Original investigation

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Prevalence of bone mineral metabolism alterations associated with chronic kidney disease not on dialysis

Prevalencia de las alteraciones del metabolismo óseo-mineral asociadas a enfermedad renal crónica no en diálisis

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Abstract

Background: chronic kidney disease (CKD) is a public health problem, and bone mineral metabolism disorder is one of its main complications that directly contributes to morbidity and mortality. Several previous studies have shown an increase in its prevalence as the glomerular filtration rate (GFR) decreases, however, we do not have data from our country or Latin America.

Methods: We conducted a unicentric cross-sectional study in a nephrology consultation service in adults with CKD G1 to 5 who were not in renal replacement therapy, evaluated between January 2014 and March 2015. Data collection was performed with an instrument predefined that included demographic data, alterations of the mineral and bone metabolism parameters, and their management.

Results: 2026 patients were included, of whom 1756 had parathyroid hormone measurement, the average age was 74 years, 62% were women. The distribution by degrees of CKD was: G1: 4.9%, G2: 22.8%, G3: 57.4%, G4: 12.5% and G5: 2.4%. The main causes were hypertensive and diabetic nephropathy. We found vitamin D deficiency in 78.16%, secondary hyperparathyroidism in 63.67% and hyperphosphatemia in 12.38%, with an increase in prevalence as GFR worsened. **Conclusions:** We found that mineral and bone metabolism alterations are frequent in patients with chronic kidney disease and start from early stages, as has been demonstrated in other studies. We believe that these Results will lead to new management investigations in patients with CKD.

Key words: Renal insufficiency chronic, hyperparathyroidism, secondary, vitamin D deficiency.

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Resumen

Introducción: la enfermedad renal crónica (ERC) es un problema de salud pública, siendo el trastorno del metabolismo óseo mineral una de sus principales complicaciones y que contribuye directamente a la morbilidad y mortalidad. Varios estudios previos han demostrado un aumento de su prevalencia a medida que disminuye la tasa de filtración glomerular (TFG), sin embargo, no contamos con datos en nuestro país ni en América Latina.

Métodos: realizamos un estudio transversal unicéntrico en un servicio de consulta de nefrología, en adultos con ERC G1 a 5 que no estuvieran en terapia de reemplazo renal, evaluados entre enero de 2014 y marzo de 2015. La recolección de datos se realizó con un instrumento predefinido que incluía datos demográficos, alteraciones de los parámetros del metabolismo mineral y óseo, y su manejo.

Resultados: se incluyeron 2026 pacientes, de los cuales 1756 tenían medición de hormona paratiroidea, la edad promedio fue 74 años, el 62 % eran mujeres. La distribución por grados de ERC fue: G1:4,9 %, G2:22,8 %, G3: 57,4 %, G4: 12,5 % y G5:2,4 %. Las principales causas fueron la nefropatía hipertensiva y diabética. Encontramos deficiencia de vitamina D en el 78,16 %, hiperparatiroidismo secundario en el 63,67 % e hiperfosfatemia en el 12,38 %, con aumento de la prevalencia a medida que la TFG empeoraba.

Conclusiones: encontramos que las alteraciones del metabolismo mineral y óseo son frecuentes en los pacientes con enfermedad renal crónica e inician desde estadios tempranos, como se ha demostrado en otros estudios. Consideramos que estos resultados llevarán a nuevas investigaciones de manejo en pacientes con ERC.

Palabras clave: enfermedad renal crónica, hiperparatiroidismo secundario, deficiencia de vitamina D.

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Introduction

Chronic kidney disease (CKD) is a real public health problem worldwide, with a high prevalence that increases as the population ages, and is associated with various complications, high risk of mortality and high costs[1-7]. One of the most important complications, and difficult to manage, is the mineral and bone metabolism disorder, since this group of alterations not only affects bone health, it is also associated with greater deterioration of renal function and an increase in overall mortality, especially of cardiovascular origin. One of the components of this disorder is secondary hyperparathyroidism, which is a multifactorial disorder that occurs as a consequence of the progressive decrease in vitamin D levels, exacerbated and perpetuated by the decrease in calcium levels and the progressive elevation of phosphorus levels[8-18].

As the deterioration of the glomerular filtration rate progresses, the prevalence of bone mineral metabolism alterations increases, as demonstrated in different studies[19-26]. However, despite being a widely known disorder in the context of chronic kidney disease, research regarding its prevalence and management show that it is often underdiagnosed and therefore undertreated, and even in cases in which it is detected, the establishment of the management is complex and with poor metabolic response.

