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CORRELATION OF SERUM FIBROBLAST GROWTH FACTOR 23 WITH LEFT VENTRICULAR DIASTOLIC FUNCTION IN CHRONIC KIDNEY PATIENTS

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ABSTRACT

Chronic Kidney Disease (CKD) is one of most common world's health problems with constantly increasing prevalence and many complications, and cardiovascular is one of them. The earliest cardiovascular damage that can be seen is left ventricular diastolic dysfunction. In patients with CKD, there will be mineral metabolism disorders, including phosphate. Persistently increased phosphate in CKD will cause rising in Fibroblast Growth Factor 23 (FGF23) that regulates phosphate in the circulation. High level of FGF23 will directly damage the heart and stimulates cardiac remodeling that will result in cardiomyocyte damage, atherosclerosis and intramyocardial cells fibrosis. This will cause myocardial stiffness and diastolic dysfunction. The purpose of the study is to discover correlation between Fibroblast Growth Factor 23 (FGF23) serum and left ventricle diastolic function in patients with chronic kidney disease. This is an observational study with cross-sectional methods. The sample is 30 patients diagnosed with chronic kidney disease (CKD). Patients are evaluated for Fibroblast Growth Factor 23 (FGF23) level in their serum, assessed the left ventricle diastolic function by measuring early diastolic velocity of the left ventricle (lateral e') using echocardiography.There is significantly increased of FGF23 serum levels and decreased of lateral e' value in chronic kidney disease case. There's also a strong correlation

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between FGF23 serum and filtration glomerulus rate (LFG) ($p<0.05$), and a strong correlation between FGF23 serum level with lateral e' as a component of left ventricle diastolic function. There's a strong correlation between FGF23 with left ventricle diastolic function in patients with CKD.

KEYWORDS *Chronic kidney disease, Fibroblast Growth Factor 23 (FGF23), left ventricle diastolic function, lateral e'*

INTRODUCTION

Chronic kidney disease is defined by Kidney Disease Improving Global Outcomes (KDIGO) 2012 as abnormalities of kidney structure or function, present for >3 months, with implications for health and marked with one or more signs of kidney damage (Kdigo, 2012). Kidney is the main organ that controls homeostasis of extracellular phosphate (Yan & Bowman, 2014), (Levin et al., n.d.) The main hormones that modulate phosphate in the kidney is *parathyroid hormone* (PTH) that produced by parathyroid glands, and FGF23 which synthesized and secreted by osteocytes and osteoblasts in the skeleton (Bergwitz & Jüppner, 2010). The change in phosphate metabolism is a consequences of CKD. Along with the decreased of LFG, there's a raise in urine fractional excretion of phosphate as a compensation to maintain normal phosphate serum level (Heron, 2018).

Fibroblast Growth Factor 23 can directly affect the left ventricle by changes in gene expression that is similar with those caused by chronic pressure overload, so there will be pathological Left Ventricular Hypertrophy (LVH) (Faul et al., 2011). LVH is an important mechanism of cardiovascular disease in CKD. Elevated levels of FGF23 are associated with higher risk of LVH and mortality in patients with CKD. in their study with mice as the test animals has found FGF23 expression in cardiac fibroblasts, cardiac myocytes hypertrophy that leads to LVH and diastolic dysfunction (Yan & Bowman, 2014).

RESEARCH METHOD

This is an observational study with cross-sectional methods. The study was conducted in Outpatient and Inpatient setting of Internal Medicine Department in Dr. M. Djamil Public Hospital of Padang along with other private hospitals in Padang in 6 months course. Population in this study is patients with CKD that came to polyclinic and those who had been admitted to Internal Medicine Department in Dr. M. Djamil Public Hospital of Padang and other private hospitals in Padang. The sample of this study is all patients with CKD in stage 3 to 5 that meet Kidney Disease Improving Global Outcomes (KDIGO) criteria and passed the exclusion criteria that were taken by consecutive sampling. The initial screening was done on the potential subjects and they were explained about the protocols of the study and already gave informed consent. The total of the sample in this study is 30 subjects. This study already got permission from the Research Ethics Committee in Medical Faculty of Andalas University.

