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SERUM CALCITRIOL AND INTACT PARATHYROID HORMONE LEVELS IN PATIENTS WITH NON-DIALYSIS CHRONIC KIDNEY DISEASE

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Abstract

Background: Chronic Kidney Disease (CKD) is associated with the processes of mineral and bone disturbance. The process results in secondary hyperparathyroidism leading to vascular calcification associated with increased morbidity and mortality of cardiovascular disease. In mineral and bone disorders, calcium and phosphate balance is disrupted and affect some biomarkers in CKD such as levels of calcitriol and parathyroid hormone. We determined the correlation between the levels of calcitriol and intact parathyroid hormone in patients with non-dialysis CKD.

Method: There were 62 CKD patients in Kidney and Hypertension Unit of Dr. Soetomo General Hospital. Patients aged >18, with no history of dialysis, were included in the study and were willing to participate by signing the informed consent. Serum calcitriol and intact PTH of subjects were measured using the Enzymeimmunoassay (EIA) and Electro-chemiluminescence immunoassay (ECLIA) method, respectively.

Results: There were 62 non-dialysis CKD patients consisted of 53 males (85.5%) and 9 females (14.5%). Out of 62, 8 patients had low calcitriol levels and 54 had normal calcitriol levels. The median values of calcitriol were 59.4 pmol/l (45-59 ml/m), 65.2 pmol/l (30-44 ml/m), 66.2 pmol/l (15-29 ml/m), and 60.1 pmol/l (<15 ml/ m), while the median values of PTH were 59.3 pg/ml (45-59 ml/m), 56.4 (30-44 ml/m), 92.1 (15-29 ml/m), 162.6 (<15 ml/m), respectively. Spearman correlation test showed no significant correlation between serum calcitriol and intact PTH levels in patients with non-dialysis CKD ($p<0.107$ and $r = -0.207$).

Conclusion: There was no significant correlation between the levels of serum calcitriol and intact PTH in patients with non-dialysis CKD.

Keywords: *chronic kidney disease, intact parathyroid hormone, calcitriol*

Introduction

Chronic kidney disease (CKD) is a public health problem in developed and developing countries. Its incidence number increases each year (1). Approximately 20 million adults in the United States suffer from various stages of chronic kidney disease. There are >400,000 patients with end-stage renal disease and >300,000 patients in need of hemodialysis. The risk of death increases with the increased progression of CKD (2). Cardiovascular complications are the leading cause of death in patients with CKD. The number of end-stage CKD patients who died from cardiovascular disorders is approximately 50%. There are two types of risk factors for cardiovascular complications, namely traditional (age, hypertension, smoking, diabetes, dyslipidemia, obesity) and non-traditional (increased CRP, liporotein a, homocysteine, chronic inflammatory disease, terminal CKD) (3, 4).

In CKD there is a decrease in renal mass and glomerular filtration rate (GFR). Renal mass and decreased GFR cause balance disturbance of calcium (Ca) and phosphate (P). Phosphate excretion through the kidneys decreases and results in increased levels of phosphate in the blood. In CKD also occurs interference production of enzyme 1α-hydroxylase in renal tubules that can inhibit the formation of inactive vitamin D (calciumol) into active vitamin D (calcitriol). Low levels of calcitriol cause the decreased absorption of Ca in the intestine. Continuously disrupted Ca and P balance may lead to increased parathyroid hormone (PTH) and osteodystrophy resulting in mineral and bone

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disorders in CKD (CKD-MBD) patients. Continuous CKD-MBD can lead to vascular calcification with an increased risk of morbidity and mortality in CKD patients (4).

Decreased levels of calcitriol begins with decreased renal function. Decreased levels of calcitriol are thought to contribute to GMT-CKD and secondary hyperparathyroidism. GMT-CKD is found in the majority of patients with chronic kidney disease stage 3-5, and is universally experienced by patients with stage 5 chronic kidney disease undergoing dialysis.

