney test, there was a significant difference in BMI between male and female groups. General characteristics and clinical profile of study subjects can be seen in Table 1.

Clinical profiles of study subjects included data on Hb levels, fasting blood glucose, two-hour post-prandial blood glucose, HbA1c, AST, ALT, lipid profiles (total cholesterol, triglycerides, LDL, HDL), serum albumin, BUN, serum creatinine, and eGFR. Based on the Kruskal-Wallis test, the variables of age, duration of DM, and statin medication differed significantly between the normoalbuminuria, microalbuminuria, and macroalbuminuria groups.

Normoalbuminuria was defined as the urine ACR level of <30 mg/g, microalbuminuria as the urine ACR level of 30-300 mg/g, and macroalbuminuria as the urine ACR level of >300 mg/g. The age and duration of DM from the microalbuminuria group were higher than the other two groups. Other variables did not differ significantly between groups of severity of albuminuria. The details can be seen in Table 2.

Table 1. General characteristics of study subjects by groups of gender.

Variable	Descriptive Analysis			p Value*
	Total Subjects	Male Subjects	Female Subjects	
Sex	50 (100%)	25 (50%)	25 (50%)	-
Age (years old)	58.0 (42-68)	59.0 (48-68)	56.0 (42-67)	0.109
Duration of DM (years)	12.0 (6-22)	13.0 (6-22)	10.0 (6-20)	0.100
Insulin Medication	27 (54%)	13 (26%)	14 (28%)	0.779
Hypertension	28 (56%)	15 (30%)	13 (26%)	0.573
Statins Medication	45 (90%)	24 (48%)	21 (42%)	0.162
BMI (kg/m^2)	21.91 ± 1,310	22.49 ± 1,026	21.33 ± 1,324	0.002

*) Mann-Whitney test. Differentiation between groups of gender is significant when the p value is <0.05. DM = diabetes mellitus; BMI = body mass index.

The average Hb level of the study subjects was 12.152 g/dL, with a standard deviation of 1.022 g/dL. Fasting blood glucose varied from 82 mg/dL to 280 mg/dL, with median fasting blood glucose of 127.00 mg/dL. The median value of two-hour post-prandial blood glucose was 178.50 mg/dL. The lowest HbA1c level in the study subjects was 5.7% and the highest was 12.3%, with a median value of 7.20%. Total cholesterol levels had a median value of 165.50 mg/dL. The median value of triglyceride levels was 113.50 mg/dL. The average LDL level was 78.46 mg/dL with a standard deviation of 16.125 mg/dL. The median HDL value was 48.00 mg/dL. The serum albumin level of the study subjects had a mean value of 4.21 mg/dL, with a standard deviation of 0.364 mg/dL. The average value of BUN levels was 17.30 mg/dL, with a standard deviation of 2.675 mg/dL. The mean serum creatinine level of the study subjects was 0.83 mg/dL, with a standard deviation of 0.18 mg/dL. The eGFR calculated using the CKD-EPI equation showed a median value of 92.85 mL/minute/1.73 m^2, with the lowest value of 61.6 and the highest value of 121.2 mL/minute/1.73 m^2.

In this study, data of serum hs-CRP levels were not normally distributed based on the Shapiro-Wilk normality test (p=0.002). The median level of serum hs-CRP was 1.20 mg/L, with the lowest value of 0.1 mg/L and the highest value of 4.0 mg/L.

The profile of severity of albuminuria can be seen in Table 3. Correlation between Serum hs-CRP Level and Severity of Albuminuria Measured by Urine ACR. Data of serum hs-CRP levels on ratio scale and severity of albuminuria on ordinal scale were analyzed for the relationship using the Spearman rank correlation test. The analysis showed the correlation coefficient (r) of 0.701 with p<0.001.

DISCUSSION

In our study, there were 50 subjects who fulfilled the requirements for analysis, with a proportional comparison of the both gender, 25 male subjects and 25 female subjects. Analysis with the Spearman rank correlation test found a

Table 2 General characteristics and clinical profile of study subjects by group of severity of albuminuria*

