Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 May 22; 9(B):470-474.
https://doi.org/10.3889/oamjms.2021.6097
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Nephrology*

OPEN ACCESS

The Correlation between Estimated Glomerular Filtration Rate and Parathyroid Hormone Levels in Predialysis-chronic Kidney Disease Adult Patients at Sanglah General Hospital, Bali, Indonesia

Sianny Herawati[1]*, Yenny Kandarini[2], I Putu Yuda Prabawa[1]

[1]*Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;* [2]*Department of Internal Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia*

Edited by: Ksenija Bogoeva-Kostovska
Citation: Herawati S, Kandarini Y, Prabawa IPY. The Correlation between Estimated Glomerular Filtration Rate and Parathyroid Hormone Levels in Predialysis-chronic Kidney Disease Adult Patients at Sanglah General Hospital, Bali, Indonesia. Open Access Maced J Med Sci. 2021 May 22; 9(B):470-474. https://doi.org/10.3889/oamjms.2021.6097
Keywords: Chronic kidney disease; Parathyroid hormone; Glomerular filtration rate
***Correspondence:** Sianny Herawati, Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia. E-mail: siannyherawati93@gmail.com
Received: 29-Mar-2021
Revised: 10-May-2021
Accepted: 12-May-2021

Funding: This study obtained an Udayana Research Grant from the Universitas Udayana, Bali, Indonesia, with the number B/20-135/UN14.4.A/LT/2020.
Competing Interests: The authors have declared that no competing interests exist.

Abstracts

BACKGROUND: Chronic kidney disease (CKD) is a structural or functional kidney disease for more than 3 months. In predialysis CKD patients, the serum parathyroid hormone levels increase progressively since the early stages of the disease to maintain phosphate homeostasis. Glomerular filtration rate (GFR) has been widely accepted to assess renal function. The GFR assessment is used to determine the CKD stadium.

AIM: This study aims to analyze the correlation between GFR and parathyroid hormone levels in predialysis CKD patients undergoing treatment at Sanglah General Hospital Denpasar.

METHODS: A cross-sectional observational study was conducted among predialysis CKD patients undergoing treatment at Sanglah General Hospital Denpasar who met the inclusion and exclusion criteria. The inclusion criteria were adult patients (≥18 years) who were accepting to participate in the study. Exclusion criteria were patients with predialysis CKD after thyroidectomy and/or parathyroidectomy and liver disease. The parathyroid hormone levels, blood urea nitrogen, creatinine, and GFR were examined and analyzed by SPSS version 17 for Windows.

RESULTS: A total of 77 patients with predialysis CKD in this study obtained a median of e-GFR of 21.09 (4.72–75.80) mL/min/1.73 m^2. The median level of parathyroid hormone was 82.07 pg/mL (15.83–716.60 pg/mL). Spearman's correlation analysis results obtained a strong and significant negative correlation between the e-GFR value and parathyroid hormone levels ($r = -0.540$; $p = 0.000$).

CONCLUSION: The parathyroid hormone levels assessment could be used as a recommendation in evaluating the CKD progressivity among predialysis adult patients at Sanglah General Hospital, Bali, Indonesia, due to the strong significant correlation.

Introduction

Chronic kidney disease (CKD) is currently increasing and has become a serious health problem [1]. The global prevalence for CKD was 13.4%, with 10.6% at CKD stages 3–5 [2]. Global Burden of Disease 2015 states that kidney disease is the 12th cause of death globally and is projected to be the 5th cause of death in 2040 [3]. Over the past 10 years, the death rate due to CKD has increased by 31.7% [4]. According to the 2018 Basic Health Research (RISKESDAS) data, the population aged ≥15 years diagnosed with chronic kidney failure in Indonesia is 0.38% and for Bali Province, the prevalence of CKD is 0.44%, with the proportion of CKD patients undergoing hemodialysis is 37.04% [5]. Data at the Sanglah Denpasar Central General Hospital (RSUP) in 2018, CKD patients ranked first out of the top 10 cases of all patients visiting the internal medicine polyclinic. In May 2019, the total number of CKD patient visits was 25% of the total patients who visited the internal medicine polyclinic [6].

