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Correlation Between Serum Parathormone Levels With Urinary Magnesium Excretion In Patients With Non-Dialytic Chronic Kidney Disease

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Abstract

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

Methods: Cross-sectional study with patients with CKD undergoing non-dialysis treatment in stages 3A, 3B and 4. Concentrations of creatinine, magnesium, calcium, phosphorus, 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 ± 11.7 years and 51.0% were male. In the highest quartile of PTH (> 89.5pg / ml), the mean levels of FEMg and ALP were higher ($p < 0.05$), as well as the levels of serum calcium and eGFR were lower ($p < 0.05$). 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 eTFG (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 CKD, with higher levels of PTH, higher mean columns of ALP and FEMg, and lower levels of serum calcium and eGFR. FEMg and ALP were some variables that remained associated with PTH.

Background

Chronic kidney disease (CKD) is a major public health problem and is characterized by a slow progressive and irreversible loss of kidney function [1]. 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 [2-3].

Disorders of mineral metabolism which 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 main focus on bone health, other vitamins and minerals have been investigated [4]. 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 [5-7].

The kidneys are the main organs involved in magnesium homeostasis, since they control its serum concentration mainly by modulating excretion in the urine [8,7]. 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 [9,10] been utilized like tubular lesion marker even in individuals without chronic kidney disease.

The importance of Mg is well known, although it has not yet received the necessary attention in clinical practice. It is known that, with the progression of CKD, there is an increase in the levels of PTH, which acts as a uremic toxin and can contribute to disorders in the metabolism of minerals [2]. 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 the majority of the 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-dialytic CKD.

Methods

Study design and Participants

Cross-sectional study developed with patients CKD non-dialysis treatment being followed up at the *Centro de Prevenção de Doenças Renais (CPDR) of the Federal University of Maranhão (HUUFMA)*. The protocol, consent form, and study documents were approved 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 both gender aged 20 years or older and who were being monitored at CPDR-HUUFMA. Pregnant women were not included, carriers of autoimmune, infectious diseases, cancer, acquired immunodeficiency syndrome, thyroid disorders and urinary tract infection, who had hypomagnesaemia in need of replacement, and those with excessive alcohol consumption and using medications such as loop diuretics, aminoglycosides, adrenergic beta-agonists, cisplatin, cyclosporine and theophylline.

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.

Blood pressure was measured using the oscillometric method (Omron® 705-IT device, Japan) and in accordance with the guidelines of the European Hypertension Society, 2018. Three measurements were taken. with an interval of one minute between them. The first value was discarded and the mean values of systolic and diastolic blood pressure between the second and third measurements were considered for analysis [11]. Blood samples were collected after a 12-hour overnight fast and included creatinine, magnesium, calcium, phosphorus, parathyroid hormone, vitamin D, albumin and alkaline phosphatase.

24-hour urine was used to measure urinary magnesium and creatinine excretion. Patients were carefully instructed to pack urine in appropriate bottles (bottles of mineral water), discard the first urine of the initial collection day and, from there on collect all urine produced during the 24-hour period and keep it refrigerated.

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: [MgU x CrS] / [(0.7xMgS) x CrU] x 100 [12], where MgU = urinary magnesium; CrS = serum creatinine; MgS = serum magnesium; CrU = urinary creatinine. Values above 6,1% were considered altered [9].

For the definition of CKD two previous assessments of renal function were considered with a minimum interval of 3 months, as instructed by KDIGO [13]. Glomerular filtration rate (GFR) was estimated using the formula derived from the CKD-EPI study [14], 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 [15] for adults and that of LIPSCHITZ [16] for the elderly. For this, the body weight was measured with the aid of a calibrated scale (Filizola®, Brazil) with a maximum capacity of 150kg and subdivisions every 100g. Height was obtained with the aid of a portable stadiometer (Alturexata®, Brazil) with a scale from 0 to 220 cm and precision of 0.1 cm.

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 ± 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. Multiple regression analysis was performed to estimate the independent association of PTH and magnesium, calcium, phosphorus, parathyroid hormone, vitamin D and alkaline phosphatase. The level of significance adopted was 5% (p <0.05) and the statistical program used was SPSS.

Results

The present study evaluated 163 patients with a mean age of 60.7 ± 11.7 years and male individuals prevailed (51.0%). Among these evaluated, 15.3% were alcoholics, 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).

