

# Correlation Between Parathyroid Hormone Levels with Urinary Magnesium Excretion in Patients with Non-Dialysis Dependent Chronic Kidney Disease

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**Background:** Disorders of mineral metabolism occur in most patients with chronic kidney disease (CKD). The aim of this work was to correlate parathyroid hormone (PTH) levels with urinary magnesium excretion in patients with non-dialysis dependent CKD.

**Methods:** Cross-sectional study. Concentrations of creatinine, magnesium, calcium, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D] and alkaline phosphatase (ALP) were determined in blood samples. The assessment of urinary magnesium levels was performed by means of total daily excretion and by the excretion fraction (FEMg).

**Results:** The study evaluated 163 patients with a mean age of  $60.7 \pm 11.7$  years and 51.0% were male. In the highest quartile of PTH ( $>89.5$ pg/mL), the mean levels of FEMg and ALP were higher ( $p < 0.05$ ). In the unadjusted regression analysis, the following variables were related to serum PTH levels: FEMg (odds ratio (OR) = 1.12; 95% confidence intervals (CI): 1.02–1.23), calcium (OR = 0.45; 95% CI: 0.22–0.90), ALP (OR = 1.02; 95% CI: 1.00–1.03) and eGFR (OR = 0.92; 95% CI: 1.00–1.03). After an adjusted analysis, only one FEMg and ALP will remain correlated with PTH.

**Conclusion:** In patients with non-dialysis dependent CKD, FEMg and ALP were some variables that remained associated with PTH.

**Keywords:** magnesium, parathyroid hormone, kidney diseases

## Background

Chronic kidney disease (CKD) is a major public health problem and is characterized by a slow progressive and irreversible loss of kidney function.<sup>1</sup> With the progression of kidney disease, changes in mineral metabolism are observed, such as hypocalcaemia, hyperphosphatemia, decreased levels of 1.25-dihydroxyvitamin D and elevated parathyroid hormone (PTH), constituting secondary hyperparathyroidism.<sup>2,3</sup>

Disorders of mineral metabolism that occur in almost all patients with CKD in the most advanced stages of the disease are associated with bone loss and fractures, cardiovascular disease, inflammation and increased mortality. Although calcium and vitamin D have been the focus of bone health, other vitamins and minerals have been investigated.<sup>4</sup> Magnesium (Mg) has attracted the interest of researchers, as a significant association has been identified between bone mineral density and levels of Mg, an essential micronutrient with a wide range of metabolic, structural and regulatory functions.<sup>5–7</sup>

The kidneys are the main organs involved in magnesium homeostasis, since they control its serum concentration mainly by modulating excretion in the urine.<sup>7,8</sup> Studies have shown that the magnesium excretion fraction (FEMg) is a sensitive and useful marker for detecting early abnormalities in the kidney's tubulointerstitial structure, like tubular lesion marker even in individuals without chronic kidney disease.<sup>9,10</sup>

The importance of Mg is well known, although it has not yet received the necessary attention in clinical practice. As CKD progresses, the levels of PTH increase, which acts as a uremic toxin and can contribute to disorders in the metabolism of minerals.<sup>2</sup> Although the literature has shown an association between the levels of PTH and serum Mg, the urinary excretion of Mg is not routinely evaluated, and most studies are performed with patients on dialysis. The hypothesis of this investigation is that the increase in serum levels of PTH is correlated with urinary excretion of Mg in patients with non-dialysis CKD.

## Methods

### Study Design and Participants

Cross-sectional study developed with non-dialysis CKD patients under treatment followed up at the Center for Prevention of Kidney Diseases (CPDR) of the Federal University of Maranhão (HUUFMA). The protocol, consent form, and study documents were approved by the HUUFMA ethics review board (2.727.940). Trial was conducted in accordance with the Declaration of Helsinki.

