





The Association of High Sensitivity C-reactive protein and Nitric Oxide with Elevated Blood Pressure during Dialysis in Intradialytic Hypertension

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Abstract

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BACKGROUND: Hemodialysis (HD) is a procedure to replace part of kidney function in patients with end-stage kidney disease. Hemodynamic disturbances during HD may include elevated blood pressure (BP). It is reported that about 5–15% of patients undergoing regular HD have increased BP during HD. This condition is called intradialytic hypertension (IDH). Increased high sensitivity C-reactive protein (hs-CRP) levels are associated with decreased endothelial dilatation response of blood vessels. Nitric Oxide (NO) is one of the mediators that act as a vasodilator to regulate vascular pressure. Endothelial dysfunction is one of the factors thought to contribute to the incidence of IDH.

AIM: This study aimed to determine the association of hs-CRP and NO with elevated BP in IDH.

METHODS: This observational cross-sectional study was conducted at Prof. Dr. R.D. Kandou General Hospital, Manado, from November 2021 to April 2022. Participants were selected through consecutive sampling methods. The levels of hs-CRP and NO were examined in all patients. The correlation between hs-CRP and NO was performed using the Spearman test, while the association of hs-CRP and NO with elevated BP was performed using the Fisher-exact test or Chi-square test.

RESULTS: Forty patients were included in this study. The median hs-CRP, NO, and systolic BP (SBP) of the patients were 6.55 mg/dL (0.50–43.5), 27.77 mg/dL (3.65–72.19), and 20 mmHg (10–30), respectively. The correlation analysis showed that there was a strong significant negative correlation between hs-CRP levels and NO ($r = -0.680$, $p = 0.000$). Based on the Chi-Square or Fisher Exact test, there was a significant association between hs-CRP levels and elevated SBP (OR = 5.06; 95% CI = 1.095–23.44; $p = 0.040$), as well as between NO levels and elevated SBP (OR = 17.14; 95% CI = 3.063–95.938; $p = 0.000$).

CONCLUSION: There was a significant association between hs-CRP and NO levels with elevated SBP in end-stage renal disease (ESRD) patients with IDH. ESRD on hemodialysis (ESRD on R-HD) patients with hs-CRP ≤ 3 mg/dL or NO levels < 25 mg/dL tends to have increased SBP ≥ 20 mmHg after HD compared to ESRD patients with low hs-CRP or high NO levels.

Introduction

Chronic kidney disease (CKD), according to kidney disease improving global outcomes (KDIGO), is an abnormalities of kidney function or structure that lasts more than 3 months, with implications for health. Glomerular filtration rate (GFR) is generally accepted as the index of kidney function. A GFR < 60 mL/min/1.73 m² is classified as decreased GFR and < 15 mL/min/1.73 m² as kidney failure (end-stage renal disease/ESRD). Hemodynamic disturbances during hemodialysis (HD) may include elevated blood pressure (BP). It is reported that around 5–15% of patients undergoing regular HD have increased BP during HD. This condition is called intradialytic hypertension (IDH). IDH according to KDIGO is an increase in systolic BP (SBP) > 10 mmHg from pre-dialysis to post-dialysis in at least 4 of 6 HD sessions [1], [2].

According to data from the Indonesian Renal Registry in 2018, IDH is the most common acute complication of HD (38%) [3]. Research conducted by Hajal *et al.* showed that endothelial dysfunction plays a role of endothelial dysfunction in the pathogenesis of IDH [4].

Systemic inflammation is a condition that can occur in HD patients and can be assessed by measuring serum levels of C-reactive protein (CRP) or high sensitivity CRP (hs-CRP), which are produced from hepatocytes in response to inflammation. CRP is produced in hepatocytes through stimulation of interleukin-6 (IL-6), interleukin 1 β , and tumor necrosis factor (TNF) α . Measurement of elevated serum CRP is a strong predictor of mortality and elevated CRP levels are associated with poor outcomes in patients with CKD undergoing HD [5].

Nitric oxide (NO) is a vasodilator that plays a role in the regulation of vascular pressure. The release

of NO will trigger the relaxation of vascular smooth muscles. Furthermore, NO also has an antiproliferative role in vascular smooth muscle cells. A decrease in NO levels can be caused by a decrease in the activity of NO synthase (NOS) enzyme. A decrease in NOS enzymes will lead to vasoconstriction and hypertension [6].