Statistical analysis was done by using SPSS 22.0 version. Absolute correlation will give value of r = 1, very strong relationship (0.8-1.0), strong relationship (0.6-0.799), moderate relationship (0.4-0.599), weak relationship (0.0-0.399). Correlation is considered significant if $p < 0.05$.

RESULTS AND DISCUSSION

This study involved 30 patients with CKD with the characteristics that can be seen from Table 1. The mean FGF 23 serum in this study is 599.19 (579.27) pg/dl (normal valuea <90 pg/dl.) FGF 23 serum levels in this study is 304.75 pg/dl, with the lowest score 39.56 pg/dl and the highest score 1,777 pg/dl. The result of Shapiro-Wilk normality test showed FGF23 serum levels in this study is not normally distributed. Table 2 presents median score for FGF 23 serum level. On this study, there is 30 samples that were obtained after performing echocardiography and the mean lateral e' is 9.83 (2.32) and septal e' is 7.39 (2.55) cm/s.

Table 1: Characteristics of the samples in the study

Characteristics	n (%)	Mean (SD)
Gender		
Male	17 (56.67%)	
Female	13 (43.33%)	
Age (year old)		44.07 (13.81)
SBP (mmHg)		127.67 (13.82)
DBP (mmHg)		78.33 (12.06)
BMI (kg/m^2)		22.96 (3.41)
Urea (mg/dl)		81.93 (42.63)
Creatinine (mg/dl)		3.01 (1.71)
FBG (gr/dl)		86.87 (8.36)
2HPPG (gr/dl)		172.27 (22.46)
GFR (ml/min/1.73 m^2)		27.83 (12.71)
Total cholesterol (mg/dl)		170.40 (26.64)
LDL (mg/dl)		108.83 (27.88)
HDL (mg/dl)		33.43 (7.04)
Triglycerides (mg/dl)		148.63 (20.33)

Table 2: FGF 23 Levels in Patients with Chronic Kidney Disease

Variable	N	Median (Min-Max)
FGF23 (pg/dl)	30	304.75 (39.56-1,777.0)

Table 3: Lateral e' Value in Patients with Chronic Kidney Disease

Variable	N	Mean (SD)
Lateral e' (cm/s)	30	9.83 (2.32)

Table 4: Septal e' Value in Patients with Chronic Kidney Disease

Variable	N	Mean (SD)
Septal e' (cm/s)	30	7.39 (2.55)

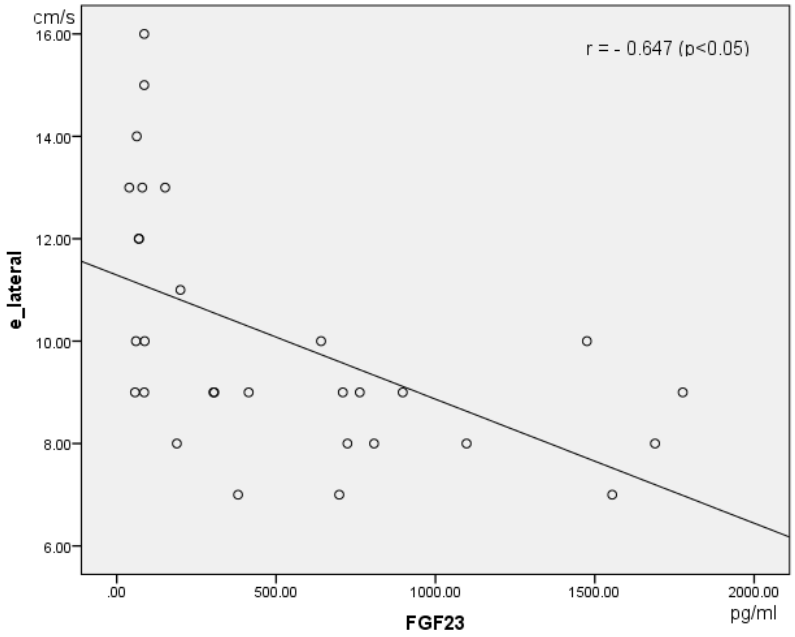

Figure 1. Correlation between FGF23 serum and lateral e'

