



Published by DiscoverSys

# The difference of nitric oxide (NO) and serum creatinine (SC) levels in hemodialyzed and non-hemodialyzed chronic kidney disease patients at H. Adam Malik Hospital, Medan, Indonesia



CrossMark

Ruslan Dame Hotmauli Marpaung,<sup>1\*</sup> Ratna Akbari Ganie,<sup>1</sup> Alwi Thamrin Nasution<sup>2</sup>

## ABSTRACT

**Background:** Chronic Kidney Disease is structural or functional abnormalities of the kidney that last more than 3 months, with or without decreased glomerular filtration rate (GFR) which can be exacerbated by reduced production of Nitric Oxide (NO) or increased serum creatinine level. Hemodialysis is a removal process of solute from the circulation of patients with an impaired renal function to the fluid dialysate by diffusion process through the semi-permeable membrane. This study aims to determine the difference of the Nitric Oxide (NO) and serum creatinine (SC) levels between regular hemodialysis and non-hemodialysis CKD patients.

**Methods:** A cross-sectional study was conducted at Outpatient and Inpatient Section of Nephrology Division, Internal Medicine Department, H. Adam Malik Hospital, Medan during July-August 2017 among 27 respondents who undergone regular Hemodialisa (HD) and

27 respondents in non-Hemodialisa (non-HD) group. The patients that fulfill the inclusion criteria of the study were enrolled. Nitric Oxide examination was carried out by using Chemwell analyzer with a double-antibody sandwich method using Enzyme method -Linked Immunosorbent Assay (ELISA).

**Results:** There was no significant difference of NO-levels between HD groups ( $1476.14 \pm 1431.1 \mu\text{M}$ ) with non HD ( $1123.06 \pm 1150.83 \mu\text{M}$ ) ( $P = 0.250$ ). However, there was a significant difference of creatinine level between HD groups ( $11.8 \pm 3.26 \text{ pg/mL}$ ) with a non-HD group ( $5.71 \pm 5.03 \text{ pg/mL}$ ) ( $P = 0.000$ ).

**Conclusion:** No significant difference of NO levels were found in HD patients and non-HD CKD patients. However, a current study exhibits a significant relationship between SC levels of CKD patients between both groups.

**Keywords:** CKD, Hemodialysis, Nitric Oxide

**Cite This Article:** Marpaung, R.D.H., Ganie, R.A., Nasution, A.T. 2019. The difference of nitric oxide (NO) and serum creatinine (SC) levels in hemodialyzed and non-hemodialyzed chronic kidney disease patients at H. Adam Malik Hospital, Medan, Indonesia. *IJBS* 13(1): 22-25. DOI:10.15562/ijbs.v13i1.173

<sup>1</sup>Department of Clinical Pathology, Faculty of Medicine, University of Sumatera Utara, H.Adam Malik Hospital Medan, Indonesia

<sup>2</sup>Department of Internal Medicine, Faculty of Medicine, University of Sumatera Utara, H.Adam Malik Hospital Medan, Indonesia

\*Correspondence to:

Ruslan Dame Hotmauli Marpaung; Department of Clinical Pathology, Faculty of Medicine, University of Sumatera Utara, H.Adam Malik Hospital Medan, Indonesia; [m\\_dame73@yahoo.com](mailto:m_dame73@yahoo.com)

Received: 2018-11-06

Accepted: 2019-03-05

Published: 2019-06-01

## INTRODUCTION

One of the chronic diseases that affect many today is Chronic Kidney Disease (CKD) where the disease is a public health problem worldwide. *End Stage Renal Disease* (ESRD) of CKD is a progressive and irreversible damaged renal function where the body is not able to maintain metabolism and failed to maintain the balance of fluid and electrolytes resulting in an increase in urea. This stage is characterized by azotemia, uremia, and uremic syndrome.<sup>1</sup>