Several studies conducted by Liu *et al.* and Dolly *et al.* reported that hs-CRP levels had a significant negative correlation with NO levels in IDH patients, indicating that an increase in CRP could decrease the bioavailability of NO. This is because CRP can decrease the expression of NOS enzymes on the endothelium. This condition can eventually lead to impaired endothelial and cardiovascular function [7], [8].

Increased levels of hs-CRP are associated with decreased vascular endothelial dilatation response, and endothelial dysfunction is one of the factors that contribute to the incidence of IDH. Therefore, this study aimed to determine the association of hs-CRP and NO with elevated BP in IDH.

Methods

Study design and participants

This observational cross-sectional study was conducted at Prof. Dr. R. D. Kandou General Hospital, Manado, North Sulawesi, from November 2021 to April 2022. The population of this study was all stage 5 ESRD patients who underwent routine HD and developed IDH. The inclusion criteria in this study included stage 5 ESRD patients who underwent regular HD 2 times a week for ≥ 3 months and had IDH, aged 18–60 years, had reached dry weight, and had a history of controlled hypertension with or without hypertension medication. Patients who developed sepsis, had congestive heart failure, malignancy, and liver disease, and had a history of autoimmune diseases were excluded from the study. Participants were selected through consecutive sampling method with a sample size of 40 patients.

Data collection

The following clinical baseline information was collected: Age, sex and HD duration, body weight, NO levels hs-CRP levels, and BP. IDH according to KDIGO is defined as an increase in SBP of at least 10 mmHg from pre-dialysis to post-dialysis in at least four of six HD sessions [7]. SBP was measured with a mercury sphygmomanometer device 5 min before HD and 5 min after completion of HD. The results were categorized as an 10–19 mmHg increase and ≥ 20 mmHg increase in SBP [7], [9]. Blood specimens

were collected through peripheral veins about 5 mL, to determine hs-CRP and NO levels. Hs-CRP is an acute phase protein secreted in response to infection, inflammation, and tissue damage. Measurement of hs-CRP is performed using the immunoturbidimetric method. Hs-CRP can measure CRP in the range of 0.1–10 mg/L. The results of hs-CRP measurement were categorized according to the cardiovascular disease risk stratification: hs-CRP < 3 mg/L (low risk) and hs-CRP ≥ 3 mg/L (high risk) [10]. NO is synthesized by the enzyme NOS, secreted by endothelial cells into the circulation. NO levels in serum were measured with Cat reagents number KGE001 in units of $\mu\text{mol/L}$. Normal serum NO levels are 25–45 $\mu\text{mol/L}$. The measurement results of NO levels were categorized as NO < 25 $\mu\text{mol/L}$ (low NO levels) and > 25 $\mu\text{mol/L}$ (high NO levels) [11].

Ethical statement

This study was approved by the Ethics Committee of Prof. Dr. R. D. Kandou Hospital Manado (Reference Number 169/EC/KEPK-KANDOU/IX/2021). The study participants were informed that all the data collected are for research purposes only and they have the right to withdraw from the study any time.

Statistical analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences program. Descriptive analysis was used to obtain the minimum, maximum, median, and frequency of all variables. The correlation test between variables was performed with the Spearman test to determine the correlation between hs-CRP and NO levels because the data distribution was not normal. To determine the association of hs-CRP with elevated SBP and the association of NO with elevated SBP, a Chi-square test was performed and if one of the cells has an expected count value < 5 , the Fisher exact test was used. $p < 0.05$ was considered statistically significant.

Results

This study involved 40 CKD patients who underwent regular HD and developed IDH. The patients consisted of 19 males (47.5%) and 21 females (52.5%). The median level of hs-CRP in this study was 6.55 mg/dL (0.50–43.5), the median level NO was 27.77 $\mu\text{mol/L}$ (3.65–72.19), and the median increase in SBP was 20 mmHg (10–30). The baseline characteristics and the distribution of the

patients based on hs-CRP, NO, and an increase in SBP are shown in Tables 1 and 2.

Table 1: Baseline characteristics of patient

Variables	N	Median	Minimum	Maximum
Age (years)	40	52.5	22	60
HD duration (months)	40	36	3	96
NO ($\mu\text{mol/L}$)	40	27.77	3.65	72.19
hs-CRP (mg/dL)	40	6.55	0.5	43.5
Body weight (kg)	40	55	44	64
Increase in SBP (mmHg)	40	20	10	30

n: Sample size, HD: Hemodialysis, NO: Nitric oxide, hs-CRP: High sensitivity C-reactive protein, SBP: Systolic blood pressure.

