ARTERIAL STIFFNESS IN END STAGE RENAL DISEASE PATIENTS WITH TWICE A WEEK HEMODIALYSIS AND ITS AFFECTING FACTORS

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ABSTRACT

Objective: To investigate the proportion of arterial stiffness in patients on twice weekly maintenance hemodialysis and the factors affecting it.

Methodology: This observational study with a cross-sectional design was performed in the Haemodialysis Unit, Kidney and Hypertension Division, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. The study enrolled 83 End Stage Renal Disease (ESRD) patients undergoing hemodialysis two times a week for at least three months. Patients with acute disease were excluded from the study. Arterial stiffness was measured as pulse wave velocity (PWV) using SphygmoCor® with PWV cut-off of 10m/s. SPSS 21.0 was used as an analysis tool; descriptive and inferential statistics were applied where needed.

Results: In the sample, 42 (50.6%) were male and 41 were female (49.4%). Among all participants, 22 (26.5%) patients were with arterial stiffness and 61 (73.5%) were without arterial stiffness. Factors independently affecting arterial stiffness were fasting glucose level (odds ratio 6.842 [CI95% 1.66-28.24]) and LDL level (odds ratio 4.887 [CI95% 1.59-16.58]).

Conclusion: The proportion of arterial stiffness in ESRD patients undergoing hemodialysis two times a week was about one third of all patients. In factors affecting arterial stiffness among ESRD patients, fasting glucose level and LDL level were found to have higher odds.

Key Words: End stage renal disease; Arterial stiffness; Pulse wave velocity; Hemodialysis.

INTRODUCTION

End Stage Renal Disease (ERSD) is a disease in which the kidney is undergoing irreversible deterioration. Morbidities and mortalities related to this disease are mainly caused by cardiovascular events and disorders.[1] Cardiovascular events are primarily induced by degenerative processes, namely atherosclerosis and arterial stiffening. Previous studies have shown that atherosclerosis is worse in ESRD patients, especially those undergoing hemodialysis, compared to patients with normal kidney function.[2] The prevalence of arterial stiffness in the normal population is about 5.7%, while in pre-ESRD patients it is about 53.3%, and progressively increased in hemodialysis patients, reaching 68.8% in hemodialysis populations with standard dose.[3]

Atherosclerosis processes mediated by increased systolic pressure and intravascular volume in ESRD patients increase arterial stiffness, resulting in increased heart workload and further damage in various organs.[4] In addition, hyperuricemia, chronic intravascular volume excess, mechanical stress caused by hypertension, excessive renin-angiotensin-aldosterone system activation, and accumulation of advanced glycosylated end product (AGE) in ESRD patients may worsen arterial stiffness.[5,6] Imbalance of mineral and bone regulation, which are commonly found in ESRD, may also contribute to arterial stiffness progressivity.[7]It has been widely known that arterial stiffness is associated with increased prevalence of cardiovascular and cerebrovascular events.[4] Factors affecting arterial stiffness have been studied extensively, such as age, sex, hypertension, diabetes, smoking, phosphate level, and hemodialysis adequacy, however the results are still contradicting.[3]In addition, factors affecting arterial stiffness in ESRD patients have not been studied thoroughly, especially in Indonesia, since the frequency and duration of hemodialysis are commonly different.

Central arterial stiffness can be measured using invasive methods such as catheterization or non-invasive methods such as ultrasound assessment, name-

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ly measuring Pulse Wave Velocity (PWV) of carotid-femoral aorta. PWV measurement in carotid-femoral (aortic) is considered a non-invasive gold-standard method to define central arterial stiffness.[8] Studies revealed that PWV score has been known to be progressively increased along with chronic kidney disease staging.[7] Although the correlation between hemodialysis adequacy and arterial stiffness is still unclear, previous study showed that PWV score was decreased in patients with a longer duration of hemodialysis.[9]However, this measurement is not routinely done, and there are small number of researchers studying it. Based on the stated facts above, the authors would like to analyze factors affecting arterial stiffness in twice-weekly hemodialysis patients since in Indonesia most patients undergo hemodialysis twice a week, so that prevention through risk factor control can be done.

METHODOLOGY

This observational cross-sectional study was conducted in the Hemodialysis Unit of Kidney-Hypertension Division, Internal Medicine Department of Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia from April 2019 to May 2019. The study was approved by the ethical committee of Faculty of Medicine, Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital. The participants were recruited consecutively. Patients with End Stage Renal Disease (ERSD) aged above 18 years old, undergoing regular hemodialysis two times a week for more than three months were included in this study. Patients with acute conditions, including acute coronary artery disease and acute heart failure, or incomplete data were excluded from the study. The characteristics of the Subjects were obtained from medical records. The measurement of arterial stiffness was done by measuring Pulse Wave Velocity (PWV) using SphygmoCor® equipment. A cut-off of 10 m/s was applied to patients' PWV to categorize patients into arterial stiffening and non-arterial stiffening (control) groups. Hemoglobin, BUN, creatinine, fasting glucose level, blood phosphate level, and LDL levels were measured in subjects from both groups.