Variable	Descriptive Analysis				p Value**
	Total Subjects (n=50)	Normo-albuminuria (n=14)	Micro-albuminuria (n=33)	Macro-albuminuria (n=3)	
Sex: Male	25 (50%)	7 (14%)	16 (32%)	2 (4%)	0.837
Age (years old)	58.0 (42-68)	52.0 (42-59)	60.0 (48-68)	56.00 (53-66)	0.001
Duration of DM (years)	12.0 (6-22)	8.50 (6-13)	14.0 (6-20)	10.00 (8-22)	0.004
Insulin Medication	27 (54%)	5 (10%)	19 (38%)	3 (6%)	0.104
Hypertension	28 (56%)	11 (22%)	15 (30%)	2 (4%)	0.109
Statins Medication	45 (90%)	10 (20%)	32 (64%)	3 (6%)	0.026
BMI (kg/m^2)	21.91 ± 1.310	22.30 ± 1.465	21.69 ± 1.260	22.54 ± f0.497	0.162
Hb (g/dL)	12.152 ± 1.022	12.471 ± 1.100	12.097 ± 0.879	11.267 ± 1.848	0.259
Fasting Blood Glucose (mg/dL)	127.00 (82-280)	124.50 (94-280)	130.00 (82-252)	105.00 (91-136)	0.388
Two-hour Post-prandial Blood Glucose (mg/dL)	178.50 (105-441)	178.50 (117-441)	182.00 (105-403)	168.00 (165-188)	0.895
HbA1c (%)	7.200 (5.7-12.3)	7.850 (5.9-12.3)	7.200 (5.7-12.0)	6.900 (6.7-7.6)	0.517
AST (U/L)	17.38 ± 3.741	17.43 ± 4.380	17.36 ± 3.613	17.33 ± 3.055	0.940
ALT (U/L)	18.34 ± 2.685	17.57 ± 2.980	18.67 ± 2.582	18.33 ± 2.517	0.691
Total Cholesterol (mg/dL)	165.50 (113-197)	166.00 (113-197)	160.00 (114-194)	181.00 (174-196)	0.165
Triglycerides (mg/dL)	113.50 (57-161)	114.50 (57-155)	112.00 (57-148)	131.00 (113-161)	0.282
LDL (mg/dL)	78.46 ± 16.125	74.57 ± 16.755	78.67 ± 15.216	94.33 ± 18.877	0.306
HDL (mg/dL)	48.00 (28-85)	44.00 (28-85)	50.00 (29-85)	45.00 (41-59)	0.648
Serum Albumin (mg/dL)	4.21 ± 0.364	4.17 ± 0.430	4.25 ± 0.3447	4.03 ± 0.231	0.405
BUN (mg/dL)	17.30 ± 2.675	17.07 ± 2.786	17.15 ± 2.502	20.00 ± 3.606	0.315
Serum Creatinine (mg/dL)	0.83 ± 0.180	0.80 ± 0.203	0.83 ± 0.156	1.02 ± 0.285	0.448
eGFR (mL/minute/1,73 m^2)	92.85 (61.6-121.2)	100.10 (63.1-121.2)	92.10 (61.6-108.9)	62.30 (61.9-96.7)	0.051

Table 3 The profile of severity of albuminuria in study subjects

Variable	Frequency (%)	Median (Min-Max Range) of Urine ACR
Severity of Albuminuria	50 (100)	
Normoalbuminuria (urine ACR of <30 mg/g)	14 (28)	16.56 (7.78-29.09) mg/g
Microalbuminuria (urine ACR of 30-300 mg/g)	33 (66)	82.22 (31.88-285.38) mg/g
Macroalbuminuria (urine ACR of >300 mg/g)	3 (6)	410.00 (346.00-426.00) mg/g

significant positive correlation between serum hs-CRP levels and severity of albuminuria in our study with a correlation coefficient (r) of 0.701 and p<0.001. Thus, in our study it was found that serum hs-CRP levels and severity of albuminuria were positively and significantly correlated.

The significant and positive correlation between serum hs-CRP levels and severity of albuminuria in our study was in accordance with many other studies in various countries. A research in India about correlation between hs-CRP and urine ACR in diabetic patients with and without DKD showed that the mean hs-CRP level in microalbuminuria group (1.705 mg/L) was significantly lower than in macroalbuminuria group (8.423 mg/L) with p<0.001 (Chauhan et al., 2017). A research in Singapore about CRP and increased albuminuria in a multiethnic Asian population indicated that the prevalence of increased albuminuria increased with increasing CRP category. Compared to the group with CRP levels of <1 mg/L, the group with CRP levels of 1-3 mg/L had an odds ratio of 1.33 (1.11-1.60) and the group with CRP levels of >3 mg/L had an odds ratio of 1.60 (1.30-1.96) with p<0.0001 (Sabanayagam et al., 2009). A study in China measuring pro-inflammatory cytokine levels in type 2 diabetic patients found that the mean serum hs-CRP level in the control (non-diabetics) group was 1.03 ± 0.94 mg/L, in the normoalbuminuria group was 2.41 ± 1.07 mg/L, in the microalbuminuria group was 3.95 ± 1.18 mg/L, and in the macroalbuminuria group was 4.51 ± 1.89 mg/L. The levels of serum hs-CRP between these groups were significantly different (Chen et al., 2013). A study in Bosnia-Herzegovina on the effect of CRP on severity of albuminuria in type 2 diabetic patients included patients with normoalbuminuria (n = 40) and microalbuminuria (n=29). Albuminuria in this study was measured using a 24-hour urine collection. This study obtained a significant positive correlation between hs-CRP and albuminuria (r=0.286; p=0.017). Each unit (mg/L) increase in hs-CRP level was associated with an 11.5% increase in the odds ratio for microalbuminuria (odds ratio = 1.115; p=0.025) (Pojskic et al., 2018).