The study included patients with chronic kidney disease undergoing non-dialysis treatment in stages 3A, 3B and 4, of both genders aged 20 years or older and who were under follow-up at CPDR-HUUFMA. Pregnant women, carriers of autoimmune, infectious diseases, cancer, acquired immunodeficiency syndrome, thyroid disorders and urinary tract infection, who had hypomagnesaemia in need for replacement, and those with excessive alcohol consumption and using medications such as loop diuretics, proton pump inhibitors, aminoglycosides, adrenergic beta-agonists, cisplatin, cyclosporine, active vitamin D and theophylline were not included in the study.

Informed consent for participating in the work was obtained from all the examinees prior to their inclusion. Patients answered a standardized questionnaire containing questions related to demographic, socioeconomic characteristics, lifestyle and history of past and current diseases, in addition to the drug therapy in use. To characterize

alcohol consumption, the AUDIT (Alcohol-use disorders identification test) was used.<sup>11</sup>

Blood pressure was measured using the oscillometric method (Omron<sup>®</sup> 705-IT device, Japan) and in accordance with the guidelines of the European Hypertension Society, 2018.<sup>12</sup> Blood samples were collected after a 12-hr overnight fast and included creatinine (Jaffé reaction colorimetric method), magnesium (colorimetric method with chlorophosphan III), calcium (colorimetric method), phosphate (UV-automated molybdate method), parathyroid hormone (electrochemiluminescence method), 25(OH)D (chemiluminescence method), albumin (Jaffé reaction colorimetric method) and alkaline phosphatase (colorimetric method). When data were expressed in alternative units by external laboratories, the following conversion factors were used: 25-(OH)D, ng/mL to nmol/L:  $\times 2.496$ ; PTH, pg/mL to pmol/L:  $\times 0.1064$ ; Calcium, mg/dL to mmol/L:  $\times 0.2495$ ; Phosphate, mg/dL to mmol/L:  $\times 0.3229$ ; Magnesium, mg/dL to mmol/L:  $\times 0.4105$ .

Twenty-four-hour urine was used to measure urinary magnesium and creatinine excretion. The assessment of urinary magnesium levels was performed by means of total daily excretion and the fraction of excretion. The calculation of the urinary magnesium excretion fraction was performed using the following formula:  $[\text{MgU} \times \text{CrS}] / [(0.7 \times \text{MgS}) \times \text{CrU}] \times 100$ ,<sup>13</sup> where MgU = urinary magnesium; CrS = serum creatinine; MgS = serum magnesium; CrU = urinary creatinine. Values above 6.1% were considered altered.<sup>9</sup> The samples of 24-hr urine with a volume below 400mL or with urinary creatinine  $<15\text{mL/Kg}/24\text{h}$  (men) and  $<10\text{mL/Kg}/24\text{h}$  (women) were considered due to the possibility of error in the collection.

For the definition of CKD, two previous assessments of renal function were considered with a minimum interval of 3 months, as instructed by KDIGO.<sup>14</sup> Glomerular filtration rate (GFR) was estimated using the formula derived from the CKD-EPI study,<sup>15</sup> using creatinine as a reference for the calculation. From the results found, it was possible to obtain CKD staging.

The assessment of nutritional status was performed by means of the body mass index (BMI), obtained by the ratio between body mass and height square, and the classification proposed by the World Health Organization<sup>16</sup> for adults and that of LIPSCHITZ<sup>17</sup> for the elderly.

### Statistical Analysis

In the statistical analysis of the data, a descriptive analysis was performed to characterize the patients. Categorical