Calcitriol and parathyroid hormone contribute in maintaining a balance of serum calcium levels until GFR decreases by less than 20-25%. Decreased levels of calcitriol and increased parathyroid hormone in CKD disease can lead to impaired bone and mineral metabolism (2). One study showed that approximately 50% of patients with chronic kidney disease undergoing dialysis had secondary hyperparathyroidism. In addition to increased secretion of parathyroid hormone, the degradation of this hormone was also impaired (5). The results showed that calcitriol levels of >17 ng/L had a four-fold higher risk of death than calcitriol levels of >44 ng/L (6). Decreased levels of calcitriol occur relatively early in CKD progression and precede the increase of parathyroid hormone levels. In CKD there is a decrease of enzyme 1α-hydroxylase which inhibits the form-changing process of calcidiol into calcitriol. This leads to decreased levels of calcitriol in the blood (7). The results showed a correlation between decreased levels of calcitriol and elevated intact PTH levels in non-dialysis CKD patients (8)

It is important to early measure the levels of calcitriol and intact PTH for calcium and phosphate management in order to prevent complications from CKD-MBD. Understanding CKD-MBD in non-dialysis CKD patients is important for clinical management. Thus, the management of Understanding of CKD-MBD has an important effect on the survival of CKD patients (9, 10). This study aims to analyze the correlation between serum calcitriol and intact parathyroid hormone levels in patients with non-dialysis CKD.

Methods

This study was an analytical observational research with cross-sectional design. Subjects were selected through inclusion and exclusion criteria from the population of non-dialysis chronic kidney disease patients in Kidney and Hypertension Outpatient Installatio of Dr. Soetomo General Hospital Surabaya. The study was conducted from July to September 2015. Inclusion criteria consisted of male and female aged of ≥18 years with albumin of ≥3.5 g/dl, and willing to participate in research by signing informed consent. Patients receiving treatments such as phosphate binders, of calcium, or vitamin D analog and patients with chronic liver diseases were excluded.

Calcitrol is an active vitamin D as result of passive vitamin D conversion by the enzyme 1α-hydroxylase in the kidneys. Each patient was checked for calcitriol levels determined by measuring serum or plasma. The method used was Enzymeimmunoassay (EIA) with quantitative measurement (11). Intact parathyroid hormone was measured from serum using Electro-chemiluminescence immunoassay (ECLIA) and stated in pg/ml unit. (12).

After sampling for Laboratory examination and basic data, calcitriol, and intact PTH was performed, the data were analyzed using SPSS 17.0 (SPSS, Inc., Chicago, IL.). The data of CKD, calcitriol and intact PTH will be processed descriptively. Kolmogorov Smirnov test was conducted to assess the normality of data. The relationship between calcitriol and intact PTH will be tested analytically using Pearson for normally distributed data Spearman test for abnormally distributed data.

Results

There were 62 non-dialysis CKD patients in the Internal Disease Outpatient Installation of Dr. Soetomo General Hospital Surabaya that met the inclusion and exclusion criteria. The characteristics of the subjects can be seen in Table 1.

The number of male patients were higher than that of female patients. The mean age of patients was 52.02 years old. The youngest patient's age was 27 years old, while the oldest age was 65 years. The mean body mass index in the study sample was 23.43 kg. The lowest BMI was 16.5 kg and the highest was 32 kg. The distribution of subjects by glomerular filtration rate group based on KDIGO 2013 was highest in CKD patients with GFR of <15 ml/min (50%). Distribution of comorbid disease in patients was Diabetes Mellitus for 41 patients and Hypertension of 48 patients, while there were 32 patients with Diabetes Mellitus (DM) and hypertension (51.6%).

Table 2 shows the specific characteristics of the subjects including the mean of serum calcium level of 8.49 mg/dl, the mean serum phosphate level of 4.78 mg/dl, the mean of albumin of 3.89 mg/dl. Meanwhile, the distribution of calcium levels in 62

Table 1.

General characteristics of subjects

Characteristics	Number (n=62)	Mean ± SD	Range
Age (year)		52.05 ± 8.27	27 – 65
Gender (%)			
Male	53 (85.5%)		
Female	9 (14.5%)		
BMI (kg/m^2)		23.43 ± 3.49	16.5 – 32.0
Glomerular filtration rate (GFR)			
45-59 (stg 3a)	9 (14.5%)		
30–44 (stg 3b)	11 (17.7%)		
15–29 (stg 4)	11 (17.7%)		
< 15 (stg 5)	31 (50.0%)		
Comorbid diseases			
DM	41 (66.1%)		
Hypertension	48 (77.4%)		
DM + HT	32 (51.6%)		

patients was categorized to <8.4 mg/dl with 27 patients, optimal levels of 8.4-9.5 mg/dl with 32 patients, >9.5 mg/dl levels with 3 patients. In 62 non-dialysis CKD patients, we obtained median value of serum calcitriol level of 62.02 pmol/L with the lowest value was 11.96 pmol/l and the highest value of 97.98 pmol/l. Distribution of calcitriol levels in 62 patients was categorized into low levels of calcitriol <40 pmol/l in 8 patients (14.8%), and normal levels 40-100 pmol/l in 54 (85.2%) patients.