Factors that influence urine ACR in Aboriginal ethnic populations in rural Australia were studied. This research enrolled 755 subjects aged 18-76 years old in a chronic disease screening program and showed a significant association between hs-CRP and severity of albuminuria only in the microalbuminuria group with odds ratio of 1.33 (p=0.007); while in the macroalbuminuria group there was no significant correlation (odds ratio=1.05; p=0.713). In this study, subjects with obesity were not excluded. Serum hs-CRP level in this study was largely influenced by individual factors such as smoking habits, high blood pressure, obesity, or lack of physical activity (Wang et al., 2013). A significant positive correlation (p=<0.0001) between serum hs-CRP levels and albumin excretion rate was also found in a study in India. Measurement of albumin excretion rate in this study was carried out with 24-hour urine collection (Aslam & Chandrasekhara, 2016). Compared with male subjects with normal hs-CRP levels, male subjects with increased hs-CRP levels were 1.97 times more likely (95% CI: 1.64-2.35, p <0.001) to experience microalbuminuria. Microalbuminuria was also more common in smokers with high hs-CRP than in smokers with normal hs-CRP. Similar finding was also found in obese subjects with high hs-CRP compared to non-obese subjects with normal hs-CRP (Yang et al., 2017). A research in Singapore showed that people with CRP levels of >3 mg/L were 1.6 times more likely to develop micro- and macroalbuminuria than people with CRP levels of <1 mg/L (odds ratio=1.60; 95% CI: 1.26- 2.04; p=0.0001) (Sabanayagam et al., 2009). A cross-sectional study in India regarding the effect of glycemic control on albuminuria and CRP in type 2 DM patients showed that the correlation between albuminuria and CRP levels was positive and significant (p<0.01) only in patients with poor glycemic control. Albuminuria in this study was measured with a 24-hour urine collection. Compared to patients with well-controlled blood glucose, patients with poor glycemic control were twice as likely to experience albuminuria with the same CRP level. In patients with good glycemic control, this correlation was not significant (p=0.065) (Bhowmick et al., 2007).

A research in China regarding the relationship between serum hs-CRP and urine microglobulin in type 2 diabetic patients, showed that there was a positive correlation between serum hs-CRP and urine ACR, but it was not statistically significant. Patients with urine ACR of ≤30 mg/g had median hs-CRP value of 1.29 (0.50-3.19) mg/L, while patients with urine ACR of >30 mg/g had slightly higher hsCRP levels of 1.32 (0.54–3.30) mg/L, and this difference was not statistically significant (p=0.566). Meanwhile, the group with low hsCRP (≤3 mg/L) had urine ACR value of 15.03 (7.20-58.83) mg/g, and the group with high hsCRP (>3 mg/L) had urine ACR value of 19.47 (8.19-57-79) mg/g, and this difference was also not statistically significant (p=0.371) (Wan et al., 2019). A different result was shown by a research in China. It was a cross-sectional study about the association between metabolic syndrome, hs-CRP, and albuminuria. This research enrolled 4200 subjects over 30 years of age, with exclusion criteria of macroalbuminuria (urine ACR of >300 mg/g) and serum hs-CRP level of >10 mg/L (clinical inflammation/infection). This research showed that CRP was not correlated with microalbuminuria, but multivariate analysis of a combination of high CRP and metabolic syndrome increased the risk of microalbuminuria (Jiang et al., 2013). Some of the differences in our study compared to previous studies might be caused by several factors, including the small number of samples in our study, differences in inclusion and exclusion criteria, as well as ethnicity difference between Indonesian and other countries' population.

