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CORRELATION BETWEEN LEVEL OF SERUM FETUIN-A AND BLOOD VESSEL CALCIFICATION IN PATIENT UNDERGOING REGULAR HEMODIALYSIS

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Abstract

Introduction: Cardiovascular disease is one of the main causes of death in patients with chronic kidney disease (CKD) undergoing hemodialysis or peritoneal dialysis therapy. This is related to calcification in large blood vessels such as the aorta. Fetuin-A is a protein that could prevent calcification process happening in blood vessel wall.

Method: This study is a cross-sectional analytic study with research subjects is the patient of chronic kidney disease undergoing regular hemodialysis in the hemodialysis unit of RSKG RASYIDA Medan starting from April 2018 (for at least ≥ 3 months) and aged≥ 18 years. Fetuin-A level test and abdominal x-ray were conducted, then statistical analysis performed to know the correlation of serum fetuin-a level with calcification of blood vessels in regular hemodialysis patients**.**

Result: Of the 113 research subjects, those who did not have calcifications had higher Fetuin-A levels than mild and severe degrees of calcification (417.02 ± 228.87 mg / dl, 353.57 ± 172.95 mg / dl, 267.04 ± 127 , 52 mg / dl, respectively).

Conclusion: Serum fetuin-A levels were associated with the occurrence of blood vessel calcification in regular hemodialysis patients (p = 0.004).

Introduction

Cardiovascular disease is one of the main causes of death in patients with chronic kidney disease (CKD) undergoing hemodialysis or peritoneal dialysis therapy. Increased mortality caused by cardiovascular disease, associated with calcification in large blood vessels, such as the aorta, where this can cause stiffness in the arteries and increase pulsation pressure and decreased myocardial perfusion at diastole.[1]

The ectopic calcification mechanism has a wide variation and has not yet been known clearly. Pathology of calcification of blood vessels as a major risk factor of cardiovascular mortality is the most studied. Basically, calcification regulation is regulated by maintaining extracellular calcium and phosphate concentration and control of various inhibitors, such as Fetuin-A.[2]

Fetuin-A is a protein that has a role in calcification of blood vessels. Fetuin-a prevent local process of calcification on the wall of blood vessels by being internalized by smooth muscle cells of blood vessels muscle cells (VSMCs) and enter the Vesicle MSMCS matrix that is apoptosis and feasible, resulting in the inhibition of the mineral core. Fetuin-A also prevent the apoptosis of VSMCs and increases the phagocytosis of vesicles. This causes limitationof mineralization of blood vessels. In systemic, fetuin-a serves as excessive mineral binders and forms a fetuin-mineral complex, called also calcitropin particles, resulting in increased of solubility by increasing the soluble apolipoprotein.[3]

In this study, we would like to know the relationship between serum fetuin-A levels and blood vessel calcification in regular hemodialysis patients.

Method

Study Samples
Samples were from populations of CKD patients who underwent regular hemodialysis in the hemodialysis unit of RSKG Rasyida Medan from April 2018 (for at least 3 months) and aged> 18 years. The subject had received information and gave consent to participate in informed and voluntary research. Patients who underwent irregular hemodialysis or were unstable were excluded from this study.

Study Design
This study is an analytical cross-sectional study. The proportion formula is used to determine the number of samples. After obtaining approval from the ethics committee, the subjects who met the inclusion and exclusion criteria were given an explanation and asked to provide informed consent to take part in the study. Then blood sampling is performed to determine serum Fetuin-A level as well as lateral abdomen x-ray. After the data collected, data processing and data analysis were then conducted.

Statistical Analysis
Univariate analysis was conducted to obtain an overview of each variable studied. Bivariate analysis is used to state the analysis of two variables, which are the dependent variable and the independent variable. To see the strength of the relationship between the dependent and independent variables, the value of the Prevalence Ratio (RP) is used. In bivariate analysis anovatest is used because the independent variable is numerical data and the dependent variable is ordinal data.

Result

Research Subjects Characteristic Distribution
This study was followed by 113 patients as research subjects who had met the inclusion and exclusion criteria. The majority of the study subjects were men (59.3%) with a median age of 57 years. Based on the results of laboratory tests, the median serum calcium level was 9.8 mg / dl, the mean serum phosphate level was 5.39 mg / dl. From the results of lateral abdominal X-ray examination in this study the majority of patients having severe calcification of 43.4%, no calcifications of 38.1%), and only 18,6% having mild calcification. (Table 1)