Although we know data from other epidemiological investigations, no studies have been conducted in Colombia or in Latin America that allow us to know their prevalence. It would not be prudent to extrapolate the Results without a local study, due to the different sociodemographic characteristics among populations. The present study was conducted seeking to find the prevalence of bone mineral metabolism alterations, according to the degree of chronic kidney disease in patients who were not in renal replacement therapy in the city of Medellin.

Materials and methods

We conducted a cross-sectional study of patients admitted to the renal protection program between January 2014 and March 2015 in the renal unit of the General Hospital of Medellin (HGM), located in the city of Medellin in the department of Antioquia, Colombia.

The main variables that we took into account were: serum creatinine to calculate the glomerular filtration rate (GFR) using the CKD-EPI formula, with which patients were classified into the different stages of CKD (degrees G1 to G5) established by the KDIGO guidelines; in addition to levels of parathormone (PTH), phosphorus, calcium and 25-hydroxyvitamin D. Vitamin D deficiency was defined with levels of 25-hydroxyvitamin D of 4.5 ng/dL, hypocalcemia with a value of 65 pg/ml. Patients under 18 years of age and in renal replacement therapy (hemodialysis, peritoneal dialysis or kidney transplant) were excluded.

The analysis of the variables was done with frequency distributions and contingency table for the categorical variables with the X2 test, and for the continuous variables with the Student's t distribution. A p-value of 0.01 or 0.02 was considered statistically significant. The statistical analysis was carried out with the statistics software package Stata version 12.

This study was approved by the Ethics Committee of the HGM, and the rules on ethical aspects of human research contained in Resolution 008430 of 1993 of the Ministry of Social Protection of the Republic of Colombia were followed. The researchers committed themselves to respect the confidentiality and privacy of the information contained in the clinical records. This work did not imply interventions in the study population (direct physical assessment, laboratory tests or application of treatment) so it did not confer risks to the participants.

Results

Table 1 shows the demographic data of the studied population (n = 2026), among which 1756 patients had a report of PTH. In the distribution of variables according to the presence or absence of hyperparathyroidism (Table 2), a significant difference was found in terms of age, weight, BMI,

Table 1. Total demographic variables and distributed by sex.

Variables	Total	Men	Women
	n = 2026	n = 762 (38 %)	n = 1262 (62 %)
Comorbility			
HBP	1868 (92 %)	690 (90 %)	1177(93%)
COAD	82 (4 %)	34 (4 %)	48 (4 %)
Coronary artery disease	234 (11 %)	106 (14 %)	128 (10 %)
COPD	329 (16 %)	123(16%)	205 (16 %)
Systemic lupus erythematosus	25 (1 %)	4 (0.5 %)	21 (2 %)
Diabetes mellitus	588 (29 %)	181 (24 %)	407 (32 %)
Calcium carbonate	245 (12 %)	78(10%)	167(13%)
Calcitriol	513(26%)	190 (25 %)	323 (26 %)
Parica1cito1	24 (1 %)	10 (1 %)	14 (1 %)
Exposure variables			
Age (years)	74 ± 13.6	74 ± 13.6	74 ± 13.6
Race- Other (mestizo)	1907 (95 %)	711 (94 %)	1196 (96 %)
Weight (Kg)	61 ± 12	65 ± 11	58 ± 12
Height (m)	1.55 ±0.09	1.63 ± 0.08	1.51 ± 0.07
BM1	25.2 ±4.7	24.5 ± 3.7	25.6 ± 5.1
Etiology			
Diabetes mellitus	371 (18.3 %)	110(14%)	261 (21 %)
Arterial hypertension	1146 (56.5 %)	419(54%)	726 (58%)
Segmenta!and focal glomerulosclerosis	23 (1.1%)	8 (1 %)	15 (1 %)
Lupus nephritis	23 (1.1%)	5 (0.7 %)	18(1 .4%)
G1omeru1onephritis	10 (0.5 %)	7 (0.9 %)	3 (0.2 %)
Membranopro1iferative g1omeru1onephritis	7 (0.4 %)	2 (0.3 %)	5 (0.4 %)
Po1ycystic kidney disease	16 (0.8 %)	6 (0.8 %)	10 (0.8 %)
IgA nephropathy	28(1.4 %)	11 (1.4 %)	17(1.3%)
Obstructive uropathy	103 (5.1 %)	74 (10 %)	29 (2.3 %)
Unknown	199 (9.8 %)	78 (10 %)	121 (10 %)
Other	99 (4.9 %)	42 (6 %)	57 (5 %)
Nephrectomy dueto cancer	2 (0.1 %)	1 (0.1 %)	1 (0.08 %)
Serum creatinine (mg/dL)	1.47 ± 0.9	1.63 ± 0.9	1.37 ± 0.9
GFR CKD-EP1 (mL/min/1.73 m2)	50.4 ± 21.4	51.7 ± 21	49.6 ± 21
PTH (pg/mL)	79(56 – 116)	76 (55 – 111)	80 (57 – 119)
25-hydroxyvitamin D (ng/mL)	24.3 ± 8.3	27.1 ± 8.3	22.6 ± 7.9
Calcium (mg/dL)	10.1 ±6.7	10 ± 6.2	10 ± 7.0
Phosphorus (mg/dL)	3.9 ± 0.7	3.7 ± 0.8	4.0 ± 0.6