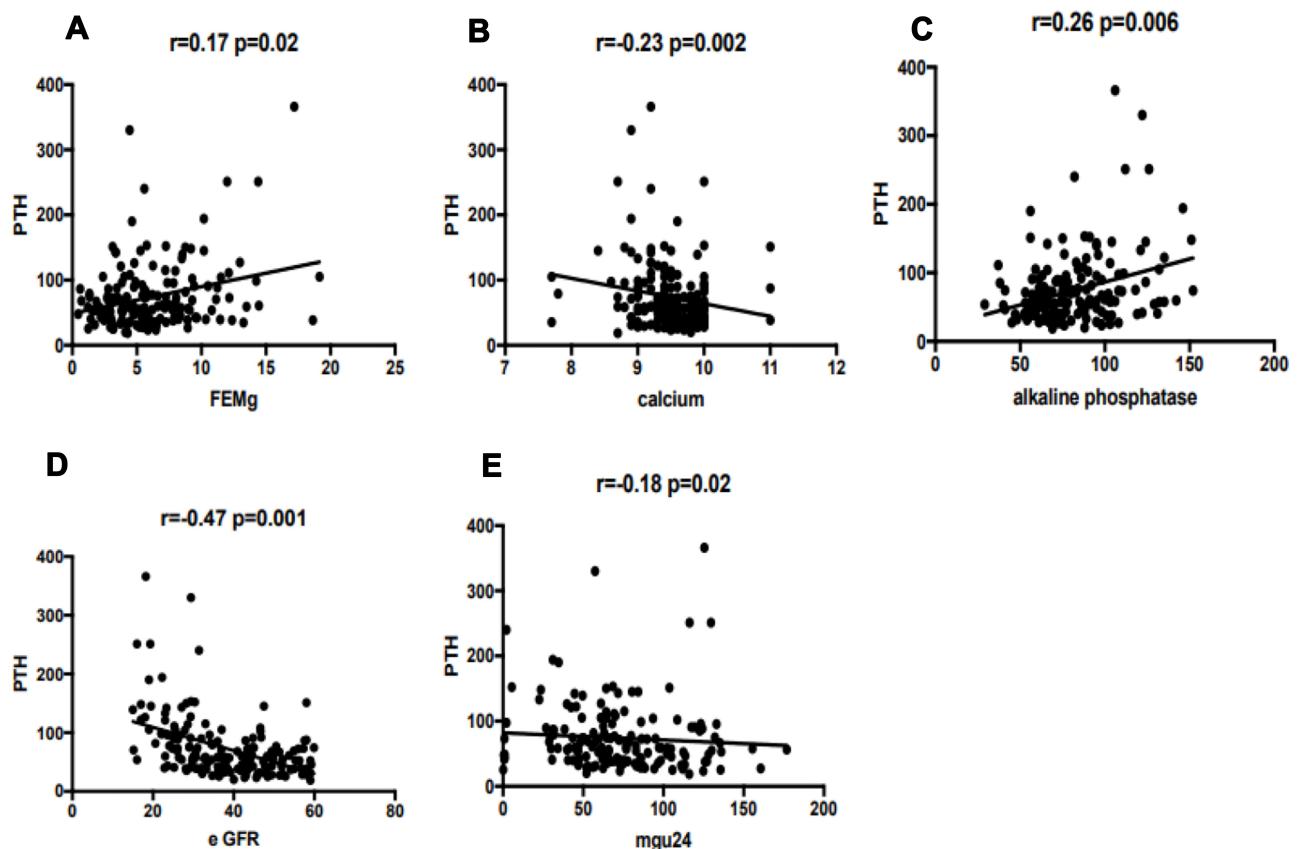
variables were presented using frequencies and percentages and quantitative variables using means and standard deviations (mean  $\pm$  SD). The normality of the variables was tested by the Shapiro–Wilk test. To assess the variables studied among the PTH quartile analysis of variance (ANOVA) or Kruskal–Wallis was performed. Pearson or Spearman linear correlation coefficient analysis was used to assess the degree of relationship between two quantitative variables (Figure 1). Logistic regression models were constructed for the PTH response variable ( $<$ quartile 4;  $\geq$  quartile 4). All variables studied were considered in the univariate model, and the final model was adjusted for the variables clinically related to PTH (25 (OH)D and phosphate) and the variables that presented  $p < 0.10$  in the univariate analysis. Odds ratio (OR) and its confidence intervals were obtained (95% CI). Statistical significance was set at a  $p$ -value  $< 0.05$ , and all analyses were performed using SPSS statistical software (Version 21; IBM Corporation, Chicago, IL).