Table 1 Study Subjects Characteristics

Characteristics	n=113
Sex, n (%)	
Male	67 (59,3%)
Female	46 (40,7%)
Age (years), Median (Min-Max)	57 (22 – 78)
Fetuin A level, mg/dl Median (Min-Max)	247.0 (102 – 936)
Calcification degree	
No Calcification	43 (38,1%)
Mild Calcification	21 (18,6%)
Severe Calcification	49 (43,4%)

Relationship between Research Subject Characteristics with the Degree of Blood Vessel Calcification
Man having more severe calcification (47.8%), compared with women who showed the same results in severe calcification and no calcification (each of 37.0%). Based on the statistical test, it was concluded that there was no significant difference between gender and the degree of calcification (p = 0.211). (Table 2)

Subjects with no calcification were 49.0 ± 13.020 years of age, lower than the average age of mild and severe degrees (54.81 ± 9.19 and 59.47 ± 8.615). Based on the statistical test, it was concluded that there were significant differences between mean of age to the degree of calcification (p = 0.001) (Table 2).

Subjects without calcification had higher Fetuin-A levels than mild and severe calcifications (417.02 ± 228.87 mg / dl, 353.57 ± 172.95 mg / dl, 267.04 ± 127.52 mg / dl, respectively). It was concluded that there were significant differences between average levels of Fetuin-A and the degree of calcification (p = 0.004). (Table 2)

Tabel 2 Correlation between Study Subjects Characteristics and Blood Vessel Calcification Degree

Characteristics	Degree of Calcification			*p*
	No Calcification	Mild	Severe	
Sex, n(%)				
Male	26 (38,8)	9 (13,4)	32 (47,8)	0,211
Female	17 (37,0)	12 (26,0)	17 (37,0)	
Age, years	49,0±13,020	54,81±9,179	59,47±8,615	0,001
Fetuin A	417,02±228,87	353,57±172,95	267,04±127,52	0,004

Disscusion

In this study the majority of the study subjects were male (59.3%), this result was consistent with the research report of Honkanen E et al. and IRR (Indonesian Renal Registry) data, The incidence of male calcification was greater than women with accompanying risk factors such as smoking history, diabetes, and coronary heart disease.[4,5]

In this study there are more severe degree of calcification found in patients with chronic renal failure (43.4%) because the study population was patients with stage V CKD on dialysis. From Kimura's research, et al. stated that one of the factors in severe blood vessel calcification is affected by the severity of CKD and also the duration of dialysis experienced by a person.[6] This is also in line with the theory described by Herrmann.[7]

Based on the results of a comparison of the mean age, there were significant mean differences in severe calcification compared to normal blood vessels, the mean age of patients having severe calcification was aged 59.47 years while those who did not experience calcification were 49 years old. Research by Turkmen, et al in Turkey get more or less the same results where the average patient who has severe calcification degree is 56 years.[8]Krauss, et al. explained that increasing age, the degree of calcification is increasingly severe in patients with chronic kidney disease.[9]Research conducted by Barreto et al on 101 routine hemodialysis patients, stated that there was a positive correlation between age and coronary artery calcification which was statistically significant with moderate correlation strength (r = 0.57; p = 0.001).[10] In line with the study Coll et al stated that there was a significant relationship between age and calcification in regular HD patients (p = 0.001).[11]

This is because with increasing age, the risk of increased blood vessel calcification coupled with decreased kidney function. Including the role of the kidney as a calcification regulation, where maintaining extracellular calcium and phosphate concentration and its inhibitory factors.[7] This is aggravated by chronic kidney disease where the process of calcification has occurred since the onset of chronic kidney disease.[1]

From the research subjects, it was concluded that there were significant differences between the average levels of Fetuin-A and the degree of calcification. The results of this study are in line with the research of Joachim et al where the lower the level of fetuin-A the higher the risk of vascular calcification (p = 0.001). This study also compared the risk of vascular calcification at fetuin-A levels <0.59 g/l compared to levels of 0.6-0.7 g/l and fetuin-A levels <0.59 g/l compared to levels > 0.7g/l where it can be concluded that the higher the level of fetuin-A is the lower/ the more protective against the incidence of vascular calsification.[12] This is in accordance with the theory that fetuin-A acts as a binding and antagonist to "Transforming Growth Facto-Beta" (TGF-β) and "Bone Morphogenic Proteins" (BMPs). Thus, fetuin-A plays a role in regulating osteogenesis through TGF-β / BMP signaling.[7]

Conclusion

The conclusion of this study was that serum fetuin-A levels were associated with the occurrence of vessel calcification from regular hemodialysis patients. The prevalence of vascular calcification in hemodialysis

patients who experienced severe calcification from this study was 49 patients, no calcifications as many as 43 patients, and only 21 patients who experienced mild calcification (18.6%).)

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