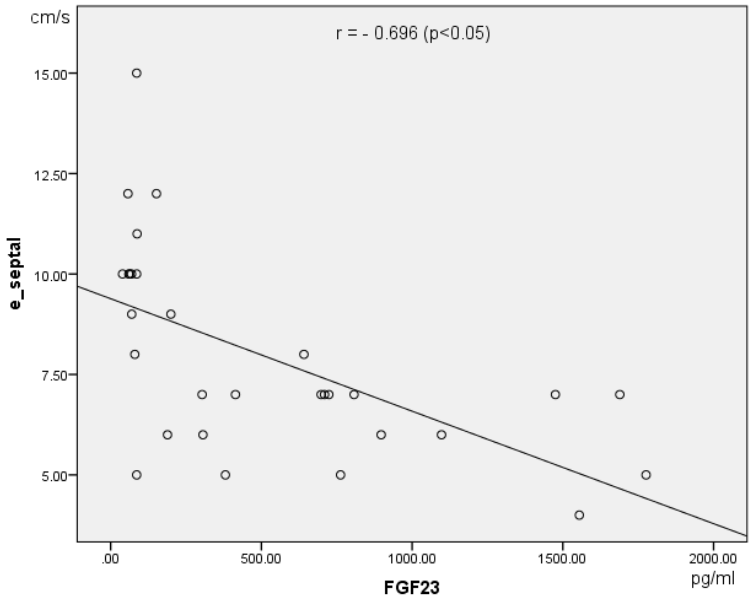

Figure 2. Correlation between FGF23 serum and septal e'

Figure 1 and 2 showed the correlation between FGF23 serum levels and left ventricle diastolic function in patients with CKD. Correlation analysis is done by using Spearman correlation test and we got p value <0.05. Analysis result showed that there is significant correlation between FGF23 serum levels with each lateral e' and septal e' ($p<0.05$) with direction of negative correlation and strong relationship (correlation coefficient lateral e' r = -0.65 and septal e' r = -0.69).

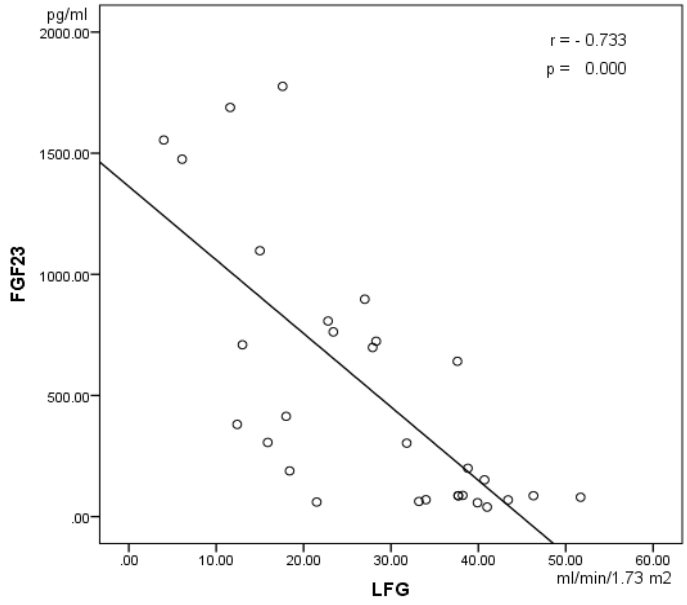

Figure 3. Correlation between FGF23 Serum with Glomerulus Filtration Rate in Patients with Chronic Kidney Disease

Figure 3 showed correlation between FGF23 serum levels with GFR in patients with CKD. Correlation analysis that's used is Spearman correlation test with confidence degree $p<0.05$. Analysis result showed there is significant correlation between FGF23 serum levels with GFR with direction of negative correlation and strong relationship (correlation coefficient $r = -0.733$).