presence of hypertension, systemic lupus erythematosus, glomerular filtration rate calculated by CKD- EPI and levels of 25-hydroxyvitamin D. It was found that 78.16 % of the studied population hada deficiency ofvitamin D, 12.38% hyperphosphatemia, and 63.67 % hyperparathyroidism. The distribution of this percentage according to each degree of CKD is shown in Table 3.

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Table 2. Variables distributed according to the presence of hyperparathyroidism.

Variables	Hyperparathyroidism	No hyperparathyroidism	P-value
	n = 1118 (64 %)	n = 638 (36 %)	
Age	75 ± 13	73 ± 14	0.004
Sex – female	706 (63 %)	380 (60 %)	0.131
Weight	62 ± 13	60 ± 12	0.011
BMI	25.6 ± 5	24.8 ± 4	<0.001
HBP	1060 (95 %)	579 (91 %)	0.001
COAD	52 (5 %)	21 (3 %)	0.17
Coronary artery disease	138 (12 %)	72 (11 %)	0.513
COPD	195 (17 %)	97 (15 %)	0.222
Lupus	7 (0.6 %)	14 (2.2 %)	0.004
Diabetes mellitus	336 (30 %)	167 (26 %)	0.081
GFR by CKD-EPI	43.8 ± 18.9	57.5 ± 19.7	<0.001
Vitamin D	23.6 ± 8.3	25.9 ± 8.3	<0.001
Calcium	10.2 ± 7.3	10.0 ± 5.8	0.647
Phosphorus	3.9 ± 0.7	3.9 ± 0.7	0.871

Table 3. Distribution of complications according to the degrees of CKD.

Complications (# of patients)	Distribution by degrees of CKD					
	G1	G2	G3a	G3b	G4	G5
	>= 90	60 - 89	45 - 59	30 - 44	15 – 29	< 15
Vitamin D deficiency (1070)	3.47%	19.96%	30.18%	30.37%	13.68%	2.34%
Hyperparathyroidism (1118)	2.24%	14.71%	27.26%	33.63%	18.39%	3.77%
Hyperphosphatemia (243)	2.89%	12.40%	22.31%	28.10%	23.97%	10.33%

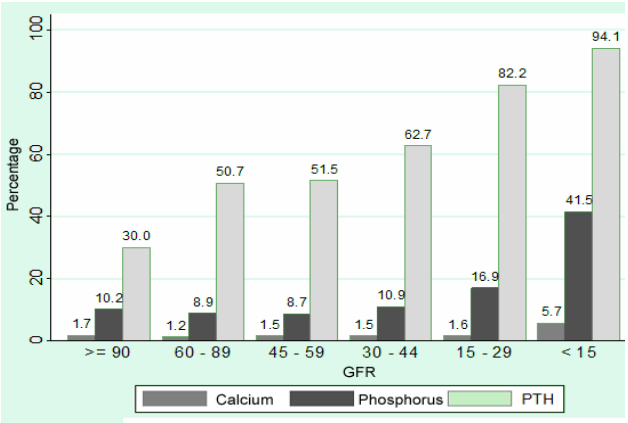

Figure 1. Prevalence of hypocalcemia, hyperphosphatemia and hyperparathyroidism according to the degrees of renal dysfunction.