The medical record data in Hemodialysis Installation General Hospital Adam Malik recorded 1,716 people with terminal renal failure (GGT) who underwent HD from January-December 2016, and as many as 143 patients who underwent regular HD today. The management of patients with CKD at this stage are dialysis, and kidney transplant Hemodialysis (HD) is the most frequent therapy by patients with chronic kidney disease worldwide.<sup>2</sup> In addition, patients with CKD have a higher risk of

suffering from cardiovascular disease than kidney failure.<sup>2</sup>

From the previous data, it seems that CKD was a disease which has a high morbidity and mortality whereas could be worsened by several factors, including the production of *Nitric Oxide (NO)* in CKD and contributed to the increased risk prevalence of cardiovascular disease.<sup>3</sup>

The cardiovascular risk factors and endothelial dysfunction Oxidized Low-Density Lipoprotein (oxidized LDL), angiotensin II hypertension, smoking, homocysteine, diabetes, and hypernatremia can stimulate Oxidase Nicotinamide adenine dinucleotide phosphate (NADPH oxidase) in the mitochondria and this enzyme will express oxidative stress properties. Oxidative stress will lead to the endothelial dysfunction that can increase the progression of atherosclerosis.<sup>3</sup>

The availability of NO on impaired renal dysfunction is related to the increased levels of

ADMA.<sup>4</sup> One hypothesis suggest that ADMA, an endogenous *inhibitor-Synthase Nitric Oxide*, was involved in mediating Heart Disease.<sup>4</sup> ADMA also work as an independent predictor of endothelial dysfunction and associated with poor prognosis in hemodialysis patients.<sup>4</sup>

Several Indonesian education centers have studied the role of NO in CKD patients. In addition, the role of serum creatinine levels in predicting kidney damage has also been extensively studied. However, in North Sumatra, the assessment of NO towards endothelial damage in patients with terminal renal failure is still lack of data. So that this study aims is to know the difference of Nitric Oxide (NO) and Serum Creatinine (SC) levels between regular hemodialysis and non-hemodialysis CKD patients.

## METHODS

A cross sectional analytic study was conducted in collaboration with the Clinical Pathology Department, Polyclinic Outpatient and Inpatient Section, Nephrology Division, Faculty of Medicine Sumatera Utara/Dr. H. Adam Malik Hospital, Medan from May-August 2017 among 54 patients. The inclusion criteria used in this study included both genders (males and females), patients with CKD who underwent HD or non-HD, age  $\geq 18$  years, already in regular HD  $\geq 3$  months, as well as Stage III-IV CKD Patients. Non-Hemodialysis patients were confirmed by physical examination, laboratory assessment, and evaluation of glomerular filtration rate. Prior the study, the informed consent form was given and assigned by the patients. Besides the inclusion criteria that have been mentioned above, the exclusion criteria used in this study was CKD patients with heart disease, malignancy, and infection.

Laboratory evaluation was carried out to determine the NO and SC levels among CKD patients

in both groups. The serum samples of patients were used for NO and SC examination. NO was evaluated by *Chemwell analyzer* with the principle of *double-antibody sandwich* using *Enzyme-Linked Immunosorbent Assay (ELISA)* and calculated in  $\mu\text{M}$ . However, SC levels were determined by using clinical hematology assessment which calculated in  $\text{pg/mL}$ .

Following laboratory evaluation, data were analyzed descriptively and analytically. Statistical analysis was done using program SPSS version 16. Based on the normality test using Kolmogorov-Smirnov, data was found not normally distributed. The baseline characteristic of respondents were presented in a Table. Mann-Whitney test was used to determine the comparison of NO and SC levels in regular hemodialysis and non-hemodialysis. Test values were considered significant if the p-value is less than 0.05

## RESULTS

### Baseline characteristic of respondents

This study involved 54 patients with CKD from December 2016 to May 2017. Of the 54 patients, 27 patients were on regular HD and 27 patients were non-HD. The characteristics of respondents were depicted in Table 1.

From table 1, most of the respondents were females (39 people), of which 27 HD and 12 non-HD. The *Chi-Square* test was conducted where the p-value found 0.000 which indicate a significant difference between the two genders in HD and non-HD patients.

The average age of the HD group was ( $49.03 \pm 13.75$  years old), while the non-HD was ( $55.51 \pm 12.05$  years old) with  $P = 0.071$ . But, there was no statistically significant in hemoglobin levels of HD ( $9.35 \pm 1.37$  g/dL) and non-HD ( $9.39 \pm 2.58$  g/dL) ( $P\text{-value} = 0.937$ ).