From 30 subjects with CKD, 17 (56.67%) of them were males and 13 (43.33%) of them were females. This supports the study by Fliser D et al in 2007 at Germany's cohort study that include 227 nondiabetic patients with CKD stage 2-5 where there are 67.84% males and 32.16% females (Fliser et al., 2007). Based on Chathoth S et al in 2016 in Arab Saudi, males percentage is also higher (70.8%) than the females (29.21%) (Chathoth et al., 2016).

Contrary from the study by Tjekyan RMS in 2012 at Palembang, where female patients is higher than male patients with ratio of 56.3% : 43.7%. This study didn't find the significant correlation between CKD based on gender. Gender isn't the main risk factor of chronic kidney disease because this also associated with genetic and environmental factors (Tjekyan, 2014).

This study found the mean age of patients with CKD is 44.07±13.81-year-old, with the youngest is 17-year-old and the oldest one is 60-year-old. The similar result is also found from the study by Fliser D et al in nondiabetic patients with CKD stage 2-5 in Germany which is 46.57 year old (Fliser et al., 2007). Chathoth S et al in 2016 got the mean age for patients with CKD stage 3-5 is 42.6±15.6-year-old (Chathoth et al., 2016).

A study by Park M et al in 2012 at California showed that the mean age of patients with CKD is 59±11-year-old with mostly CKD stage 5 (Tjekyan, 2014). The mean age differences that has been found is may be caused by characteristics differences from the studied subjects. Krol GD in 2011 also said that CKD can occur in all age groups and gender and influenced by dietary and lifestyle (Bergwitz & Jüppner, 2010).

Mean body mass index or BMI in patients from this study is 22.96±3.41 kg/m^2. This result is similar with study by Chathoth S et al in 2016 at Arab Saudi with mean BMI 27.7±6.7 kg/m (Tonelli, Wanner, & Members*, 2014).

While Park M et al in 2012 got the mean BMI of 32 kg/m^2 with metabolic syndrome presents in most patients Park et al., (2012) In patients with CKD there might be changes in calories and proteins intake. Reduction in GFR will also reduce the protein and calory intake because of raised uremic toxin accumulation that leads to dietary habit and anorexia. But, patients with CKD only show the symptoms in end stage of kidney disease, so the low BMI with malnutrition is commonly found in CKD patients that already undergo hemodyalisis.

The mean systolic blood pressure (SBP) in the patients is 127.67±13.82 mmHg, and the mean diastolic blood pressure (DBP) is 78.33±112.06 mmHg. Patients who has history of hypertension is excluded from this study. Similar result is found in the study by Fliser et al., (2007) in Germany, from 227 patients with CKD and haven't been on hemodialysis yet, the mean SBP is 137.4 mmHg and DBP is 87 mmHg. The blood pressure in this study by Fliser can be

considered in control because the subjects are given antihypertensive drugs and the blood pressure was monitored. The study by Chathoth et al in 2016 shows mean SBP 146.3±22.4 mmHg, DBP 78.3±13.5 mmHg. In this study, patient with uncontrolled hypertension is still included.

Blood pressure in CKD patients tend to rise, especially in end stage renal disease, the blood pressure is significantly increased. Hypertension in CKD patients may be the result from vascular that happen because of the renal dysfunction (Ramadhan, n.d.). The mean fasting blood glucose of the patients in this study is 86.87±8.36 gr/dl and the 2 hour post prandial glucose is 172.27 gr/dl. This is similar to the criteria of the study where patient with history of diabetes mellitus is excluded from this patient.

Mean total cholesterol level of the patients is 170.40±26.64 mg/dl, mean LDL level is 108.33±27.88 mg/dl, mean HDL level is 33.43±7.04 mg/dl, and mean triglycerides level is 148.63±20.30 mg/dl. This result is similar with the study by Park M et al in 2012 at California, with mean LDL level is 100.25 (15.75) mg/dl, mean HDL level is 48.25(15.75) mg/dl, mean triglycerides level is 155.75(104.75) mg/dl and mean total cholesterol is 183.25 (44.25) mg/dl.