The data was then analyzed using SPSS 21.0. Descriptive analysis was applied for the demographic, anthropometric, and clinical characteristics of the patients, while bivariate and multivariate analysis was applied to determine factors affecting arterial stiffness in ESRD patients at a confidence interval od 95% and was considered to be statistically significant at a p value of ≤0.05.

RESULTS

Among 83 subjects, 22 (26.5%) had Pulse Wave Velocity (PWV) above 10 m/s and was considered to have arterial stiffness, while 61 subjects remained without arterial stiffness. Of the 83 subjects included, 42 were male (50.6%) and 41 were female (49.4%). Details of other characteristics given in Table 1.

Based on bivariate analysis, it is concluded that risk factors of arterial stiffness in hemodialysis patients were fasting glucose level ≥ 126 mg/dL (p = 0.007, OR 2.51, CI95% 1.28-4.93), systolic blood pressure ≥ 140 mmHg (p = 0.034, OR 3.05, CI 95% 0.99-9.43), and blood LDL level ≥ 100 mg/dL (p = 0.022, OR 2.48, CI95% 1.08-5.71).

Using risk factors associated with higher PWV levels in this study, multivariate analysis by logistic regression was done. It was found that fasting glucose level ≥126 mg/dL (p = 0.008, OR 6.842, CI95% 1.66-28.24) and LDL level ≥ 100 mg/dL (p = 0.011, OR 4.887, CI95% 1.44-16.58) were significantly associated with higher PWV in hemodialysis patients. (Table 2).

Data was presented in percentage for categorical variables (%). Chi-square or Fisher's exact test was used to assess the analysis between the categorical groups while parametric t-test or Mann-Whitney was used for numerical groups. BP: Blood pressure, LDL: low density lipoprotein, ORF: odds ratio, CI: confidence interval, HD: hemodialysis.

DISCUSSION

Based on the study conducted, it was found that 22 (26.5%) of subjects fell into the positive arterial stiffness study group, while 61 (73.5%) subjects did not have arterial stiffness. The proportion of patients with arterial stiffness in this study was higher than the normal population (5.7%), yet lower than studies performed before on Thailand with patients having three times a week hemodialysis (68.8%).[3] Lower arterial stiffness proportion in this study might be attributed to various factors, such as the lower average of age in the subjects of this study (50.76 years) compared to the previous study (57.8 years). Age plays a significant role in determining PWV, as in a study done by Scholze et al. with r = 0.22 (p < 0.001).[10] One of the pathophysiology regarding age's role in arterial stiffening is upregulation of matrix metalloproteinase=2 (MMP-2) which is further accelerated vasodilatation and arterial stiffening.[5]

In this study, there was a higher risk of having arterial stiffness in patients with higher fasting glucose levels (p = 0.008, OR 6.842, CI95% 1.66-28.24). This result is similar from that of Fu et al[11] who observed the roles of fasting and postprandial blood glucose in the effect of type 2 diabetes on central arterial stiffness. Fu et al. showed that fasting glucose level is independent predictive factor of arterial stiffness. Moreover, Ravikumar et al[12] showed that diabetic mellitus is associated with arterial stiffness, in which diabetic subjects had a significantly higher augmentation index (AI) and lower flow-mediated dilatation (FMD) values compared with nondiabetic subjects. This is also

Table 1: Clinical Characteristics of the Subjects

Variable		Groups		Odds Ratio	Confidence Interval	p value
		Arterial stiffness (+) n = 22	Arterial stiffness (-) n = 61			
Age	60 years	6 (24.0%)	19 (76.0%)	0.87	0.39-1.96	0.737
	< 60 years	16 (27.6%)	42 (72.4%)			
Sex	Male	12 (28.6%)	30 (71.4%)	1.17	0.57-2.41	0.430
	Female	10 (24.4%)	31 (75.6%)			
Fasting glucose level	> 126 mg/dL	7 (53.8%)	6 (46.2%)	2.51	1.28-4.93	0.007
	< 126 mg/dL	15 (21.4%)	55 (78.6%)			
Systolic BP	> 140 mmHg	19 (33.9%)	37 (66.1%)	3.05	0.99-9.43	0.034
	< 140 mmHg	3 (11.1%)	24 (88.9%)			
LDL	> 100 mg/dL	16 (37.2%)	27 (62.8%)	2.48	1.08-5.71	0.022
	< 100 mg/dL	6 (15.0%)	34 (85.0%)			
Kt/v	> 1.8	11 (25.6%)	32 (74.4%)	0.93	0.45-1.90	0.843
	< 1.8	11 (27.5%)	29 (72.5%)			
Smoking	Yes	2 (28.6%)	5 (71.4%)	1.08	0.32-3.71	1.00
	No	20 (26.3%)	56 (73.7%)			
Phosphate level	>47	14 (24.1%)	44 (75.9%)	0.75	0.36-1.56	0.457
	< 4.7	8 (32.0%)	17 (68.0%)			