We found that hypocalcemia, hyperphosphatemia, hyperparathyroidism, and vitamin D deficiency were more prevalent as renal dysfunction progressed (Figure 1). The percentage of the total population as per degree of deficiency of vitamin D according to each stage of CKD is shown in Figure 2.

Figure 3 shows the dispersion between levels of PTH and GFR, as well as the relationship between levels of 25-hydroxyvitamin D and GFR. The correlation between age and levels of 25-hydroxyvitamin D discriminated by the different stages of CKD is shown in Figure 4, and the correlation between vitamin D and PTH according to the degree of CKD is shown in Figure 5.

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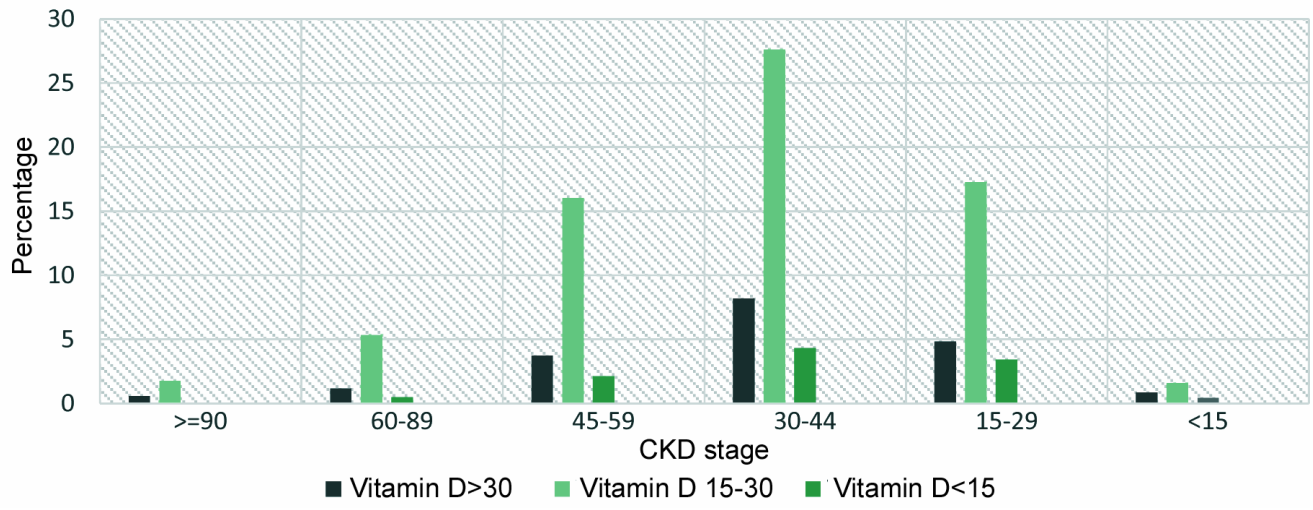

Figure 2. Vitamin D levels distributed according to the degree of renal dysfunction.