The correlation test between hs-CRP and NO using the Spearman test showed a strong negative correlation ($r = -0.680$) and the correlation was statistically significant ($p = 0.000$).

Table 2: Distribution of patients based on high sensitivity C-reactive protein, nitric oxide, and increase in systolic blood pressure (n=40)

Variables	n (%)
hs-CRP levels (mg/L)	
hs-CRP \leq 3	11 (27.5)
hs-CRP \geq 3	29 (72.5)
NO levels ($\mu\text{mol/L}$)	
NO \geq 25	23 (57.5)
NO \leq 25	17 (42.5)
Increase in SBP (mmHg)	
SBP 10–19	18 (45)
SBP \geq 20	22 (55)

n: Sample size, NO: Nitric oxide, hs-CRP: High sensitivity C-reactive protein, SBP: Systolic blood pressure.

This indicates that the higher the hs-CRP levels, the lower the NO levels. The correlation analysis between hs-CRP and NO is shown in Table 3.

Table 3: Correlation analysis between high sensitivity C-reactive protein and nitric oxide levels

Variable	N	Correlation coefficient*	p*
hs-CRP-NO	40	- 0.680	0.000

*Spearman test. n: Number of samples, NO: Nitric oxide.

The association between hs-CRP levels and NO levels with elevated BP was assessed using the Chi-square or Fisher Exact test (Table 4). Chi-square test results showed a significant relationship between hs-CRP levels and an increase in SBP (OR = 5.06; 95% CI = 1.095–23.44; $p = 0.040$) as well as between NO levels and an increase in SBP (OR = 17.143; 95% CI = 3.063–95.938; $p = 0.000$). This indicates that patients with hs-CRP levels \geq 3 mg/L had a tendency to increase SBP \geq 20 mmHg after HD by 5.06 times compared to patients who had hs-CRP levels of $<$ 3 mg/L. Similarly, patients with NO levels $<$ 25 $\mu\text{mol/L}$ had a tendency to increase BP \geq 20 mmHg after HD by 17.14 times compared to patients with NO levels \geq 25 $\mu\text{mol/L}$.

Table 4: Association of high sensitivity C-reactive protein and nitric oxide with elevated systolic blood pressure (n=40)

Variables	10–19 mmHg increase in SBP	\geq 20 mmHg increase in SBP	Total	p	OR (95% CI)
hs-CRP levels (mg/L)					
$<$ 3	8	3	11	0.040	5.6
\geq 3	10	19	29		(1.095–23.44)
NO levels ($\mu\text{mol/L}$)					
\geq 25	16	7	23	0.000	17.143
$<$ 25	2	15	17		(3.063–95.938)

hs-CRP: High sensitivity C-reactive protein, SBP: Systolic blood pressure, OR: Odd ratio, CI: Confidence interval.

Discussion

The study involved 40 patients with a mean age of 49.58 and a median age of 52.5 years. These results are in accordance with data obtained from the Indonesia Renal Registry in 2018, where ESRD on HD patients was mostly aged 45–54 years (30.82%). The study by Labarcon and Bad-ang in Davao, in 2017, also reported similar results, where the mean age of ESRD patients who developed IDH was 46.59 years [12].

CRP is an acute phase protein and is one of the most sensitive and prominent markers of inflammation. CRP synthesis and excretion occurs in hepatocytes in response to proinflammatory cytokines. CRP is present in the serum of normal individuals in small amounts and can rapidly increase as an inflammatory response [13]. In this study, hs-CRP was examined because the detectable levels were smaller and more sensitive. Normal hs-CRP levels in the blood were $<$ 3.0 mg/L. The median levels of hs-CRP in this study were 6.55 mg/dL with a mean of 9.73 mg/L. These results are in accordance with the results of a study reported by the Kalender *et al.* in 2010, where the average CRP level in ESRD on HD patients in Turkey was found to be 13.7 mg/L [14]. The same result was also reported in the study by Wetmore *et al.* in San Francisco in 2008, where the average CRP levels of ESRD on HD patients were 10.7 mg/L, 12.5 mg/L, and 7.5 mg/L [15]. Inflammation is frequently occurred in stage 5 ESRD on HD patients and increased CRP was common in these patients [13], [15]. Several studies suggest that an increase in levels of proinflammatory cytokines such as TNF- α , IL-1, IL-2, IL-6, and CRP is opposed to a decrease in GFR [13], [14], [15]. Elevated CRP levels in stage 5 ESRD on HD patients may be due to decreased filtration of inflammatory cytokines in the kidneys, exposure to HD equipment and materials, susceptibility to infection, and comorbid conditions that accompany stage 5 ESRD on HD patients. Elevated CRP levels also lead to more severe conditions and a worse prognosis [15].