## Results

The present study evaluated 163 patients with a mean age of  $60.7 \pm 11.7$  years and male individuals prevailed (51.0%). Among those evaluated, 15.3% consumed alcoholic beverages, 6.7% smokers, 50.3% practiced physical activity and 57.1% were overweight according to the BMI. Arterial hypertension was present in 89.0% of patients, 45.4% were diabetic and 68.7% were in stage 3 (3A and 3B) of CKD (Table 1).

Most patients (68.7%) were in stage 3A and 3B (eGFR  $59\text{--}30$  mL/min/1.73m<sup>2</sup>) with an average eGFR of  $37.6$  mL/min/1.73m<sup>2</sup>. The serum levels of magnesium, calcium, phosphate and vitamin D were within normal parameters. On the other hand, FEMg and serum levels of alkaline phosphatase and PTH were increased (Table 1).

Table 2 shows the biochemical indicators according to PTH quartiles. In the highest quartile of PTH ( $>89.5$ pg/mL), the mean levels of FEMg and alkaline phosphatase were higher ( $p < 0.05$ ), as well as the levels of serum calcium and eGFR were lower ( $p < 0.05$ ).



**Figure 1** Linear correlation between PTH with FEMg (A), total calcium (B), alkaline phosphatase (C) estimated Glomerular Filtration Rate (D) and urinary magnesium 24hs (E) in non-dialysis CKD patients.

**Notes:** Figure 1 demonstrates the correlations between laboratory variables and serum PTH levels. There was a positive correlation between PTH and alkaline phosphatase ( $r = 0.26$ ;  $p = 0.006$ ) and FEMg ( $r = 0.17$ ;  $p = 0.020$ ). Calcium ( $r = -0.23$ ;  $p = 0.002$ ), 24-hr urinary magnesium ( $r = -0.18$ ;  $p = 0.020$ ) and eGFR ( $r = -0.47$ ;  $p = 0.001$ ) showed a negative correlation with parathyroid hormone.

**Abbreviations:** FEMg, magnesium excretion fraction; eGFR, estimated glomerular filtration rate; Mgu24, urinary magnesium 24hs.

**Table 1** Sociodemographic, Lifestyle and Clinical Characteristics of the Study Population

Variables	n	%	Mean ± SD
<b>Age (years)</b>			60.7±11.7
20–44	16	9.8	
45–59	45	27.6	
>60	102	62.6	
<b>Gender</b>			
Male	85	51.0	
<b>Alcohol consumption</b>	25	15.3	
<b>Smoking</b>	11	6.7	
<b>Physical activity</b>	82	50.3	
<b>Body mass index</b>			27.7±4.60
Overweight	93	57.1	
Hypertension	145	89.0	
Diabetes	74	45.4	
<b>eGFR (mL/min/1.73m<sup>2</sup>)</b>			37.6±11.90
45–59	49	30.0	
30–44	63	38.7	
15–29	51	31.3	
<b>Parathyroid hormone (pg/mL)</b>			74.2±52.60
Quartile 1 (< 39.9)	41	25.15	
Quartile 2 (40.0–58.5)	41	25.15	
Quartile 3 (58.6–89.5)	41	25.15	
Quartile 4 (> 89.5)	40	24.55	
<b>Magnesium (mg/dL)</b>			2.0±0.25
<b>Urinary magnesium (mg/24hs)</b>			71.7±35.24
<b>FEMg (%)</b>			6.2±3.56
<b>Alkaline phosphatase (U/L)</b>			81.5±24.60
<b>Phosphate (mg/dL)</b>			3.5±0.60
<b>Calcium (mg/dL)</b>			9.5±0.48
<b>25-hydroxyvitamin D (ng/dL)</b>			37.7±12.82

**Notes:** Conversion factors: 25-hydroxyvitamin D, ng/mL to nmol/L: × 2.496; parathyroid hormone, pg/mL to pmol/L: × 0.1064; calcium, mg/dL to mmol/L: × 0.2495; phosphate, mg/dL to mmol/L: × 0.3229; magnesium, mg/dL to mmol/L: ×0.4105.