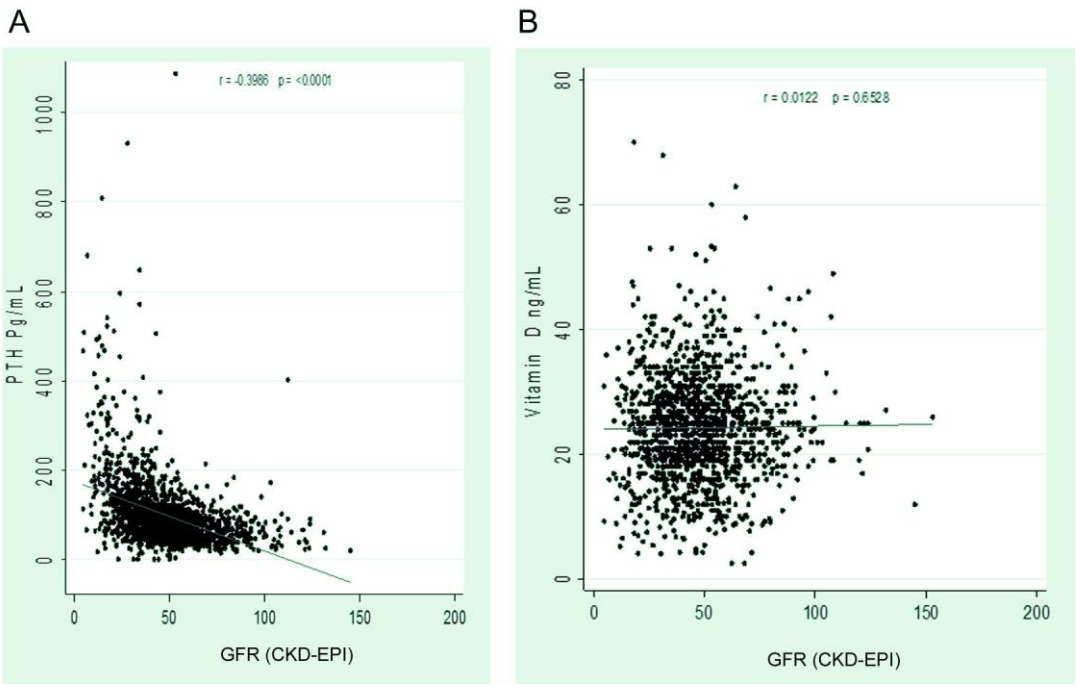

Figure 3. Scatter plot, PTH Vs. GFR (A) and vitamin D Vs. GFR (B).

In the logistic regression analysis, taking into account hyperparathyroidism as a dependent variable (Table 4), we found that for every 1 ml/min that the GFR falls below the mean (50.4 ml/min), the prevalence of secondary hyperparathyroidism increases between 3 and 5%; In addition, for every 1 ng/ml of 25-hydroxyvitamin D below the average, the prevalence of hyperparathyroidism increases 2 to 5%.

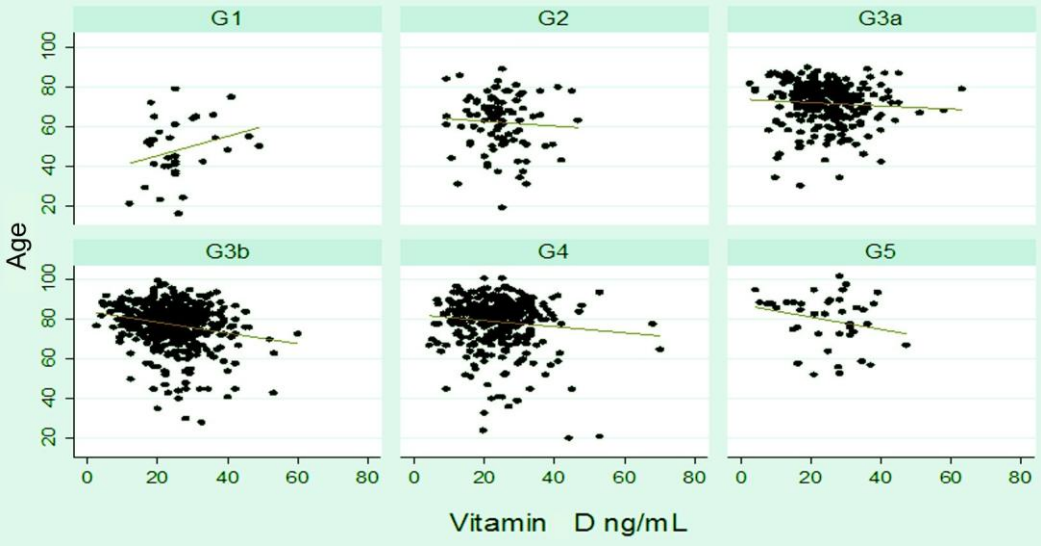

Figure 4. Correlation between age and vitamin D by degree of CKD.