Secondary hyperparathyroidism is a complication that often occurs in patients with CKD, which is a mineral and bone metabolism disorder known as mineral and bone disorders in CKD (MBD-CKD) [7]. This disorder's pathogenesis is characterized by increased secretion of parathyroid hormone and hyperplasia of the parathyroid glands in response to low phosphate and serum 1,25-dihydroxy Vitamin D retention [7]. Secondary hyperparathyroidism will cause vascular calcification associated with increased cardiovascular disease mortality [8], [9], [10]. The prevalence and burden of cardiovascular complications increase with decreasing kidney function. The risk of death from cardiovascular disease is 8 times, 2 times greater in patients with stage CKD G5 A3 (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2 and urine albumin to creatinine ratio >300 mg/g) than in populations without kidney disease [10].

In predialysis CKD serum, parathyroid hormone levels increase progressively from the early stages of the disease to maintain phosphate homeostasis [11]. Nearly 20% of patients with eGFR >60 mL/min/1.73 m^2 experienced increased parathyroid hormone levels

and increased when kidney function deteriorated [12]. The incidence of secondary hyperparathyroidism was reported to increase according to the increase in the CKD stage, namely: 40% at Stage 3, 70% at Stage 4, and> 80% at Stage 5 [8]. Research by de Boer *et al*. found that parathyroid hormone levels have a negative significant correlation with e-GFR ($r = -0.48$; $p < 0.0001$) [13]. However, a previous study by de Boer *et al*. did not mention the etiology diagnosis regarding the CKD-patients in evaluating the parathyroid level. In addition, a multicenter cohort study in predialysis CKD patients found that a persistent increase in serum parathyroid hormone was associated with a worse prognosis independent of baseline serum parathyroid hormone and phosphate values [12].

Kidney Disease Improving Global Outcomes (KDIGO) 2017 recommends routine parathyroid hormone, calcium, and phosphate checks on CKD patients starting from stage 3–5 to prevent or delay complications related to CKD [14]. KDIGO also suggests that MBD-PGK management should be based on serial measurements of parathyroid hormone serum and the tendency to persistently increase parathyroid hormone levels above the upper limit of normal value has more clinical significance than just one measurement [15]. Based on those mentioned above, this study aims to analyze the correlation between e-GFR and parathyroid hormone levels in predialysis CKD patients undergoing treatment at Sanglah General Hospital.

Methods

Sample criteria

A cross-sectional observational study has been conducted among 77 CKD patients at the Nephrology Polyclinic and inpatient rooms of the Sanglah General Hospital Denpasar from July 2020 to September 2020. The inclusion criteria were patients who had been diagnosed with CKD and have not undergone dialysis. Male and female aged ≥ 18 years who are participating in this study had been signed the informed consent. In comparison, the exclusion criteria in this study included patients with a history of post-thyroidectomy and/or parathyroidectomy as well as a history of chronic liver disease. The sampling technique was carried out consecutively. The etiology of CKD mention in this study was diabetic nephropathy, chronic pyelonephritis, obstructive nephropathy, polycystic kidney, gout nephropathy, and nephrosclerosis.

Variables assessed

e-GFR is GFR measured numerically using the CKD Epidemiology Collaboration (CKD-EPI) formula. e-GFR is the GFR measured using the CKD-EPI formula, which has units of ml/min/1.73 m^2. Parathyroid hormone level is the parathyroid hormone level of the predialysis CKD patient who was checked using the Cobas e601 Roche Diagnostics, GmbH, Germany, using the Electrochemiluminescence immunoassay method. The sample used was venous blood serum using a tube using a 3 ml red cap tube. The unit used in the measurement scale in this study is pg/ml. Meanwhile, what is meant by patients with CKD are patients who have been diagnosed with CKD according to the KDIGO criteria upheld by a doctor in the Internal Medicine department and have never undergone dialysis based on medical record records. Other clinical data assessed in this study included proteinuria (mg/dL), status of diabetes mellitus, blood pressure (mmHg), and body mass index (BMI) (kg/m^2).

