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Correlation between Osteoprotegerin Serum Levels and Arterial Stiffness Assessed by Cardio-ankle Vascular Index (CAVI) in Hypertensive Patients

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Abstract. The cardio-ankle vascular index (CAVI) is a newly developed clinical measurement for evaluating arterial stiffness from the origin of the aorta to the ankle. Osteoprotegerin (OPG) is widely known as a vascular calcification mediator, which have a role to affect atherogenesis. Thirty subjects participated in this research and each subject underwent a CAVI examination to assess arterial stiffness and their blood samples were collected for OPG measurement. This study is analyzed with Pearson Correlation Test. There is a positive, strong and significant correlation between osteoprotegerin serum level and arterial stiffness using Cardio-Ankle Vascular Index (CAVI) in hypertensive patients. ($r = 0.730$ and $p < 0,0001$). There was a positive, strong and significant correlation between osteoprotegerin serum level and arterial stiffness using Cardio-Ankle Vascular Index (CAVI) in hypertensive patients.

1. Introduction

Hypertension is one of the main risk factors for heart disease, kidney disease, stroke, and even death worldwide. In 2000, it was found that there were around 1 billion people with hypertension and this number is estimated to increase to 1.56 billion people by 2025. The World Health Organization (WHO) shows that hypertension is responsible for 45% of deaths from heart disease and 51% of deaths from stroke. Early detection and treatment of hypertension and other risk factors play a role in decreasing mortality from heart disease and stroke in the last three decades in developed countries, but not in developing countries[1].

Arterial stiffness is a marker of heart disease, in which age, hypertension, smoking, dyslipidemia, diabetes, and obesity play a role in this event. Risk factors improvements have been the target of therapy to improve arterial stiffness so that, in 2003, the European Society of Hypertension guideline suggested the importance of measuring arterial stiffness in the management of hypertension [2][3]. Cardio-Ankle Vascular Index (CAVI) is a new non-invasive arterial stiffness measurement method in which this method is considered to cover the lack of pulse wave velocity (PWV). The advantage of this method is that it does not depend on blood pressure at the time of measurement.

CAVI increases with age and is associated with several risk factors for other heart and blood vessel diseases, such as hypertension, diabetes mellitus, dyslipidemia and smoking. The main objective of arterial stiffness assessment by CAVI is not only to detect the process of atherosclerosis so that it can



start therapy or lifestyle changes as soon as possible, but also to see the course of the disease and the response to the treatment given [4][5].

Besides using non-invasive methods, a number of markers are also related to arterial stiffness. Some recent studies suggest that osteoprotegerin (OPG) is associated with increased pulse wave velocity and describes endothelial dysfunction. High OPG levels are associated with arterial stiffness and other comorbid factors, and this affects cardiovascular events and strokes [6][7].

Research on OPG has been carried out considering its role in the incidence of vascular calcification and arterial stiffness, as well as CAVI examination, which is one of the non-invasive examinations, performed in patients with cardiovascular disease to assess arterial stiffness. In this study, we linked serum osteoprotegerin (OPG) levels with arterial stiffness events measured by cardio ankle vascular index (CAVI) in hypertensive patients.

2. Methods

This type of research is observational analytic research using a correlational research approach. The research was conducted at General Hospital Dr. Soetomo Surabaya in February 2016 to May 2016. Affordable population in this study were patients with hypertension and outpatient at the heart clinic at the RSUD Dr. Soetomo Surabaya period February 2016 - May 2016. The sample of this study was all hypertension sufferers and outpatients at the cardiac clinic Dr. Soetomo Surabaya for the period of February 2016 - May 2016 that fulfilled the inclusion and exclusion criteria and were willing to take part in the study. The research sampling technique in this study was consecutive sampling.

The inclusion criteria in this study were men and women aged 40-60 years who suffer from hypertension or have received antihypertensive treatment, and were willing to participate in research by signing an informed consent.

The exclusion criteria of this study were patients with a history of atherosclerotic cardiovascular disease (coronary heart disease, stroke, peripheral arterial disease / PAD, aortic or thoracic aneurysm), heart failure / cardiomyopathy, permanent atrial fibrillation, tumors and malignancies or cancer, diabetes mellitus, chronic inflammatory diseases (rheumatoid arthritis, osteoarthritis, HIV, etc.) and undergoing immunosuppressant or corticosteroid therapy. Additionally, patients who suffer from chronic kidney failure, genetic disorders, smoking were excluded from the study.

Data were collected, managed with descriptive statistics, and then presented in the form of exposures, tables and diagrams. The relationship between serum osteoprotegerin levels and arterial stiffness was determined using the Pearson product moment correlation test for the distribution of normally distributed data. The results are said to be significant if the significance value is $p < 0.05$. Data were analyzed using SPSS version 20.0.

