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

Raimunda Sheyla Cameiro Dias (sheylak75@yahoo.com.br)
Hospital Universitário da Universidade Federal do Maranhão https://orcid.org/0000-0003-1851-9495

Dyego José Araújo Brito
Centro de Prevenção de Doenças Renais, Hospital Universitário da UFMA

Joyce Santos Lages
Hospital Universitário da Universidade Federal do Maranhão

Alcione Miranda Santos
Universidade Federal do Maranhão

Elisangela Milhomen Santos
Universidade Federal do Maranhão

Rayanna Cadilhe Costa
Centro de Prevenção de Doenças Renais, Hospital Universitário da Universidade Federal do Maranhão

Elane Viana Furtado
Universidade Federal do Maranhão

Elton Jonh Freitas Santos
Hospital Universitário da Universidade Federal do Maranhão

Erika Cristina Cameiro
Centro de Prevenção de Doenças Renais, Hospital Universitário da Universidade Federal do Maranhão

Andrea Martins Fontenele
Hospital Universitário da Universidade Federal do Maranhão

Maria Célia Diniz
Centro de Prevenção de Doenças Renais, Hospital Universitário da Universidade Federal do Maranhão

Carla Déa Barbosa
Hospital Universitário da Universidade Federal do Maranhão

Alessandra Costa Muniz
Hospital Universitário da Universidade Federal do Maranhão

Ana Karina Teixeira França
Universidade Federal do Maranhão

Natalino Salgado-Filho
Universidade Federal do Maranhão

Denizar Vianna Araújo
Research article

Keywords: Magnesium, Parathyroid hormone, Kidney diseases

DOI: https://doi.org/10.21203/rs.3.rs-32675/v2

License: Creative Commons Attribution 4.0 International License. Read Full License
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: 
\[
\frac{\text{MgU} \times \text{CrS}}{(0.7 \times \text{MgS}) \times \text{CrU}} \times 100
\]
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       |    |     |
| 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|

Most patients (68.7%) were in stage 3A and 3B (eGFR 60-30ml / min) with an average eGFR of 37.6 ml/min/1.73m². 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.
The biochemical indicators according to quartiles 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  |
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.
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, hypocalemia 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 hyperparathyroidism.

**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.

**ACKNOWLEDGEMENTS**

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 of the 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.
CORRESPONDING AUTHOR

Correspondence to Raimunda Sheyla Carneiro Dias.

AUTHOR INFORMATION

Mario Bernardo-Filho, E-mail: bernardofilhom@gmail.com
Natalino Salgado-Filho, E-mail: natalinosalgadofilho@uol.com.br
Denizar Vianna Araújo, E-mail: denizarvianna@gmail.com
Joyce Santos Lages, E-mail: joyce_lages@uol.com.br
Dyego José de Araújo Brito, E-mail: djabrito@uol.com.br
Alcione Miranda dos Santos, E-mail: alcione.miranda@gmail.com
Elisangela Milhomen dos Santos, E-mail: elismilhomem@hotmail.com
Rayanna Cadilhe de Oliveira Costa, E-mail: rayannacadilhe@live.com
Elane Viana Hortegal Furtado, E-mail: elane.hortegal@ufma.br
Elton Jonh Freitas Santos, E-mail: eltonfreitas86@yahoo.com.br
Erika Cristina Ribeiro de Lima Carneiro, E-mail: erikacarneiro0204@gmail.com
Andrea Martins Melo Fontenele, E-mail: andrea.fontenele@yahoo.com.br
Maria Célia Diniz, E-mail: mcruzdiniz@yahoo.com.br
Carla Déa Trindade Barbosa, E-mail: deatrandade22@hotmail.com
Alessandra Costa de Sales Muniz, E-mail: alessandramuniz02@hotmail.com
Ana Karina Teixeira França, E-mail: karinafranca2@yahoo.com.br

CONSENT FOR PUBLICATION

Not applicable.
FUNDING

This study was funded by the Research Support National Council for Scientific and Technological Development (CNPq).

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.

References

1- Stevens, P.E.; Levin, A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of Internal Medicine. 2013, 158, 825-30.

3- Andersson, P.; Rydberg, E.; Willenheimer, R. Primary hyperparathyroidism and heart disease—a review. European Heart Journal. 2004, 25, 1776-1787.