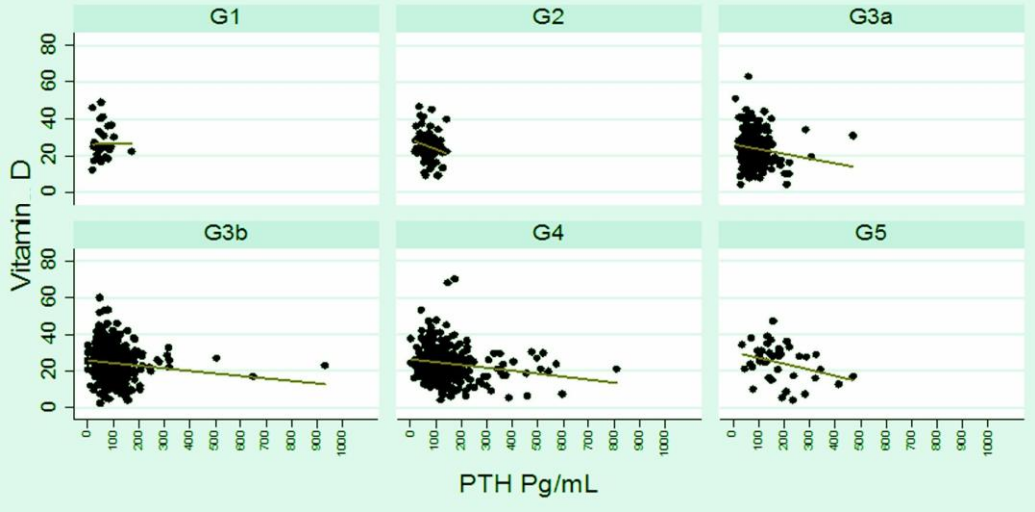

Figure 5. Correlation between vitamin D and PTH by degree of CKD.

Table 4. Univariate and multivariate analysis of the prevalence of secondary hyperparathyroidism.

Covariables	Univariate			Multivariate		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Age	0.99	0.98 – 0.99	0.004	1.00	0.99 – 1.01	0.354
Sex	1.17	0.95 – 1.42	0.131	1.01	0.76 – 1.34	0.930
GFR CKD-EPI	1.04	1.03 – 1.04	0.000	1.04	1.03 – 1.05	0.000
Vitamin D (ng/mL)	1.03	1.02 – 1.04	0.000	1.04	1.02 – 1.05	0.000
Calcium (mg/dL)	1.00	0.98 – 1.01	0.648	1.00	0.98 – 1.02	0.911
Phosphorus (mg/dL)	1.01	0.88 – 1.16	0.871	1.32	1.09 – 1.61	0.004
Diabetes	1.21	0.98 – 1.51	0.081	1.04	0.77 – 1.39	0.813
BMI	0.96	0.94 – 0.98	0.000	0.96	0.93 – 0.99	0.007

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Discussion

This study is the largest of its type published in Latin America; the population was predominantly of elderly people, with an average age of 74 years and a predominance of women, constituting 62% of the population.

The main etiology of chronic kidney disease was arterial hypertension with 56.5% of the cases, a figure higher than that reported in other studies evaluated, and it was also the main comorbidity in the population regardless of the etiology. We must take into account that it is also possible that patients with age-related changes of nephrosclerosis which contributed to the high prevalence of chronic kidney disease secondary to arterial hypertension and patients with other etiologies of CKD who have arterial hypertension as a complication were included within the group of patients with hypertension and renal disease. The second most common etiology was diabetes mellitus with 18.3% of cases and up to 10% of people had an unknown etiology, which is a significant percentage of the population. Probably due to the advanced age of the patients and the comorbidities, other etiologies such as glomerulopathies represented a smaller percentage of cases.

We decided to use the CKD-EPI formula for the calculation of the GFR, since it has been demonstrated that is the one that best discriminates the stages of CKD[27-28]. The mean GFR of the population was 50.4 ml/min, with 21% of patients with degrees G1 and G2-A1, so it is likely that they have no complications secondary to chronic kidney disease and it would not even be absolutely necessary to follow up them in a nephrology unit. The majority of the population was within the degree G3, with 57.4% of patients, and a smaller number in degrees G4 and G5 with 12.5% and 2.5% respectively. As we did not perform follow-up of renal function, we were not able to evaluate the evolution of patients in each of the groups.

Like other authors and according to our knowledge of the pathophysiology of mineral and bone metabolism in chronic kidney disease, we found that as the GFR deteriorated, the changes in the levels of PTH, vitamin D and phosphorus became accentuated. We found that 63.6% of the population met the criteria for hyperparathyroidism; even from the earliest stages of the disease such as degrees G1 and G2, between 30 and 50% of people already have hyperparathyroidism, with the highest prevalence in degrees G4 and G5 with 82 and 94%, respectively. Other studies[19-22] show a progressive increase in PTH levels as GFR decreases, although unlike our findings, the prevalence of hyperparathyroidism in the earliest stages of chronic kidney disease was lower, with ranges between 13 and 17% when GFR was greater than 60ml/min, as reported by Levin, et al[19].