Previous studies showed that serum hs-CRP level, a widely used marker of chronic subclinical inflammation, was significantly and positively correlated with albuminuria through multiple pathways in the metabolic syndrome (Sabanayagam et al., 2009). There is an association between chronic inflammation and albuminuria in patients with or without DM. Increase in inflammatory markers can be a result of the atherosclerosis process in patients with increased albuminuria, either in diabetic patients or in the general population. When the atherosclerotic process occurs in the heart, it will increase the cardiovascular morbidity and mortality rates, while if it occurs in the kidneys it can cause a decrease in glomerular function and affect the development of albuminuria (Pojskic et al., 2018). Subclinical inflammation may cause direct injury to the renal glomerulus. Increased CRP could result in vascular endothelial dysfunction by decreasing nitric oxide production and inhibiting endothelial nitric oxide synthase, ultimately resulting in platelet activation and vascular inflammation. In addition, elevated CRP also promotes overproduction of pro-inflammatory cytokines, then leads to glomerular mesangial cell proliferation and increases in renal vascular permeability, eventually resulting in albuminuria. There is a close relationship between inflammation and activation of the renin-angiotensin system and oxidative stress, leading to glomerular hyperfiltration and albuminuria (Yang et al., 2017).

Our study had several limitations. There were some confounding factors such as HbA1c level, difference in duration of DM, insulin medication, hypertension, dyslipidemia, and statin medication, that might have an effect on serum hs-CRP level and severity of albuminuria. In our study, infection was only generally confirmed through anamnesis and physical examination. However, to reduce bias, patients with serum hs-CRP levels of >10 mg/L were excluded from the study.

CONCLUSION

Our study showed a positive and significant correlation between serum hs-CRP level and severity of albuminuria. An increase in serum hs-CRP level is expected to raise awareness of an increase in severity of albuminuria, which is one of the early markers of DKD. However, it remains to be elucidated that other factors may have effects on serum hs-CRP level and severity of albuminuria, and further prospective cohort studies are needed to clarify these relationships

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding the publication of this paper.

ETHICS CONSIDERATION

The study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital in Surabaya with Ethical Clearance No. 0016/KEPK/VI/2020 issued on June 22, 2020.

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AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

REFERENCES

Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical Journal of American Society of Nephrology. 13, 2017, pp. 1-14.

Aryan Z, Ghajar A, Faghihi-Kashani S, Afarideh M, Nakhjavani M, Esteghamati A. Baseline High-Sensitivity C-Reactive Protein Predicts Macrovascular and Microvascular Complications of Type 2 Diabetes: A Population-Based Study. Annals of Nutrition and Metabolism. 2018, pp. 287-95.

Aslam M, Chandrasekhara P. Correlation of Fibrinogen and hs-CRP with Microvascular Complications of Type 2 Diabetes Mellitus. International Journal of Health Sciences and Research. 6, 2016, Vol. 5, pp. 25-32.

Bhowmick K, Kutty AVM, Shetty HV. Glycemic Control Modifies the Association between Microalbuminuria and C-Reactive Protein in Type 2 Diabetes Mellitus. Indian Journal of Clinical Biochemistry. 22, 2007, Vol. 2, pp. 53-9.

Chauhan R, Singh R, Lal R. Correlation of hs-CRP with Urinary Albumin Creatinin Ratio (UACR) in Patients of Diabetes with and without Nephropathy. IOSR Journal of Dental and Medical Sciences. 16, 2017, Vol. 4, pp. 51-4.

Chen F, Wang J, Liu X, Ma X, Zhang X, Huang T, Ma D, Wang Q. Levels of Inflammatory Cytokines in Type 2 Diabetes Patients with Different Urinary Albumin Excretion Rates and Their Correlation with Clinical Variables. Journal of Diabetes Research. 2013, pp. 1-6.

Gupta A, Kumar D, Rajvanshi S, Kumar A, Arya TVS. To Study the Association of High Sensitivity C-Reactive Protein with Newly Diagnosed DM Type 2. Journal of Indian Academy of Clinical Medicine. 16, 2015, Vol. 1, pp. 12-8.

Harbuwono DS, Pramono LA, Yunir E, Subekti I. Obesity and Central Obesity in Indonesia: Evidence from A National Health Survey. Medical Journal of Indonesia. 27, 2018, pp. 114-20.

Heerspink HJL, Kropelin TF, Hoekman J, de Zeeuw D. Drug-Induced Reduction in Albuminuria is Associated with Subsequent Renoprotection: A Meta-Analysis. Journal of American Society of Nephrology. 26, 2015, Vol. 8, pp. 2055-64.