4- Nieves, J.W. Skeletal effects of nutrients and nutraceuticals, beyond calcium and vitamin D. Osteoporosis International. 2013, 24, 771–786.

5- Ahmed, F.; Mohammed, A. Magnesium: The Forgotten Electrolyte - A Review on Hypomagnesemia. Medical Sciences. 2019, 7, 56.

6- Volpe, S. L. Magnesium in disease prevention and overall health. Advances in Nutrition. 2013, 4, 378S-83S.
7- Jahnen-Dechent, W.; Ketteler, M. Magnesium basics. *Clinical Kidney Journal*. **2012**, **5**, i3–i14.

8- Blaine, J.; Chonchol, M.; Levi, M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clinical Journal of the American Society of Nephrology*. **2015**, **10**, 1257–1272.

9- Žeravica, R.; Ilinčić, B.; Čabarkapa, V.; Radosavkić, I.; Samac, J.; Nikoletić, K.; Stošić, Z. Fractional excretion of magnesium and kidney function parameters in nondiabetic chronic kidney disease. *Magnesium Research*. **2018**, **31**, 49-57.

10- Gheissari, A.; Andalib, A.; Labibzadeh, N.; Modarresi, M.; Azhir, A.; Merrikhi, A. Fractional excretion of magnesium (FEMg), a marker for tubular dysfunction in children with clinically recovered ischemic acute tubular necrosis. *Saudi Journal of Kidney Diseases and Transplantation*. **2011**, **22**, 476.

11- Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Kahan, T. ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *European Heart Journal*. **2018**, **39**, 3021-3104.

12- Vendrame, I. S.; Scattolini, M.; Brito, V. P. Hipomagnesemia. In Equilíbrio Ácido-Base e Hidroeletrolítico, 3ª ed.; Lopes, R.D.; Editora Atheneu, São Paulo, Brasil, 2007; Volume 16, pp.171-178, **2009**.

13- Levin, A.; Stevens, P. E.; Bilous, R. W.; Coresh, J.; De Francisco, A. L.; De Jong, P. E.; Levey, A. S. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements*. **2013**, **3**, 1-150.

14- Levy, A. R.; Perkins, R. M.; Johnston, K. M.; Sullivan, S. D.; Sood, V. C.; Agnese, W.; Schnitzler, M. A. An epidemiologic model to project the impact of changes in glomerular filtration rate on quality of life and
survival among persons with chronic kidney disease. *International Journal of Nephrology and Renovascular Disease*. 2014, 7, 271.

15- World Health Organization (WHO). Physical Status: the use and interpretation of anthropometry. Report of a WHO Expert Committee, n. 854. Geneva; 2000.

16- Lipschitz, D. A. (1994). Screening for nutritional status in the elderly. *Primary Care*. 1994, 21, 55-67.

17- Căpuşă, C.; Chirculescu, B.; Vladu, I.; Viaşu, L.; Lipan, M., Moţa, E.; Mircescu, G. The prevalence of biochemical abnormalities of chronic kidney disease. Mineral and bone disorders in untreated non-dialysis patients–a multicenter study. *Acta Endocrinologica*. 2016, 12, 282.

18-Anderson, J.L.; Vanwoerkom, R.C.; Horne, B.D.; Bair, T.L.; May, H.T.; Lappé, D.L.; Muhlestein, J. B. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? *American Heart Journal*. 2011, 162, 331-339.

19- Wang, W. H.; Chen, L. W.; Lee, C. C.; Sun, C. Y.; Shyu, Y. C.; Hsu, H. R.; Wu, I. W. Association between parathyroid hormone, 25 (OH) vitamin D, and chronic kidney disease: a population-based study. *BioMed Research International*, 2017.

20- Peacock, M. Calcium metabolism in health and disease. *Clinical Journal of the American Society of Nephrology*. 2010, 5, S23–S30.

21- Schiepatti, A.; Pisoni, R.; Remuzzi, G. Pathophysiology and management of chronic kidney disease. *Primer on Kidney Diseases*. 4th ed. Philadelphia: Elsevier Saunders; 2005, p.444-454.