**Abbreviations:** FEMg, magnesium excretion fraction; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

In the unadjusted regression analysis, the following variables were related to serum PTH levels: FEMg (OR 1.12; 95% CI: 1.02–1.23), Calcium (OR = 0.45; 95% CI: 0.22–0.90), Alkaline phosphatase (OR = 1.02; 95% CI: 1.00–1.03) and eGFR (OR = 0.92; 95% CI: 1.00–1.03) (Table 3). After the adjusted analysis, PTH was independently correlated with FEMg (OR= 1.10; 95% CI: 1.01–1.22) and alkaline phosphatase (OR= 1.01; 95% CI: 1.00–1.03) (Table 3).

## Discussion

In the present study, FEMg was associated with serum PTH levels in patients with non-dialysis CKD. The highest

mean FEMg (8.0±4.08%) was identified in the highest PTH quartile (>89.5pg/mL). Mg is the second most abundant intracellular cation and the fourth most abundant cation in the body.<sup>18</sup> Mg is a significant component of the mineral phase of bone, plays a critical role in neuromuscular function and is a cofactor in many enzymatic reactions and biological processes. Mg reduces PTH secretion mainly when a moderately low calcium concentration is present; Mg also modulates parathyroid gland function through the positive regulation of major cell receptors, calcium-sensitive receptor, vitamin D receptor and fibroblast-23 growth factor.<sup>19</sup> According to Dai et al,<sup>20</sup> PTH improves the absorption of magnesium in the distal tubule, and the increase of FEMg in patients with CKD works as a compensatory mechanism to maintain serum Mg levels within the normal range.<sup>21</sup> The deficiency in the production or performance of PTH causes a decrease in the renal excretion of Mg because PTH causes changes in membrane potential and cell permeability, in order to increase tubular magnesium resorption.<sup>22,23</sup>

In CKD, studies on the relationship between PTH and serum Mg were performed preferentially in patients on dialysis and showed an inverse association between these variables,<sup>24,25</sup> but prospective studies on this effect in non-dialysis patients investigating urinary levels of Mg are scarce. To the best of our knowledge, this is the first study that evaluates the association between FEMg and the serum levels of PTH. With progressive renal dysfunction, PTH levels increase, serum calcium decreases and serum Mg remains, due to increasing FEMg, this is because patients still preserve tubular function.<sup>26</sup> In dialysis patients, there is a considerable increase in serum Mg levels that is associated with hyperparathyroidism, but, in the present study, this association was not verified probably because these patients still preserved tubular function (most patients have eGFR 30–60 mL/min/1.73 m<sup>2</sup>). A recent study with stage 3 and 4 patients found that the serum Mg was not related to the different stages of the glomerular filtration rate.<sup>27</sup>

The kidneys play an important role in magnesium homeostasis. Under physiological conditions, 70% to 80% of plasma magnesium are filtered from glomeruli, and more than 95% of this ion is reabsorbed along the tubular system by various coordinated transport processes, leaving only 3%–5% that will be excreted in urine.<sup>8</sup> Anatomically, the main sites of renal magnesium resorption are the proximal tubule (10%–20%), the thick ascending portion of the Henle loop (65%–70%) and the distal contorted tubule (10%).<sup>28</sup> Tubular damage

**Table 2** Biochemical Indicators According to PTH Quartile in Non-Dialysis CKD Patients

	PTH (pg/mL)				p value
	Q1 (<39.9)	Q2 (40.0–58.5)	Q3 (58.6–89.5)	Q4 (>89.5)	
FEMg (%)	6.0±3.41	5.1±2.74	5.7±3.42	8.0±4.08	0.007
Urinary magnesium (mg/24hs)	80.9±31.80	72.0±41.40	64.7±31.10	69.0±36.10	0.206
Magnesium (mg/dL)	1.9±0.22	2.0±0.31	2.0±0.22	2.0±0.23	0.214
Calcium (mg/dL)	9.6±0.49	9.5±0.34	9.4±0.50	9.3±0.55	0.014 <sup>a</sup>
Phosphate (mg/dL)	3.5±0.46	3.5±0.64	3.5±0.54	3.6±0.64	0.627
25-hydroxyvitamin D (ng/dL)	39.0±12.80	38.3±12.00	36.6±11.90	36.4±14.60	0.610
Alkaline phosphatase (U/L)	73.7±17.60	78.8±25.60	81.1±24.50	92.6±26.90	0.009 <sup>a</sup>
eGFR (mg/min/1.73m <sup>2</sup> )	43.3±9.76	39.3±12.00	37.9±12.50	28.6±10.10	<0.001