NO is one of the vasodilators that act as catecholamine antagonists, where NO can also play a role in angiogenesis, anti-aggregation, anti-thrombotic, and anti-inflammatory [16], [17], [18]. In patients with IDH, there was an increase in systemic vascular resistance and a significant decrease in NO [18], the results of this study showed a negative correlation between hs-CRP levels and NO levels ($r = -0.680$, $p = 0.000$). Dolly reported similar results, in which hs-CRP levels had a significant negative correlation with NO levels in IHD patients [19]. CRP is an acute phase protein produced by hepatocytes in response to proinflammatory cytokines. CRP levels are also related to metabolic components and can be found in normal individuals in

small levels which may increase progressively due to the response to inflammation [20], [21]. Tsuda in Japan, in 2012, reported that hs-CRP levels had a significant negative correlation with NO levels in IDH patients ($p < 0.05$) [22].

This study showed a significant association between hs-CRP and increased SBP (OR = 5.06; 95% CI = 1.095–23.44; $p = 0.040$). This indicates that patients with hs-CRP levels ≥ 3 mg/L have a tendency to increase SBP ≥ 20 mmHg after HD by 5.06 times compared to patients who had hs-CRP levels of < 3 mg/L. Similarly, Jalali *et al.* reported in a study of 179 patients with stage 5 ESRD on HD, it was found that an increase in hs-CRP was associated with endothelial dysfunction. hs-CRP levels also increase with age and worsening of the disease, which can lead to an increase in BP ($p < 0.001$) [23]. Some acute phase reactants such as CRP and ferritin are markers of inflammatory reactions caused by the stimulation of proinflammatory cytokines. High levels of CRP indicated that there is a high inflammatory process that triggers an increase in BP in IDH patients. Several studies have revealed that the higher hs-CRP value, the more inflammation occurs in IDH patients [16], [24].

Analysis of the relationship between NO levels and an increase in SBP in this study also showed a significant association (OR = 17.143; 95% CI = 3.063–95.938; $p = 0.000$). This indicates that patients with NO levels of < 25 $\mu\text{mol/L}$ have a tendency to increase SBP ≥ 20 mmHg after HD by 17.14 times compared to patients who had NO levels of < 25 $\mu\text{mol/L}$. The study by Chou *et al.*, comparing between 30 patients with IDH and 30 controls, reported an increase in systemic vascular resistance and a significant decrease in NO relative to ET-1 at the time of HD [17]. Nitric oxide is formed at various sites that can determine its physiological activity. In ESRD patients, there is endothelial dysfunction characterized by decreased NO production by the endothelium. This also supports the theory that one of the mechanisms of IDH is due to endothelial dysfunction, which is characterized by a decrease in serum NO [11], [21], [22].

This finding supports previous research on the involvement of endothelial dysfunction in IDH [11]. A decreased in serum NO levels in patients with IDH and the association between NO and IDH indicate the role of endothelial dysfunction in the pathogenesis of IDH. A decrease in NO causes impaired vasodilation of smooth muscles, resulting in vasoconstriction which plays a role in increasing BP during HD [11], [22].

The limitation of this study was the use of consecutive sampling method for participant selection. This made that the 95% CI value had a wide difference in determining the association between hs-CRP and NO with an increase in SBP which indicates that there was a bias in this study. This technique was chosen due to the limited research time. However, future research with random sampling method should be conducted

to obtain the results with minimum bias. In addition, potential confounding factors such as comorbidity or other clinical and laboratory factors can be controlled to obtain more accurate results.

Conclusion

There is a significant association between hs-CRP levels and NO levels with increased SBP in ESRD patients who developed IDH. ESRD on R-HD patients with hs-CRP ≥ 3 mg/dL or NO levels < 25 mg/dL tends to have increased SBP after hemodialysis compared to ESRD patients with hs-CRP < 3 mg/L or NO levels ≥ 25 $\mu\text{mol/L}$.

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