Data analysis

All data obtained in this study were analyzed descriptively. The results will be presented in the form of mean ± standard deviation if the data are normally distributed and in the median (minimum-maximum) form if the data are not normally distributed. Respondent characteristic data are displayed in the form of absolute numbers and percentages. The data normality test used Kolmogorov–Smirnov and the correlation between GFR and intact PTH levels used the Spearman correlation. Data were analyzed using SPSS version 17 for Windows.

Results

About 77 patients with predialysis CKD followed this study at the Sanglah Hospital Nephrology polyclinic, who met the inclusion and exclusion criteria. The characteristics of CKD patients who are research subjects are shown in Table 1. In this study, the median age of the patients was 61 years. The youngest patient was 23 years old, while the oldest patient was 81 years old. The number of male patients is more than the number of female patients. The patient's median BMI was 22.9 kg/m^2, the lowest BMI was 16.3 kg/m^2, and the highest was 34.4 kg/m^2 (Table 1).

Based on the CKD stage according to KDIGO 2017, at Stage 2 it was 2.6%, Stage 3a: 9.1%, Stage 3b: 16.9%, Stage 4: 28.6%, and Stage 5: 42.9%. Based on the etiological diagnosis, the patients were diabetic nephropathy 44.2%, chronic pyelonephritis 31.2%, obstructive nephropathy 18.9%, nephrosclerosis 5.2%, polycystic kidney, and uric acid nephropathy, respectively, 1.3% (Table 1). In addition, a total of 77 predialysis CKD patients had a median e-GFR (CKD-EPI) value of 21.09 (4.72–75.80) mL/min/1.73 m^2

Table 1: Baseline characteristic of respondents

Characteristics	Percentage	Median (min-max)
Age (years)		61 (23.00–81.00)
Gender		
Male	50 (64.90)	
Female	27 (35.10)	
BMI (kg/m^2)		22.9 (16.30-34.40)
CKD stage (kg/m^2)		
Stadium 2 (60–89)	2 (2.60)	
Stadium 3a (45–59)	7 (9.10)	
Stadium 3b (30–44)	13 (16.90)	
Stadium 4 (15–29)	22 (28.60)	
Stadium 5 (<15)	33 (42.90)	
Etiology diagnosis		
Diabetic nephropathy	34 (44.20)	
Chronic pyelonephritis	24 (31.20)	
Obstructive nephropathy	13 (16.90)	
Polycystic kidney	1 (1.30)	
Gout nephropathy	1 (1.30)	
Nephrosclerosis	4 (5.20)	
Predialysis assessment		
e-GFR (CKD-EPI) (mL/min/1.73 m^2)		21.09 (4.72–75.80)
Parathyroid hormone (pg/mL)		82.07 (15.83–716.60)
Parathyroid hormone classification (pg/mL)		
Low (<15)	0 (0.00)	
Normal (15–65)	30 (38.96)	
High (> 65)	47 (61.04)	
BUN (mg/dL)		36.60 (11.40–107.90)
Serum creatinine (mg/dL)		2.94 (0.96-10.30)
Blood pressure (mmHg)		
Systole		120 (120-170)
Diastole		80 (80-90)
Diabetes mellitus		
Yes	48 (62.30)	
No	29 (37.70)	
Proteinuria (mg/dL)		100.00 (0.00–600.00)

GFR: Glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration, BMI: Body mass index, BUN: Blood urea nitrogen

(Table 1). Besides, the median value of parathyroid hormone levels in predialysis CKD patients was 82.07 (15.83–716.60) pg/mL (Table 1). The distribution of parathyroid hormone levels in 77 patients was categorized into normal (15–65 pg/mL) in 30 (38.96%) patients and high (>65 pg/mL) in 47 (61.04%) patients. There were no low parathyroid hormone levels <15 pg/mL in the study patients (0.00%) (Table 1).