Table 1. Sociodemographic, lifestyle and clinical characteristics of the study population.

Variables	n	%
Age (years), mean±SD	60.7±11.7	
20-44	16	9.8
45-59	45	27.6
>60	102	62.6
Gender		
Male	85	51.0
Etilism	25	15.3
Smoking	11	6.7
Physical activity	82	50.3
Nutritional status		
Overweight	93	57.1
Hypertension	145	89.0
Diabetes	74	45.4
CKD		
Stage 3A	49	30.0
Stage 3B	63	38.7
Stage 4	51	31.3

CKD-chronic kidney disease

Most patients (68.7%) were in stage 3A and 3B (eGFR 60-30ml / min) with an average eGFR of 37.6 ml/min/1.73m^2. The serum levels of magnesium, calcium, phosphorus and vitamin D were within normal parameters. On the other hand, FEMg and serum levels of alkaline phosphatase and PTH were increased (Table 2).

Table 2. Biochemical indicators of the study population.

Variables	Mean ± SD
eGFR (mg/min/1.73m2)	37.6±11.90
Creatinine(mg/dl)	1.8±0.63
Magnesium(mg/dl)	2.0±0.25
Magnesium urinary 24hs	71.7±35.24
FEMg(%)	6.2±3.56
Alkaline phosphatase(mg/dl)	81.5±24.60
Phosphorus(mg/dl)	3.5±0.60
Albumin(g/dl)	4.5±0.41
Calcium(mg/dl)	9.5±0.48
PTH(pg/ml)	74.2±52.60
1-25 OHVitamin D(ng/dl)	37.7±12.82

FEMg- magnesium excretion fraction;

eGFR- estimated glomerular filtration rate;

PTH- parathyroid hormone

The biochemical indicators according to quartis PTH are showed on table 3. It appears that in the highest quartile of PTH (> 89.5pg / 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 ($p<0.05$).

Table 3- Biochemical indicators according to PTH quartile in non-dialysis CKD patients.

	PTH (pg/ml)				
	Q1 (<39,9)	Q2 (40,0-58,5)	Q3 (58,6-89,5)	Q4 (> 89,5)	*p* value
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**[#]
Phosphorus (mg/dl)	3.5±0.46	3.5±0.64	3.5±0.54	3.6±0.64	0.627
1-25 OHVitamin D (ng/dl)	39.0±12.80	38.3±12.00	36.6±11.90	36.4±14.60	0.610
Alkaline phosphatase (mg/dl)	73.7±17.60	78.8±25.60	81.1±24.50	92.6±26.90	**0.009**[#]
eGFR (mg/min/1.73m2)	43.3±9.76	39.3±12.00	37.9±12.50	28.6±10.10	**<0.001**

#Kruskal-Wallis test; PTH- parathyroid hormone; FEMg- magnesium excretion fraction; eGFR- estimated glomerular filtration rate;

Q1- quartil 1; Q2- quartil 2, Q3-quartil 3; Q4- quartil 4

The correlations between laboratory variables and serum PTH levels are demonstrated on table 4 and figure 1. A positive correlation between PTH and alkaline phosphatase (r = 0.26; *p* = 0.006) and FEMg e (r = 0.17; *p* = 0.020) was observed. Calcium (r = -0.23; *p* = 0.002), 24-hour urinary magnesium (r = -0.18; *p* = 0.020) and eGFR (r = -0.47; *p* = 0.001) showed a negative correlation with parathyroid hormone.

Table 4. Correlations between laboratory variables and PTH in non-dialysis CKD patients.

Variables	r	*P* value
Phosphorus (mg/dl)	0.05	0.480
Calcium (mg/dl)	-0.23	**0.002#**
Alkaline phosphatase (mg/dl)	0.26	**0.006#**
1-25OHVitamin d (ng/dl)	-0.10	0.170
eGFR (mg/min/1.73m2)	-0.47	**0.001***
Magnesium (mg/dl)	0.12	0.110
Urinary magnesium (mg/24hs)	-0.18	**0.020#**
FEMg(%)	0.17	**0.020***

* Pearson correlation # Spearman correlation

FEMg- magnesium excretion fraction; CKD-chronic kidney disease

eGFR- estimated glomerular filtration rate

Discussion

The progression of CKD leads to changes in mineral metabolism such as hypocalcemia, hyperphosphatemia, decreased levels of 1,25-hydroxyvitamin D and elevated PTH [17,18]. The present work with non-dialysis CKD patients demonstrated a positive correlation between PTH levels, alkaline phosphatase and magnesium excretion fraction and a negative correlation between PTH concentrations, total calcium and eGFR.