**Table 1** Baseline Characteristics of Respondents

Characteristics	HD group		Non-HD group		P-values
	N (%)	mean $\pm$ SD	N (%)	mean $\pm$ SD	
<b>Gender</b>					
Men	0 (0)		15 (100)		0,000*
Women	27 (69.23)		12 (30.77)		
<b>Age (years)</b>		49.03 $\pm$ 13.75		55.51 $\pm$ 12.05	0.071
<b>Hemoglobin (g/dL)</b>		9.35 $\pm$ 1.37		9.39 $\pm$ 2.58	0.937
<b>Creatinine (pg/mL)</b>		11.8 $\pm$ 3.26		5.71 $\pm$ 5.03	0.000
<b>Urea (mg/dL)</b>		132.22 $\pm$ 42.31		145.44 $\pm$ 87.65	0.665
<b>Nitric Oxide (<math>\mu\text{M}</math>)</b>		1,476.14 $\pm$ 1,431.1		1,123.06 $\pm$ 1,150.83	0.250

\*) Statistically significant if P-value less than 0.05; SD = Standard Deviation.

### Assessment of Serum Creatinine, Nitric Oxide, and Urea Levels

Table 1 also suggests a significant difference in creatinine levels between HD ( $11.8 \pm 3.26$  pg/mL) and Non-HD ( $5.71 \pm 5.03$  pg/mL) ( $p$ -value = 0.000). On the other hand, the urea had no significant difference between HD ( $132.22 \pm 42.31$  mg/dL) and non-HD ( $145.44 \pm 87.65$  mg/dL) ( $p$ -value = 0.665).

In addition, based on Table 1 above, it appears there was no significant difference in NO levels between the HD group ( $1476.14 \pm 1431.1$   $\mu$ M) and non-HD ( $1123.06 \pm 1150.83$   $\mu$ M) ( $p$ -value = 0.250).

## DISCUSSION

In this study CKD generally was found mostly in female and all men did not undergo HD. There was a slight difference from the data in Asia, which stated that the prevalence of CKD in men (0.3%), slightly higher than in women (0.2%).<sup>5</sup> For the number of patients who underwent HD is in accordance to the IRR data in 2015 where more women experienced HD as compared to men.<sup>6</sup>

Research on the lifestyle and habits of patients with renal impairment suggested that men mostly did not adhere to treatment and tended to refuse HD before falling to the terminal stage and hemodialysis is required.<sup>7</sup> More female patients underwent HD due to the high prevalence of diabetic nephropathy in women which is the primary cause of CKD.<sup>7</sup>

In this study, no significant difference was found between the average value of Hb levels in the HD and non-HD ( $P = 0.937$ ). This result is consistent with a study conducted by Meyer C et al in 2010 where the Hb concentration was not affected by the HD process ( $114 \pm 15$  g/L vs.  $115 \pm 15$  g/L;  $P = 0.8$ ), but HD could affect the increase of cell-free hemoglobin levels significantly compared to the baseline ( $196 \pm 43$  mg/L vs.  $285 \pm 109$  mg/L;  $P = 0.01$ ).<sup>8</sup>

The urea levels in this study showed no statistically significant difference between HD and non-HD groups ( $P = 0.665$ ). Urea levels were not different and was probably due to the routine treatment in the polyclinic of Nephrology, SMF Medicine Dr. Haji Adam Malik to the severity of disease (stage), which almost all of the patients were in the same stage (stage III-IV) and the blood samples for urea examination were drawn before the patients underwent HD.

In contrast to the urea levels, serum creatinine levels of the patients were significantly different between the groups of HD compared with non HD groups ( $P=0.000$ ). It appears that the creatinine levels were much higher in the HD group compared to the non HD. This corresponds to the study conducted by Nisha R et al whereas the indications

of dialysis therapy were conducted when serum creatinine levels increase  $>10\%$  or  $>90$  mmol/L.<sup>9</sup> The creatinine level alone indicated that the level of kidney damage was more severe in the HD group compared to the non-HD.<sup>9</sup>