Patients with CKD also experience dyslipidemia. The abnormal lipid and lipoproteins in renal disease is varied, which include hypertriglyceridemia, hypercholesterolemia, elevation of LDL and low HDL level. Abnormality of lipid metabolism is caused by proteinuria that will increase 3-hydroxy-3-methylglutaryl CoA reductase level resulting in hypercholesterolemia (Tonelli et al., 2014).

The mean urea level in patients is 81.93±42.63 mg/dl and creatinine 3.01±1.71 mg/dl. This result is not much different from the study by Fliser D in 2007 on nondiabetic patients with CKD stage 2-5 with mean serum creatinine level 2.155. (Fliser et al., 2007).

Mean glomerulus filtration rate (GFR) in the patients is 27.83±12.71 ml/min/1.73 m^2, where the mean stage of CKD patients in is stage 4. This result is similar with Chathoth S et al in 2016, where the GFR is 24.44±4.73 ml/min/1.73m^2 (CKD stage 4).[8] Fliser D et al in 2017 stated that mean GFR in their study is 64.25 ml/min/1.73m^2 (CKD stage 3) (Fliser et al., 2007).

Fibroblast Growth Factor 23 (FGF23) is the most important phosphaturic hormone. FGF23 is secreted by osteocytes and osteoblasts.[14] The main organ target of FGF23 is the renal. Fibroblast Growth Factor 23 inhibits phosphate reabsorption by suppresses sodium phosphate cotransporter 2a and 2c in proximal tubules (Heron, 2018), (Shimada et al., 2004), (Kdigo, 2012). High level of FGF23 in chronic kidney disease is stimulated by persistent hyperphosphatemia, resulting in high plasma FGF23 concentrations and lead to target organ damage, including cardiovascular system (Scialla & Wolf, 2014).

Mean FGF23 in this study is 518.66 mg/dl. The median FGF23 serum is 304.75 mg/dl, with minimum level is 39.56 pg/dl and maximum 1,777 pg/dl. This study shows wide range FGF23 value that similar with study by Chathoth in 2016 that stated FGF23 level is volatile and has wide range (Chathoth et al., 2016)

Sakan H et al in 2014 conducted study with 236 CKD patients and showed that FGF23 serum is increased significantly in the early and intermediate CKD with p<0.005.[19] Negishi K et al in 2010 stated that mean FGF23 serum in patients who routinely had hemodialysis is 1,171±553 pg/ml (r=0.433, P=0.0001) (Bergwitz & Jüppner, 2010)

Chathoth et al in 2016 got mean FGF23 serum in stage 3 CKD patients as 61.2±14.1 pg/dl, while in stage 4 CKD patients 118.5±62.3 pg/dl and patients in stage 5 CKD is 1,526±1,456 pg/dl. This study showed that there is elevation in FGF23 on stage 3 CKD patients and it skyrocketed in stage 5 patients.

A prospective study by Titan et al in 2009 in patients with early to moderate CKD shows that there is elevation in plasma FGF23 level, and this event will accelerate worsening the CKD.[21] Juppner in 2011 also found unreasonable FGF23 elevation in patients with stage 3-5 CKD where serum levels may increase to more than 1000 times (Bergwitz & Jüppner, 2010).

Systolic dysfunction represents abnormality of the left ventricle that includes decreased of distensibility, impaired relaxation and abnormal filling that may be found symptomatic or asymptomatic (Ito et al., 2005), (Faul et al., 2011). Diastolic dysfunction of the left ventricle is the early stage of heart failure that can occur without any sign of heart failure, but there is already abnormality in the structure. Examination of e' from Tissue Doppler imaging (TDI) echocardiography is the first test that performed to assess the flow of left ventricle tissues in the early mitral flow (Sanderson, 2007).