**Notes:** <sup>a</sup>Kruskal–Wallis test. Conversion factors: 25-hydroxyvitamin D, ng/mL to nmol/L: × 2.496; parathyroid hormone, pg/mL to pmol/L: × 0.1064; calcium, mg/dL to mmol/L: × 0.2495; phosphate, mg/dL to mmol/L: × 0.3229; magnesium, mg/dL to mmol/L: ×0.4105.

**Abbreviations:** PTH, parathyroid hormone; FEMg, magnesium excretion fraction; eGFR, estimated glomerular filtration rate; Q1, quartile 1; Q2, quartile 2, Q3, quartile 3; Q4, quartile 4.

**Table 3** Logistic Regression Model of the Variables Associated with PTH Quartile 4 in Non-Dialysis CKD Patients

Variables	Non-Adjusted				Adjusted			
	OR	CI [95%]		p value	OR	CI [95%]		p value
FEMg (%)	1.12	1.02	1.23	0.018	1.10	1.01	1.22	0.040
Calcium (mg/dL)	0.45	0.22	0.90	0.024	0.61	0.24	1.51	0.287
Phosphate (mg/dL)	1.28	0.73	2.24	0.393	1.00	0.54	1.88	0.987
25-hydroxyvitamin D (ng/dL)	0.98	0.96	1.00	0.212	0.99	0.96	1.02	0.604
Alkaline phosphatase (U/L)	1.02	1.00	1.03	0.011	1.01	1.00	1.03	0.044
eGFR (mL/min/1.73m <sup>2</sup> )	0.92	0.89	0.95	0.000	–	–	–	–
Male sex	0.85	0.44	1.62	0.617	–	–	–	–
Etilism (yes)	0.62	0.22	1.73	0.361	–	–	–	–
Smoking (yes)	0.20	0.02	1.65	0.136	–	–	–	–
Physical activity (yes)	1.59	0.82	3.07	0.167	–	–	–	–
Body mass index (kg/m <sup>2</sup> )	0.82	0.42	1.62	0.573	–	–	–	–
Presence of diabetes mellitus	1.05	0.55	2.03	0.871	–	–	–	–
Presence of hypertension	0.75	0.27	2.07	0.583	–	–	–	–

**Notes:** Conversion factors: 25-hydroxyvitamin D, ng/mL to nmol/L: × 2.496; calcium, mg/dL to mmol/L: × 0.2495; phosphate, mg/dL to mmol/L: × 0.3229.

**Abbreviations:** CI, confidence interval; OR, odds ratio; FEMg, magnesium excretion fraction; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

leads to the development of a tubular glomeruli and decreases the number of functioning nephrons, with consequent reduction of GFR. Tubular-interstitial damage also reduces blood flow in the corresponding region and induces ischemic lesion of nephrons, with reduced renal plasma flow.<sup>29,30</sup>

In the current study, no correlation was observed between the excretion of Mg in 24-hr urine and PTH. The literature has shown that in advanced CKD there is an increase in PTH levels and a reduction in Mg urinary excretion. As a compensatory mechanism, the FEMg increases as the CKD progresses, maintaining the serum concentrations of Mg within normal limits.<sup>21,24</sup> The FEMg has been reported as one of the most sensitive markers in the identification of

early stages of tubulointerstitial lesions.<sup>9</sup> Evidence of increased FEMg in patients with renal disease derives from clinical and experimental studies that have pointed out the fundamental role of the kidney in the regulation of magnesium excretion.<sup>26,31</sup> In the study by Chie Noiri et al,<sup>21</sup> the FEMg showed an inverse correlation with the GFR, suggesting that the FEMg is strongly affected by the decrease in the number of functioning nephrons. Another study performed with 111 adults with CKD in Serbia demonstrated that a FEMg value greater than 6.1% would provide a more accurate estimate for the reduction of the glomerular filtration rate (GFR) below 60mL/min/1.73m<sup>2</sup> in patients with CKD and without diabetes.<sup>9</sup>