Besides urea and serum creatinine evaluation, this study found no statistically significant difference between the levels of NO in HD group compared with non-HD group ( $P = 0.250$ ). Ghobrial EE et al in 2013 found the same thing. 23 children with regular HD were compared to the control group and no significant difference was found in the levels of NO in both groups ( $6.76 \pm 0.64$  pg/mL vs.  $6.34 \pm 1.50$  pg/mL;  $P = 0.77$ ).<sup>10</sup> However, different study conducted by Meenakshi SR in 2013 found that the NO levels tended to be increased in maintenance HD (MHD).<sup>11</sup>

The not-significant NO levels in this study may be caused by comparing 2 groups of patients that were already diagnosed with CKD concurrently. This could be the reason why the NO levels were not significantly different between HD and non-HD CKD patients (separated according to the therapy) although it is known that HD could eliminate NO that was supposedly eliminated by healthy kidneys.

## CONCLUSIONS

In studies in not found significant differences in the levels of urea among patients with CKD with HD and non HD. found a significant difference in the levels of creatinine among CKD patients with HD and non HD. and not found significant difference of NO levels among patients with CKD with HD and non HD.

## ETHICAL CLEARANCE

Ethical approval had been conducted by Ethics of Committee at University of Sumatera Utara.

## CONFLICT OF INTEREST

The authors declare there is no competing interest regarding manuscript.

## FUNDING

The authors are responsible for author's funding without any involvement of any grant, scholarship, or any other resource of funding.

## AUTHOR CONTRIBUTION

All authors are responsible as contributor regarding the content of manuscript.

## REFERENCES

1. Gaweda AE. Markers of iron status in chronic kidney disease. *Hemodial Int.* 2017; 21 Suppl 1:S21-S27
2. Guajardo I, Ayer A, Johnson AD, Ganz P, Mills C, Donovan C et al. Sex differences in vascular dysfunction and cardiovascular outcomes: The cardiac, endothelial function, and arterial stiffness in ESRD (CERES) study. *Hemodial Int.* 2018; 22(1):93-102
3. Gibbons GH. Vasculoprotective and cardioprotective mechanism of Angiotensin-Converting Enzyme Inhibition the homeostatic Balance Between Angiotensin II and Nitric Oxide. *Clin Cardiol.* 1997; 20(11 Suppl 2):II-18-25.
4. Di Pietro N, Giardinelli A, Sirolli V, Riganti C, Di Tomo P, Gazzano E et al. Nitric oxide synthetic pathway and cGMP levels are altered in red blood cells from end-stage renal disease patients. *Mol Cell Biochem.* 2016; 417(1-2):155-67
5. Prasad N, Jha V. Hemodialysis in Asia. *Kidney Dis (Basel).* 2015; 1(3): 165–177
6. Afiatin, Khoe LC, Kristin E, Masytoh LS, Herlinawaty E, Werayingyong P, Nadjib M, Sastroasmoro S, Teerawattananon Y. Economic evaluation of policy options for dialysis in end-stage renal disease patients under the universal health coverage in Indonesia. *PLoS One.* 2017; 12(5): e0177436.
7. Son YJ, Choi KS, Park YR, Bae JS, Lee JB. Depression, Symptoms and the quality of life patients on hemodialysis for end-stage renal disease. *Am J Nephrol.* 2009; 29(1):36-42
8. Meyer C, Heiss C, Drexhage C, Kehmeier ES, Balzer J, Mühlfeld A et al. Hemodialysis - Limits Hemoglobin Induced Release of Nitric Oxide bioavailability and impairs vascular function. *J Am Coll Cardiol.* 2010; 2;55(5):454-9
9. Nisha R, Srinivasa Kannan SR, Thanga Mariappan K, Jagatha P. Biochemical evaluation of creatinine and urea in patients with renal failure undergoing hemodialysis. *J Clin Path Lab Med.* 2017;1(2):1-5.
10. Ghobrial EE, Mahfouz NN, Fathy GA, Elwakkad AA, Sebaili HM. Oxidative stress in Egyptian hemodialysis children. *Iran J Kidney Dis.* 2013; 7(6):485-91.
11. Meenakshi SR, Agarwal R. Nitric Oxide Levels in Patients with Chronic Renal Disease. *J Clin Diagn Res.* 2013; 7(7): 1288–1290



This work is licensed under a Creative Commons Attribution