* BP = Blood Pressure, LDL = Low-Density Lipoprotein

Table 2: Multivariate Analysis of Variables

Variables	Odds Ratio	Confidence Interval	p value
Fasting Glucose Level	6.842	1.66-28.24	0.008
LDL	4.887	1.44-16.58	0.011

* Low-Density Lipoprotein

supported by Wang et al[13] who found that arterial stiffness proportion was significantly different in diabetic mellitus patients. Higher fasting glucose level was identified as potential risk factors for arterial stiffness based on PWV measurement in both men and women. Fasting glucose level is directly associated with hyperglycemia and diabetes. Diabetes in hemodialysis patients would accelerate renin-angiotensin-aldosterone system activity, increasing hypertrophy and fibrosis of the vascular wall, altering vascular collagen composition, and promoting endothelial dysfunction.[14] In hemodialysis patients, it is further aggravated by factors associated with hemodialysis, such as mineral disorders, uremia, and elevated blood pressure.[6] It is also known that arterial stiffening does not start when patients are already diagnosed with diabetes, but when insulin resistance is already taking place.[8] Similar to previous studies, only fasting blood glucose level was measured in this study, with cut-off level >126 mg/dL. HbA1C was not performed because most hemodialysis patients tend to have lower hemoglobin level which may affect the HbA1C result and would not describe the actual condition.

LDL level is also one of the risk factors associated with a greater risk of arterial stiffening (p = 0.011, OR 4.887, CI95% 1.44-16.58). Elevated LDL levels promote endothelial dysfunction, reduce vascular elasticity, and cause arterial stiffness. This result is similar with a study from China that showed higher LDL levels in patients with arterial stiffness compared with patients of similar age.[13] Other study also revealed similar results, with the additional conclusion that statin administration in higher LDL patients can reduce arterial stiffness progressivity experienced by patients.[8]

Although from the bivariate analysis the systolic blood pressure p score <0.25, multivariate analysis showed that there was no association between systolic blood pressure and arterial stiffness in ESRD patients undergoing chronic hemodialysis. This result differs from prior studies that observed chronic hypertension as one of the main factors in arterial stiffness development through its stress effect in aortic vessels.[15] McEniery et al[16] in their 20-year follow-up study revealed that chronic elevation in systolic blood pressure can increase arterial stiffness. Moreover, Kitahara et al[17] in their study to define the impact of Brachial-Ankle Pulse Wave Velocity and Ankle-Brachial Blood Pressure Index on Mortality in Hemodialysis Patients, also showed that systolic blood pressure is significantly correlated with arterial stiffness,

and vice versa. Those differences in the results were possibly due to other confounding factors, such as artery-protective drugs, which include antihypertensive drugs and statin since 72.3% of subjects in this study were on at least one antihypertensive drug with different classes and durations. Also, 60% of the subjects in this study did not suffer from chronic hypertension. Subjects tend to have hypertension after ESRD occurs, so the duration of hypertension may not be sufficient to cause structural arterial changes.

Due to its cross-sectional method in this study, a causal relationship cannot be determined. In addition, the definitive diagnosis for current or previous coronary artery disease through coronary angiography, which can cause bias, was not performed in this study. However, despite its limitations, this study determined the proportion of arterial stiffness in ESRD patients along with various factors that influence it particularly in the Indonesian hemodialysis population in which the hemodialysis dose is commonly different from the recommended dose.

CONCLUSION

In conclusion, the proportion of arterial stiffness in patients with end-stage kidney disease undergoing hemodialysis twice-weekly was about one third of all patients. Fasting blood glucose levels and LDL levels are two risk factors that influence arterial stiffness.

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Author's Contribution

NP initiated and designed the study, collected the data, contributed in data interpretation, wrote the original manuscript, TH initiated and designed the study, collected the data, contributed in data interpretation, wrote the original manuscript, CAN drafted the manuscript, RP supervised the study and reviewed the manuscript, CMR supervised the study and reviewed the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.