The distribution and median values of calcitriol and calcium were influenced by glomerular filtration rate. The lower GFR median values of calcitriol and calcium showed a downward trend. Meanwhile, the distribution and median values of calcitriol and phosphate were affected by glomerular filtration rate. The lower the GFR, the median value of calcitriol showed a downward trend while the median phosphate values show an increasing trend.

In 62 non-dialysis CKD patients, median of serum intact parathyroid hormone level was 97.89 pg/ml with the lowest value of 15.46 pg/ml and the highest value of 477.3 pg/ml. The distribution and median values of PTH and calcium were influenced by glomerular filtration rate. With lower GFR, the median PTH value showed an increasing trend, while the median calcium value showed a downward trend. The distribution and median values of PTH and phosphate were influenced by glomerular filtration rate. With lower GFR, the median PTH and phosphate values showed an increasing trend. The median values of calcitriol and intact PTH levels were based on the rate of gomerular filtration rate. Decreased glomerular fascial rate was accompanied by decreased median value of calcitriol and elevated intravenous PTH median values.

Table 2.

Special characteristics of subjects

Parameter	Hasil	Nilai
Serum calsium (mg/dl)	8.49 ± 0.68	8.4 – 9.5
Serum phosphat (mg/dl)	4.79 ± 1.86	3.5 – 5.5

Data normality test shows abnormal distribution so and thus Rank Spearman analysis was used to analyze the data. The result of Rank Spearman test shows that the correlation was not significant. Scatter diagram of calcitriol toward intact PTH concentration showed that the relation of calcitriol with intact PTH concentration in this study was negative or significant counterclockwise. This indicates that with decreasing calcitriol, the intact PTH level will be higher. The association between calcitriol and intact PTH levels indicates that the direction of the linear relationship was negative although the direction of the line did not decrease sharply.

Discussion

In this research, there were 62 samples of non-dialysis CKD patients at Kidney and Hypertension Outpatient Installation Dr. Soetomo General Hospital Surabaya. The number of samples is almost the same as the research, which is 76 patients with non-dialysis CKD (13). Meanwhile, this research obtained the number of samples larger than other studies, i.e. 1,814 patients with non-dialysis CKD (14). The mean of the subjects' age was 52 years old. The highest proportion of groups was aged 41-60 years old. The average age was 58 years (13). The mean of age in the United States was 66 years old (15).

The samples of the study were mostly male with ratio of 5,9: 1. The comparison of male and female gender was 2: 1 (13). CKD progression in postmenopausal women is higher than in men (16), which is similar to the number of CKD patients where the number of female is greater than male (14).

The subjects' obtained mean of body mass index in this study was normal, i.e. equal to 23.43 kg/m^2. This result was not different from that obtained in another study with 23.0 kg/m^2 (13). The mean of albumin content in our study was normal at 3.89 g/dl. The mean of albumin in our study was not much different from those in other studies with 3.7 g/dl (15), 3.9 g/dl (13) and 4.2 g/dl (14). These results indicate that the

nutritional status of CKD patients as samples in most studies were under normal conditions.

Comorbid disease accompanying CKD patients in this study was only diabetes mellitus and hypertension obtained from anamnesis of patients. The number of diabetes mellitus patients in our study was much higher than that of the other, with 66.1% of all samples. In another study it was found that the comorbids were diabetes mellitus with 47.3% and hypertension with 86.7% (14). In another study, diabetes mellitus was found in about 48.6% of the patients (13). Meanwhile, other studies found DM in about 26% of the patients (8). Other comorbid diseases found in our study is hypertension with 77.4%. Diabetic nephropathy occurs due to complications of diabetes and hypertension leading to chronic kidney disease. Some Asian countries are currently affected by the type 2 diabetes mellitus epidemic or Insulin Independent Diabetes Mellitus (IIDM). This is due to the increase of elderly population, the prevalence of obesity, and lifestyle changes.