PTH, a hormone secreted by the parathyroid glands in response to low serum calcium levels, is recognized as a key contributor to bone homeostasis. This triggers the hydroxylation of 25-hydroxyvitamin D in the active form, 1,25-dihydroxyvitamin D, leading to better intestinal calcium

absorption. At high levels, PTH acts as a uremic toxin and is associated with several adverse outcomes [19-21], particularly musculoskeletal [22,23]. Secondary hyperparathyroidism can lead to bone loss due to increased bone turnover rates [24].

The low intake of calcium and vitamin D in the diet, as well as inadequate levels of vitamin D, can contribute to high concentrations of PTH [25]. The present investigation demonstrated a negative correlation between PTH levels and serum calcium concentrations. In addition, the lowest mean of calcium (9.30 ± 0.55 mg / dL) was observed in the highest PTH quartile (> 89.5pg / mL). Considering the decisive role of calcium in stimulating PTH synthesis, hypocalcemia would be expected to precede the increase in serum PTH in the course of CKD [17]. There was no correlation between PTH and 1-25OHvitamin D. Jaqueto et al [26], in a work with 132 patients on hemodialysis, also found no association between PTH levels and vitamin D. In another study, a prospective and observational cohort performed with nondialysis CKD patients in Australia, the authors demonstrated that the higher mean of vitamin D did not cancel the increase in PTH [27]. On the other hand, in the study by Anderson et al. [18], who analyzed data from electronic medical records of 9,369 individuals in the United States, PTH was inversely but weakly associated with vitamin D levels (r = -0.15).

Although calcium and vitamin D have been extensively correlated with bone health, other vitamins (A, B, C, E, folate) and minerals (copper, zinc, selenium, iron and magnesium) have also aroused the interest of researchers [4]. In particular, a significant association was found between bone density and intake of Mg, an essential micronutrient with a wide range of metabolic, structural and regulatory functions [7].
In the present study, a positive correlation was identified between PTH and FEMg. In addition, the highest mean of FEMg (7.96 ± 4.08%) was found in the highest PTH quartile (> 89.5pg / mL). According to Dai et al. [28], PTH improves the absorption of magnesium in the distal contoured tubule and the increase in FEMg in patients with CKD in the early stages, works as a compensatory mechanism to keep serum serum Mg levels within the normal range [29]. In CKD, studies on the relationship between PTH and serum Mg were preferably performed in dialysis patients and showed an inverse association between these variables [30,31], but prospective studies on this effect in non-dialysis patients are lacking.

FEMg is a sensitive marker of renal function and can be used to identify the initial stage of renal tubular damage. In the work by Chie Noiri et al. [29] with 94 Japanese patients, it was reported that FEMg above 6% would provide a more accurate and non-invasive assessment of the presence of tubulointerstitial nephropathy in a group of patients with nondialysis kidney disease. Another study conducted with 111 adults with CKD in Serbia found that an 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^2 in patients with CKD and without diabetes [9].

During the past decade, great advances have been made in understanding the renal handling of Mg. The kidneys play an important role in the homeostasis of this mineral. Under physiological conditions, 70 to 80% of plasma Mg is filtered from the glomeruli, with more than 95% of this ion being reabsorbed along the tubular system by several coordinated transport processes, leaving only 3-5% that will be excreted in

the urine [8]. In the present work, a negative correlation was observed between PTH levels and urinary Mg excretion. Studies have shown that in advanced CKD there is an increase in PTH levels and a reduction in urinary Mg excretion. However, fractional excretion of magnesium increases as CKD progresses, keeping serum Mg concentrations within normal limits [29,30].