Spearman correlation test was also conducted between the CKD stage and parathyroid hormone levels. There was a significant low-positive correlation between the CKD stage and parathyroid hormone levels ($r = 0.362$; $p = 0.000$) in predialysis CKD patients (Table 2). However, a Spearman correlation test found a significant moderate negative correlation between e-GFR and parathyroid hormone levels ($r = -0.540$; $p = 0.000$) in predialysis CKD patients (Table 2).

Table 2: Spearman correlation test of parathyroid hormone levels to the CKD stages and e-GFR levels in predialysis CKD patients

Variables	Parathyroid hormone levels (pg/mL)	
	r	p
CKD stages	0.362	0.000*
e-GFR (mL/min/1.73 m^2)	−0.540	0.000*

CKD: Chronic kidney disease, e-GFR: Estimation of glomerular filtration rate, *Statistically significant if p<0.001.

Discussion

CKD is a common condition that refers to a long-term loss of kidney function [16]. CKD in primary care is commonly asymptomatic, and the exact pathology underlying its development is often unknown (as no renal biopsy is usually performed) [16]. It is identified and defined by the presence of an abnormality of kidney structure or function (or both) present for at least 3 months by evaluating the GFR [17]. Several studies have shown that there was a relationship between GFR and parathyroid hormone levels in predialysis-CKD where it could lead to the parathyroid hormone levels increase progressively from the early stages of the disease to maintain phosphate homeostasis and worsening the prognosis [18], [19], [20].

A significant negative correlation was found between the e-GFR value and parathyroid hormone levels in CKD predialysis patients at Sanglah General Hospital, Bali, Indonesia. Research Pala *et al*. found that 57.5% of their study patients had hyperparathyroidism with a significantly higher frequency of stage four CKD compared to third stage CKD (47.1% third stage CKD, and 89.3% fourth stage CKD, $p < 0.001$) [21]. A cross-sectional study involving 415 CKD patients in Spain received the median parathyroid hormone at stage three CKD of 86 pg/mL and 120 pg/mL at stage four CKD [22]. In addition, the previous studies by Levin *et al*. and Wei *et al*. stated that the prevalence of significantly increased parathyroid hormone levels occurs at eGFR <50 ml/min/1.73 m^2 [8], [23]. Based on the eGFR group, it can be concluded that the median distribution of parathyroid hormone levels in the eGFR group Stages 2–5 shows a tendency to increase with decreasing eGFR values.

This study also suggests a significant low-positive correlation between the CKD stage and parathyroid hormone levels. Several previous studies also showed a significant correlation between eGFR and parathyroid hormone levels, namely, de Boer *et al*. ($r=-0.48$; $p<0.0001$) and Malawadi *et al*. ($r = -0.718$; $p < 0.001$) [13], [24]. An increase in parathyroid hormone is considered an early marker of MBD-CKD. Examination of parathyroid hormone levels in CKD is a significant predictor of cardiovascular morbidity and mortality, endothelial dysfunction, or systemic inflammation. KDIGO 2017 recommends performing routine parathyroid hormone examinations for CKD patients starting at Stage 3–5 to prevent or delay complications of BMD-CKD [10], [13], [24].

Based on the discussion above, the authors assume that early evaluation of parathyroid hormone evaluation, from the Stage 1, has a significant role in preventing the progressivity of CKD among predialysis adult patients as well as delaying the future complications. However, further study with bigger sample size, longitudinal study, and follow-up evaluation of parathyroid hormone are suggested to clarify the limitation of this study.

Conclusion

The parathyroid hormone levels assessment could be used as a recommendation in evaluating the CKD progressivity among predialysis adult patients at Sanglah General Hospital, Bali, Indonesia, due to the strong significant correlation.

Ethics Consideration

Ethics approval has been received from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia with Number:1613/UN14.2.2.VII.14/LT/2020 prior to the study being conducted.

Author Contribution

All authors equally contributed to the study from the conceptual framework, data gathering, and data analysis until the publication of the study results.

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