In this study we got mean septal e' level 7.93 (2.55) cm/s (normal septal e' ≥8 cm/s) and lateral e' 9.83 (2.32) cm/s (normal lateral e' ≥10 cm/s). This study result is similar with the study by Seifert. ME et al in 2014 at America that observed 31 patients with 3 stage CKD and got the mean lateral e' 8 cm/s, it also showed that there is left ventricular diastolic dysfunction in 15 subjects from 48 subjects with p=1.00 (Zile et al., 2011).

In the study by Okamoto Y in Japan on patients with increased FGF23 level, it was found that the median e' for diastolic dysfunction in 5 (4,3-6,5) cm/s and p<0.05. Zoccali et al in 2004 stated that there is cardiovascular complications in CKD patients that may cause diastolic dysfunction (Zoccali et al., 2004).

The result of correlation test between FGF233 serum with lateral e' and septal e' as a component of left ventricle diastolic function from this study shows that it's statistically significant (p<0.05) with direction of negative correlation and strong relationship (correlation coefficient septal e' r=0.69 and lateral e' r=0.65). This study also found there's strong relationship between FGF23 serum and septal e' also lateral e', what we can conclude is the higher FGF23 serum level, the lower e' value that represents the left ventricle tissues and the poorer elasticity the left ventricle tissues have, and it also represents that the left ventricular diastolic dysfunction in chronic kidney disease patient is already happened.

We haven't found another study investigating relationship between FGF23 serum with septal and lateral e' that also evaluate left ventricle diastolic function in patients with CKD. Faul et al in 2011 had already done it in animals, where the

result show increased in FGF23 level will stimulate myocytes hypertrophy of the left ventricle and activated gene transcription that involved in cardiomyocytes hypertrophy. The high FGF23 level is independently associated with left ventricle hypertrophy and diastolic dysfunction.

While the study by Park M et al in 2012 shows reduced in GFR in patients with CKD associated with LVH and left ventricular mass index (LVMI). Okamoto Y et al in 2016 also found that FGF23 is associated with cardiac hypertrophy and reduced ejection fraction of the ventricle. As much as 269 patients (69 females, 200 males) with ejection fraction >50% were studied. This study shows insignificant relationship between FGF23 and left ventricular diastolic dysfunction, where only 30 (11.2%) from 269 patients that experience diastolic dysfunction.[28] It also happens in the study by Negishi K et al in 2010 in patients who routinely undergo hemodialysis, only LVMI is significantly correlated to FGF23 with r=0.268 and p=0.039.

Spearman test result between GFR and FGF23 serum level in this study shows statistically significant result ($p<0.05$) with direction of negative correlation and moderate relationship (correlation coefficient r= -0.733). Correlation between GFR and FGF23 serum level will be higher. From this study we can see that the poorer renal function is, the higher phosphate retention that happen and it represented from increased of FGF23 serum.

According to Fliser D et al in 2007 in nondiabetic patients with stage 3-5 CKD it found that there's negative correlation (r= -0.6) between GFE and FGF23 with $p<0.001$. In this study we get independent predictor factor that significantly has a role in the progressivity of CKD, which is GFR ($p<0.001$), FGF23 ($p=0.005$).[69]

Another study by Orlando Gutierrez et al in 2002 also found there's significant correlation between FGF23 and GFR with $r^2=0.44$ and p=0.001. The lower GFR represents poorer renal function that will increase phosphate retention and lead to FGF23 elevation. Elevation of FGF23 will also worsen the damage in the kidney and it can affect remodeling of the heart (Faul et al., 2011). Limitation of this study is there may be genetic factors that can affect FGF23 level and the diastolic function was not evaluated

CONCLUSION

There is increased in FGF23 serum in patients with CKD. There is reduction in the lateral e' value as a component of diastolic function in patients with CKD. There is strong correlation between FGF23 serum with lateral e' as a component of diastolic function in patients with CKD with the direction of negative correlation. There is strong correlation between FGF23 serum level with GFR in patients with CKD and negative correlation direction.

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