22- Bouillon, R.; Van Schoor, N.M.; Gielen, E.; Boonen, S.; Mathieu, C.; Vanderschueren, D.; Lips, P. Optimal vitamin D status: A critical analysis on the basis of evidence-based medicine. *The Journal of Clinical Endocrinology & Metabolism*. 2013, 98, E1283–E1304.
23- Choi, C. K.; Kweon, S. S.; Lee, Y. H.; Nam, H. S.; Park, K. S.; Ryu, S. Y.; Shin, M. H. Serum level vitamin D and parathyroid hormone, and mortality, with or without chronic kidney disease. *Journal of Bone and Mineral Metabolism*. **2019**, *37*, 825-834.

24- Sahota, O.; Mundey, M.K.; San, P; Godber, I.M.; Lawson, N.; Hosking, D.J. The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. *Bone*. **2004**, *35*, 312–319.

25- Vieth, R.; Yasmin, L.; Paul, G. W. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *Journal of Clinical Endocrinology and Metabolism*. **2003**, *88*, 185–191.

26- Jaqueto, M.; Delfino, V. D. A.; Bortolasci, C. C.; Barbosa, D. S.; Morimoto, H. K.; Frange, R. F. N.; Guimaraes, F. B. D. S. Os níveis de PTH estão relacionados com estresse oxidativo e inflamação em pacientes renais crônicos em hemodiálise?. *Brazilian Journal of Nephrology*. **2016**, *38*, 288-295.

27- Petchey, W.G.; Johnson, D.W.; Hawley, C.M.; Isbel, N.M.; Predictors of vitamin D status in predialysis chronic kidney disease patients: a cross-sectional analysis in a high ultraviolet climate. *Journal of Renal Nutrition*. **2012**, *22*, 400-408.

28- Dai, L. J.; Ritchie, G.; Kerstan, D.; Kang, H. S.; Cole, D. E.; Quamme, G. A. Magnesium transport in the renal distal convoluted tubule. *Physiological Reviews*. **2001**, *81*, 51-84.

29- Noiri, C.; Shimizu, T.; Takayanagi, K.; Tayama, Y.; Iwashita, T.; Okazaki, S.; Mitarai, T. Clinical significance of fractional magnesium excretion (FEMg) as a predictor of interstitial nephropathy and its correlation with conventional parameters. *Clinical and Experimental Nephrology*. **2015**, *19*, 1071-8.

30- Felsenfeld, A.J.; Levine, B.S.; Rodriguez, M. Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. *Seminars in Dialysis*. **2015**, *28*, 564-577.
31- Navarro-Gonzales, J.F.; Mora-Fernandez, C.; Garcia-Perez, J. Clinical implications of disordered magnesium homeostasis in chronic renal failure and dialysis. *Seminars in Dialysis*. 2009, 22, 37–44.

32- Chandran, M.; Wong, J. Secondary and tertiary hyperparathyroidism in chronic kidney disease: An endocrine and renal perspective. *Indian Journal of Endocrinology and Metabolism*. 2019, 23, 391.

33- Hedgeman, E.; Lipworth, L.; Lowe, K.; Saran, R.; Do, T.; Fryzek, J. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. *International Journal of Nephrology*. 2015.

34- Koc, H.; Hoser, H.; Akdag, Y.; Kendir, C.; Ersoy, F. F. Treatment of secondary hyperparathyroidism with paricalcitol in patients with end-stage renal disease undergoing hemodialysis in Turkey: an observational study. *International Urology and Nephrology*. 2019, 51, 1261-1270.

35- Tentori, F.; Wang, M.; Bieber, B. A.; Karaboyas, A.; Li, Y.; Jacobson, S. H.; Port, F. K. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clinical Journal of the American Society of Nephrology*. 2015, 10, 98-109.

36- Regidor, D. L.; Kovesdy, C. P.; Mehrotra, R.; Rambod, M.; Jing, J.; McAllister, C. J.; Kalantar-Zadeh, K. Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. *Journal of the American Society of Nephrology*. 2008, 19, 2193-2203.

37- Bover, J.; Ureña, P.; Aguilar, A.; Mazzaferro, S.; Benito, S.; López-Báez, V.; Cozzolino, M. Alkaline phosphatases in the complex chronic kidney disease-mineral and bone disorders. *Calcified Tissue International*. 2018, 103, 111-124.

38- Behets, J.; Spasovski, G.; Sterling, R.; Goodman, G.; Spiegel, D.M.; De Broe, M.E.; D'haese, P.C. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. *Kidney International*. 2015, 87, 846–8
Figures

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.

FEMg: magnesium excretion fraction;
eGFR: estimated glomerular filtration rate;
Mg24: urinary magnesium 24hs