This study also demonstrated an association between PTH and ALP levels. ALP is another biochemical marker of CKD that has traditionally been associated with bone remodeling and cardiovascular risk in uremic patients, also increased as renal function decreases.<sup>32</sup> The mean values of ALP increased as PTH concentrations increased. The combination of low serum levels of PTH and ALP suggests bone disease with low remodeling, while high levels of both present high sensitivity and specificity for the disease with increased bone remodeling, that is, secondary hyperparathyroidism.<sup>33,34</sup>

The progression of CKD leads to changes in mineral metabolism, such as hypocalcemia, hyperphosphatemia, a decrease in levels of vitamin D and an increase in PTH.<sup>35,36</sup> In the present study, it was observed that the GFR decreased with the increase in serum PTH levels. Observational data in patients with CKD associated increased levels of PTH with unfavorable results, such as bone abnormalities, cardiovascular diseases and mortality.<sup>37,38</sup>

Secondary hyperparathyroidism and mineral and bone disorders are characterized by complex, multifaceted and still incomplete physiopathology and may be associated with vascular calcifications and low patient survival.<sup>39</sup> Low dietary calcium and vitamin D intake, as well as inadequate levels of vitamin D, may contribute to high concentrations of PTH.<sup>40</sup> This investigation has shown a negative correlation between PTH levels and serum calcium concentrations. In addition, the lowest mean calcium ( $9.30 \pm 0.55$  mg/dL) was observed in the highest PTH quartile ( $>89.5$  pg/mL). Considering the decisive role of calcium in stimulating PTH synthesis, one would expect that hypocalcemia would require an increase in serum PTH during the course of CKD.<sup>35</sup>

The prevalence of 25(OH)D deficiency is common in CKD and is implicated in the progressive increase in PTH, which is observed with declining renal function and leads to secondary hyperparathyroidism, bone mineral disease and increased cardiovascular risk.<sup>41</sup> In the study, no correlation between PTH and 25(OH)D was observed. This result is similar to that observed by Cuppari et al,<sup>42</sup> in a cohort that involved 144 patients with CKD who did not yet receive dialysis (CKD stages 2 to 5), demonstrated that the 25 (OH) D levels were not associated with PTH. A prospective and observational cohort performed with patients with non-dialysis CKD in Australia, the authors demonstrated that the higher mean 25(OH)D did not cancel the increase in PTH.<sup>43</sup> On the other hand, in the study by Anderson et al,<sup>36</sup> which analyzed data from electronic

records of 9369 individuals in the United States, PTH was inversely but poorly associated with 25(OH)D levels ( $r = -0.15$ ).

This study presents some limitations. First, there was no monitoring of food consumption of Mg in the study group and urinary excretion of this mineral is associated with its daily intake. Second, the cross-sectional nature of the study prevents the determination of cause and effect relationships.

## Conclusion

This investigation unveiled that, in individuals with chronic kidney disease on non-dialysis treatment, those with higher levels of PTH had higher averages of ALP and FEMg, and lower levels of serum calcium and eGFR. The FEMg and ALP were the only variables independently associated with PTH.

## Abbreviations

ALP, alkaline phosphatase; CKD, chronic kidney disease; PTH, parathyroid hormone; FEMg, magnesium excretion fraction; Mg, magnesium; MgU, urinary magnesium; CrS, serum creatinine; MgS, serum magnesium; CrU, urinary creatinine; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiologic collaboration equation; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

## Data Sharing Statement

Data not yet completed generated. All data from this study will be available as open access after publication of the articles. Any other information may be requested in writing from the chief investigator.

## Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Maranhão (n. 2.727.940). All participants had provided written informed consent prior to participation in any study activities.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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