In advanced CKD, secondary hyperparathyroidism and mineral and bone disorders are characterized by complex, multifaceted and still incomplete pathophysiology and may be associated with vascular calcifications and poor patient survival [32]. It is estimated that 30% to 50% of patients with stage 5 CKD have PTH levels > 300 pg/mL [33]. In the present investigation, eGFR was negatively correlated with PTH and it was observed that eGFR decreased with an increase in PTH. Observational data in CKD patients have associated increased PTH levels with unfavorable outcomes such as bone abnormalities, cardiovascular disease and mortality [34,35].

Alkaline phosphatase has also been associated with mineral and bone disorders and represents a biochemical marker of bone turnover used to monitor metabolic bone disease associated with renal failure [36]. In the present work, a positive correlation between PTH levels and alkaline phosphatase was demonstrated. The mean values of alkaline phosphatase increased with increasing PTH concentrations. Thus, the measurement of alkaline phosphatase in conjunction with PTH, can assist in the diagnosis of different forms of bone disease associated with CKD. The combination of low serum PTH levels and alkaline phosphatase suggests bone disease with low remodeling, while high levels of both have high sensitivity and specificity for the disease with increased bone remodeling, that is, secondary hyperparathyroidism [37,38].

There are limitations to this study. 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.

Conclusions

In this investigation, it was found that in individuals with chronic kidney disease undergoing non-dialysis treatment, those with higher levels of PTH had higher means of alkaline phosphatase and FEMg, and lower levels of serum calcium and eGFR. In addition, high levels of PTH were positively correlated with FEMg, regardless of the presence of serum magnesium changes, and FEMg may be used as another signal for the treatment of hyperparathyoidism.

Abbreviations

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

Declarations

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.

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Not applicable

AUTHORS CONTRIBUTIONS

All authors have contributed sufficiently to the project to be included as authors. Trial procedures were performed under the oversight of the principal investigator (NSF). MBF designed and reviewed the manuscript. AMS, DJAB and EJFS took responsibility for the integrity of the data and the accuracy of the data analysis. RSCD, DJAB, ECRLC, EMS, JSL, AMMF and AKTF wrote the manuscript, elaborated tables and figures, participated in the analysis and interpretation of data. EVHF participated in data analysis. MBF, NSF, DVA, AMS and AKTF participated in drafting the article or revising it critically for important intellectual content. ECRLC participated in the research design and development and refinement ofthe methodological approach. RSCD, DJAB, EMS, AMMF, RCOC, MCD, CDTB and ACSM are responsible for data collection. All authors read and approved the final version to be published.

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CONSENT FOR PUBLICATION

Not applicable.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

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.

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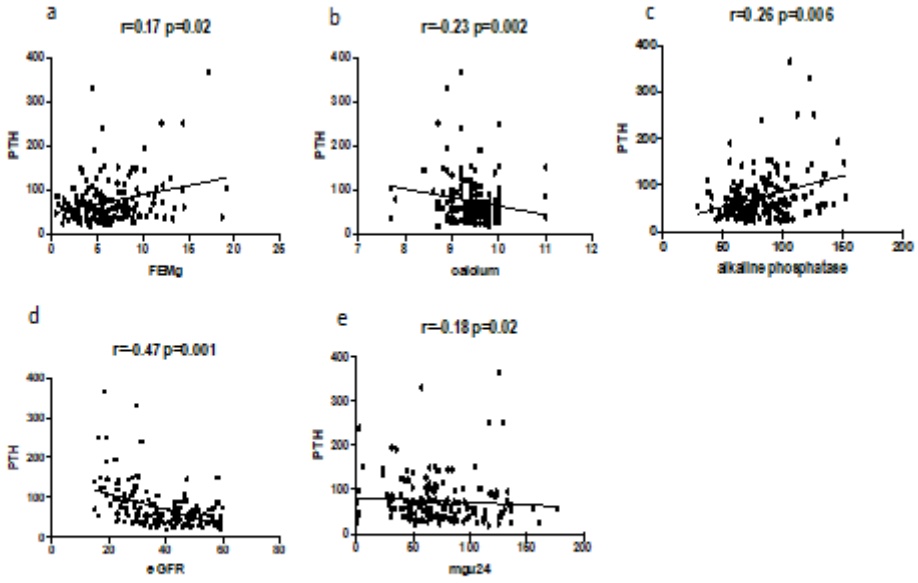
Figures



FEMg- magnesium excretion fraction;
eGFR- estimated glomerular filtration rate;
Mgu24: urinary magnesium 24hs

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.