3. Results

There were thirty research subjects with controlled and uncontrolled hypertension who met the inclusion and exclusion criteria participating and analyzed in this study. The age range of the subject is 40-60 years, with a mean of 53.13 ± 5.79 years. The number of male and female subjects was 10 male (33.3%) and 20 female subjects (66.7%), respectively.

Body mass index (Body mass index-BMI) with a mean of 26.65 ± 3.93 . The lowest systolic blood pressure was 102mmHg and the highest was 175mmHg with a mean TDS of 132.36 ± 16.85 mmHg. The lowest diastolic blood pressure was 62mmHg and the highest was 105 mmHg with a mean TDD of 81.36 ± 8.98 mmHg. It is known that all subjects received anti-hypertensive therapy. Dyslipidemia was 26 subjects (86.7%), of which 14 subjects received lipid-lowering therapy. There were 20 research subjects or around 66.7% had a body weight that was not ideal (body mass index ≥ 25 kg / m²) with a mean body mass index of 26.65 ± 3.93 kg / m². The following will describe the basic characteristic data using Table 1.

Based on the examination of 30 subjects, the lowest serum osteoprotegerin level was 2.99pmol / L and the highest was 8.18pmol / L. The mean serum osteoprotegerin level was 5.52 ± 1.52 pmol / L as seen in Table 2.

CAVI is classified based on index value, which is <8 categorized as normal, > 8 - <9 categorized as borderline, and > 9 categorized as abnormal. The minimum CAVI value is 5.1 and the maximum value is 9.9 with a mean of 7.69. Examination of CAVI values on research subjects will be presented in Table 5.3.

Before testing the relationship between the two variables, the normality of the variable data distribution was tested between the CAVI value and the serum OPG level variable using the Kolmogorov-Smirnov test normality test. Normality test results show $p \geq 0.05$, because of the normal distribution of data so that the statistical analysis of the correlation between the levels of OPG and the CAVI value uses the parametric correlation test, namely Pearson Product Correlation Test. From this test $p < 0.001$; $r = 0.730$. A positive r value means that the correlation is unidirectional, which shows that the higher the CAVI value the higher the serum OPG level. The value of $p < 0.05$ indicates a significant positive correlation. The r value in this study is in the range 0.600 - 0.790, which indicates a strong correlation. The results of the analysis will be presented in Table 5.4.

Table 1. Basic Characteristics of Research Subjects.

Variable	N (%) or Average \pm SD
Age (Years)	53.13 \pm 5.79
40-49	9 (30)
50-59	13 (43.3)
\geq 60	8 (26.7)
Sex	
Male	10 (33.3m)
Female	20 (66.7)
Body Height (m)	1.58 \pm 0.07
Body Weight (kg)	67.50 \pm 1.89
Body Mass Index (kg/m ²)	26.65 \pm 3.93
18.5 – 24.9	10 (33.3)
25 – 29.9	14 (46.7)
\geq 60	6 (20)
SBP (mmHg)	132.36 \pm 16.85
DBP (mmHg)	81.36 \pm 8.98
ABI	1.05 \pm 0.06
Dislipidemia	26 (86.7)
Dislipidemia Treatment	14 (46.7)

Table 2 Serum Osteoprotegerin (OPG) Levels in The Research Subject (n = 30).

Variable	Average \pm SD	Min	Max
Osteoprotegerin Levels (OPG) serum (pmol/L)	5.52 \pm 1.5	2.99	8.18

Table 3. CAVI Value in research subjects (n = 30).

Variables	n (%)	Average \pm SD	Min	Max
CAVI Value		7.69 \pm 1.3	5.10	9.9
Normal	17 (56.7%)			
Borderline	7 (23.3%)			
Abnormal	6 (20%)			

Table 4. Correlation Analysis of OPG Levels with Arterial Stiffness Assessed by The CAVI.

Variable	P ^a	R
CAVI value and OPG (pmol/L)	0001	0730

^aAnalyzed by Pearson Product Correlation Test ($\alpha = 0.05$; $\beta = 80\%$)

4. Discussion

The role of OPG in the event of arterial stiffness has been widely discussed and proven. Several studies that have been carried out in vivo in humans show a positive relationship between OPG and the incidence of cardiovascular disease. In their study, Wang et al. analyzed circulating osteoprotegerin levels with arterial stiffness events assessed using carotid-femoral pulse wave velocity (cfPWV) in hypertensive patients and found that circulating osteoprotegerin levels were higher in individuals with more severe arterial stiffness compared to individuals without arterial stiffness [8]. In this study it was intended to analyze the correlation between serum OPG levels and arterial stiffness assessed by CAVI in hypertensive patients.