Jiang L, Huang W, Liang Y, Wang F, Duan X, Yang X, Wen J, Wang N. Metabolic Syndrome, C-Reactive Protein and Microalbuminuria in a Rural Chinese Population: A Cross-Sectional Study. BMC Nephrology. 14, 2013, p. 118.

KDIGO (Kidney Disease Improving Global Outcomes). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Official Journal of the International Society of Nephrology. 3, 2012, Vol. 1, pp. 1-150.

Miroliaee A, Nasiri-Toosi M, Khalilzadeh O, Esteghamati A, Abdollahi A, Mazloumi M. Disturbances of Parathyroid Hormone-Vitamin D Axis in Non-Cholestatic Chronic Liver Disease: A Cross-Sectional Study. Hepatology International. 4, 2010, pp. 634-40.

Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, Fadl YY, Fortman SP, Hong Y, Myers GL, Rifai N, Smith Jr SC, Taubert K, Tracy RP, Vinicor F. Markers of Inflammation and Cardiovascular Disease. Circulation. 107, 2003, pp. 499-511.

Persson F, Rossing P. Diagnosis of Diabetic Kidney Disease: State of the Art and Future Perspective. Kidney International Supplements. 8, 2018, pp. 2-7.

Pojskic L, Hasic S, Tahto E, Arnautovic-Torlak V, Pojskic B. Influence of C-Reactive Protein on the Occurrence and Assessing of Albuminuria Severity in Diabetics. Medicinski Glasnik (Zenica). 15, 2018, Vol. 1, pp. 1-7.

Sabanayagam C, Lee J, Shankar A, Lim SC, Wong TY, Tai ES. C-Reactive Protein and Microalbuminuria in a Multi-ethnic Asian Population. Nephrology Dialysis Transplantation. 25, 2009, pp. 1167-72.

Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Frontiers in Immunology. 9, 2018, p. 754.

Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE,Whaley-Connell AT, Molitch ME. Diabetic Kidney Disease: A

Report from an ADA Consensus Conference. Diabetes Care. 37, 2014, pp. 2864-83.

Tutuncu Y, Satman I, Celik S, Dinccag N, Karsidag K, Telci A, Genc S, Issever H, Tuomilehto J, Omer B. A Comparison of hs-CRP Levels in New Diabetes Groups Diagnosed Based on FPG, 2-hPG, or HbA1c Criteria. Journal of Diabetes Research. 2016, pp. 1-9.

Uemura H, Katsuura-Kamano S, Yamaguchi M, Bahari T, Ishizu M, Fujioka M, Arisawa K. Relationships of Serum High-Sensitivity C-Reactive Protein and Body Size with Insulin Resistance in a Japanese Cohort. PLoS ONE. 12, 2017, Vol. 6, p. e0178672.

Volker D, Grunhage F, Wagenpfeil S, Lammert F, Stokes CS. Serum 25-Hydroxyvitamin D Levels and Mortality Risk in Patients with Liver Cirrhosis: A Protocol for A Systemic Review and Meta-analysis of Observational Studies. Systematic Reviews. 8, 2019, Vol. 73, pp. 1-6.

Wan X, Zhang L, Gu H, Wang S, Liu X. The Association of Serum hs-CRP and Urinary Alpha1-Microglobulin in Patients with Type 2 Diabetes Mellitus. BioMed Research International. 2019, pp. 1-10.

Wang Z, Hoy WE, Wang Z. The Correlates of Urinary Albumin to Creatinine Ratio (ACR) in a High Risk Australian Aboriginal Community. BMC Nephrology. 14, 2013, p. 176.

Yang S, Liu J, Yi B, Mao J, Zhang X, Liu Y, Lei D, Gui M, Zhang H. Elevated High Sensitivity C-Reactive Protein Increases the Risk of Microalbuminuria in Subjects with Cardiovascular Disease Risk Factors. Therapeutic Apheresis and Dialysis. 2017, pp. 1-8.

Yorulmaz E, Uzunlulu M, Alpaslan B, Oguz A. hs-CRP for Cardiovascular Risk in Diabetes: Problems in Daily Practice. Turkish Journal of Endocrinology and Metabolism. 2, 2006, pp. 35-38.

Zylka A, Dumnicka P, Kusnierz-Cabala B, Gala-Bladzinska A, Ceranowicz P, Kucharz J, Zabek-Adamska A, Maziarz B, Drozdz R, Kuzniewski M. Markers of Glomerular and Tubular Damage in the Early Stage of Kidney Disease in Type 2 Diabetic Patients. Mediators of Inflammation. 2018, pp. 1-12.