The mean of calcium level in this study is normal with 8.49 mg/dl. However, there are studies showing higher mean of calcium levels with 9.1 mg/dl (17) 9.0 mg/dl (13), and 9.4 mg/dl (8). The normal mean of calcium level is likely to be influenced by a lower calcium content diet in some populations in Indonesia. In addition, it is also likely influenced by exposure to sunlight that many found in Asian countries.

In this study the mean of phosphate level is normal, i.e. 4.79 mg/dl. The mean of phosphate content is 4.8 mg/dl (13). Another study has the mean phosphate content that is lower than the other studies, which is 3.4 mg/dl (8). The average normal phosphate levels in our study may be influenced by the lower phosphate dietary content in some populations in Indonesia.

In this study, the highest calcitriol content of the sample was 97.98 pmol/L and the lowest was 11.96 pmol/L. Most of the samples in our study had normal levels of calcitriol of 54 samples, while 8 samples had low levels of calcitriol. This is similar to the research obtained low levels of calcitriol and normal (14). The data distribution of median values of calcitriol content in this study was grouped according to GFR decrease as follows: GFR 45-59 ml/min with median value of 59.4 pmol/L, 30-44 ml/min with median value of 65.2 pmol/L, 15-29 ml/min with median value of 66.2, less than 15 ml/min with median value of 60.1 pmo/L. The median value is used because the data distribution is not normal.

Most calcitriol levels showed normal values because the amount of the 1α-hydroxylase enzyme in this study sample was likely to be in normal condition, probably because of the effect of more sun exposure in Asian countries or possibly because of the effect of extra renal 1α-hydroxylase enzymes. Although levels of calcitriol were mostly normal, the calcitriol levels at GFR of 15-29 ml/min and GFR of less than 15 ml/min indicated a downward trend.

In this study obtained median serum intact PTH levels of 97.89 pg/ml. Meanwhile this study reported that the mean of intact PTH levels in whole race was 101 pg/ml (15). Several studies have also shown that intact PTH levels in various regions vary widely. The mean of intake PTH of each racial group were 130 pg/ml for the white race, 249 pg/ml African-American race, 93 pg/ml of Asian race and 130 pg/ml for hispanic race. The levels of intact PTH among the races have different results and the Asian race has lower mean of intact PTH than other races.

In this study, the intact PTH levels were not too high High number of patients with DM (66%) was suspected to influence the PTH levels. . Patients with DM turned out to have a relatively lower PTH levels when compared with non-DM patients. The relatively shorter progression of CKD in CKD patients with DM was thought to be a factor that caused lower PTH levels in CKD patients with DM. A shorter progression in DM patients was thought to have an effect on the reduced parathyroid gland hyperplasia and thus the PTH was relatively lower than in non-DM patients.

This study showed a non-significant relationship between decreased levels of calcitriol and elevated intact PTH levels, but trend line showed decreased levels of calcitriol with elevated PTH levels in accordance with decreased glomerular filtration rate and showed an inverse relationship. This study showed that the trend line relationship was reversed between levels of calcitriol decreased with levels of increased intact PTH (14). Meanwhile, another study found a significant relationship between levels of calcitriol with intact parathyroid hormone levels (8). Other studies showed a non-significant association between the levels of calcitriol and intact PTH levels (13). The results were not significant in the study, suggesting a possible influence of other variables This is suspected because there are that affect the increase in PTH is also caused by the number of samples of the study is less than other studies. Geographical factors are also suspected to affect the results of research.

In study that attempted to analyzecalcitriol, phosphate, calcium and intact PTH. A significant correlation (p=0.012 and r=0.316) between intravenous and phosphate PTH levels was obtained. This showed an increased phosphate level associated with elevated intact PTH levels. Phosphate levels had an effect on intact PTH rather than calcium and calcitriol levels.

Conclusion

There was no significant association between levels of calcitriol and intravenous PTH levels in non-dialysis CKD patients. This study did not show an association between decreased levels of calcitriol and increased intact PTH in non-dialysis CKD patients, suggesting a possible influence by other variables resulting in the intensive PTH increase.

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