Previous research has proven the influence of several risk factors related to the progression of arterial stiffness, namely age, hypertension, smoking and diabetes, while factors such as dyslipidemia and obesity play a role in the incidence of arterial stiffness.

The aging process in the arterial system is followed by progressive structural changes, such as the occurrence of elastin fragmentation and degeneration, increased collagen, thickening of the arterial wall and damage to the endothelium and causing increased arterial stiffness. The study by Choi et al. which involved 1380 healthy subjects, stated that the addition of age was associated with the incidence of arterial stiffness [9].

The incidence of dyslipidemia in the subject of this study was quite high at 86.7%. This indicated a lack of attention to health in the community. However, studies by Razman et al. stated that dyslipidemia was not associated with arterial stiffness.

Blood pressure plays an important role in determining the structure of blood vessel walls, and the remodeling process occurs as compensation due to changes in blood vessel walls, so that an increase in blood pressure affects the incidence of arterial stiffness, especially in old age. In this study, the subjects were patients suffering from hypertension who either received or did not receive therapy [10].

In this study, osteoprotegerin was examined with a minimum value of 2.99pmol / L and a maximum value of 8.18pmol / L with a mean serum osteoprotegerin level of 5.52 ± 1.5 pmol / L. At present, there is no standard cut-off point value, but OPG values obtained from unselected donors (n = 7; age 35-65 years) in reference laboratories are associated with a mean of 4.1 ± 2.3 pmol / L and previous studies by Lee et al. found that the average osteoprotegerin levels in control subjects were 4.22 ± 5.48 pmol / L and in hypertensive subjects 4.17 ± 4.65 pmol / L [11].

CAVI assessment was performed on hypertensive patients where hypertension is one of the conditions most often associated with arterial stiffness.

Arterial stiffness can cause an increase in systolic blood pressure because the heart pumps blood to a rigid artery where the artery is less able to accommodate the amount of blood from the left ventricle and ultimately causes an increase in systolic blood pressure. Of the 30 research subjects there were six (20%) subjects with abnormal CAVI values, and 17 subjects (56.7%) subjects with normal CAVI values. The increase in CAVI value shows the progressiveness of arterial stiffness. Normal CAVI values in some hypertensive subjects can be caused by the use of antihypertensive therapies, such as antihypertensive ARB and CCB groups [12].

In accordance with a study conducted by Lee et al. (2015) where osteoprotegerin levels correlated with arterial stiffness assessed using CAVI in hypertensive patients compared with controls ($p < 0.001$; $r = .484$), research by Wang, et al. (2014) also suggested that serum osteoprotegerin levels also showed a correlation with arterial stiffness assessed by Carotid-Femoral Pulse Wave Velocity (c-f PWV) in hypertensive patients ($p < 0.001$; $r = 0.392$).

One other study by Kim et al. (2013) also showed that there was a correlation between osteoprotegerin ($p < 0.004$; $r = 0.248$) and the ratio of osteoprotegerin / fetuin-A ($p < 0.031$; $r = 0.260$)

with increased arterial stiffness. The increased arterial stiffness was assessed by CAVI in patients undergoing hemodialysis. Hypertension is an important health problem throughout the world and is a risk factor for cardiac morbidity and mortality. Hence, in 2003, the European Society of Hypertension Guideline suggested the importance of measuring arterial stiffness in managing risk factors in patients with hypertension and evaluating therapy.

The strong and significant positive correlation between serum osteoprotegerin and arterial stiffness assessed by CAVI in this study is in accordance with the existing hypothesis, and this also further supports the role of osteoprotegerin in the arterial stiffness process. The mechanism underlying the role of OPG in the occurrence of arterial stiffness is thought to involve the process of calcification, inflammation and endothelial and ventricular dysfunction.

Several studies have mentioned the relationship between OPG and vascular calcification, although the exact mechanism by which glycoproteins affect cardiovascular pathophysiology is still unclear. so as to further strengthen this statement further evaluation and research are needed with a better research method with a larger number of samples [13].

In this study, there are several limitations, for example homogenization was carried out but no randomization was carried out due to limited time, number of patients and funds research. This study has a small scope and has not been done in a multicenter with a broader scope and this study does not limit the use of basic disease therapy in research subjects in the form of antihypertensive therapy and dyslipidemia.

5. Conclusion

There is a positive, strong and significant correlation between serum osteoprotegerin levels and arterial stiffness assessed by Cardio-Ankle Vascular Index (CAVI) in hypertensive patients ($p < 0.001$; $r = 0.730$).

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