The high prevalence of hyperparathyroidism is probably in part a result of the vitamin D deficiency, which was found in 78% of the population and the level was very similar among the different degrees of chronic kidney disease, except in G5 where only 56% had levels <30 ng/ml; although the value of deficiency <15 ng/ml was infrequent in the population and this value did show a more direct relationship with the fall of the GFR. Although it is not clear which is the level of vitamin D ideal for the maximum suppression of PTH, recent data show that it is around 27.5 to 30 ng/ml[27]. Gorriz, et al., found a prevalence of vitamin D deficiency of up to 82 %, with levels <15 ng/ml in up to 32 % of the population[20]. We think that other causes for the difference in terms of hyperparathyroidism could be due to the management provided, which was not specified in the majority of the studies evaluated, and in ours we did not evaluate vitamin D supplementation or the use of medications other than vitamin D analogues for suppression of PTH. We consider that the main causal factors of the high prevalence of vitamin D deficiencies are probably the poor intake, the elderly population with less sun exposure and the chronic kidney disease itself, factors that are common in the majority of the populations evaluated.

12.3% of the population presented hyperphosphatemia, remarkably, even in the degree G1 8.7% presented it, progressing to a prevalence of 16.5% and 41.5% in those who were in G4 and G5, respectively. Levin, et al., found a very similar progression of phosphorus levels, but in stage G3a

less than 5% had hyperphosphatemia, which differs slightly from our data; in addition, the other studies evaluated showed that phosphorus levels did not rise until patients had a GFR <20 ml/min[19-23]. The difference found, although small, could have been due to the medications used for the treatment, since the use of phosphate binders other than calcium was not evaluated, the use of calcitriol was not discriminated by level of CKD and no follow-up was performed; In addition, other etiologies of hyperphosphatemia were not considered.

When we carried out the multivariate analysis we found that the factors directly related to the level of PTH were GFR, vitamin D and phosphorus, which is to be expected if we know the bone mineral metabolism in chronic kidney disease. We did not find a relationship with calcium, in contrast to the study conducted by Levin, et al[19], and the analysis of Vassalotti et al., of two large North American cohorts;[22] the lack of relationship with the calcium levels was probably due to the small number of patients with hypocalcemia found in the studied group. Vassalotti, et al[22] found a relationship between hyperparathyroidism and obesity, age and diabetes, data not found in our study, probably due to the small number of obese individuals, the homogeneity of age in the population, the greater weight of other variables and the biases inherent in observational studies; in addition, we did not take into account other influential variables in this regard, such as albuminuria, the medications used or the race, regarding this last parameter, it was found that the prevalence of hyperparathyroidism is higher in African-Americans.

One important conclusion that we can draw is that a large number of patients had parameters of PTH, vitamin D and phosphorus out of goals, according to the current recommendations[1,8,9] for the management of the alterations in the mineral and bone profile, which were previously commented, and despite the number of patients with hyperparathyroidism, only 27% of patients were managed with calcitriol or another vitamin D analogue for their control; but we must take into account that we did not follow up the patients to evaluate the control and that most of the analyzed data were measured during the admission to the renal protection program. Although it is an interesting data to be analyzed, since studies in other regions show that the adherence to the objectives established in general does not exceed 40 %[20-23], which is a major problem, given that by allowing these alterations to persist since the initial phases, their control becomes more complex later, perpetuating their systemic effects and as a consequence there is an increase in cardiovascular morbidity and mortality[24-27].

Among the strengths of this study is the size of the evaluated population, which allows for an overview of the chronic kidney disease and the management provided in our country, it is also a basis for intervention and follow-up studies that will help us to improve the care provided to the population. The population was evaluated in a renal protection unit of Medellin managed by Nephrologists and the follow-up tests were carried out in a single center with standardized methods, so the variability of the measurements is probably minimal.

Regarding the weaknesses, it is a cross-sectional study in a single center with data taken retrospectively, which inevitably introduces biases and inaccuracies in the measurements; in addition, the data cannot be generalized to the entire population with kidney disease that is not followed-up in nephrology units. Important data were missing such as a more accurate discrimination of the race of the patients, although the predominant population was mestizo; and the replacement of vitamin D, the use of phosphorus binders other than calcium, the use of cinacalcet or the distribution of the medications according to the degrees of CKD were not evaluated. The Results according to the different causes of chronic kidney disease were not assessed either, although in general there was a low prevalence of glomerular diseases, and other etiologies such as interstitial nephritis, drug toxicity, sequels of acute kidney disease or renal vascular diseases were not determined, in part because an initial limitation in the list of the collection form, the lower prevalence and the difficulty in making the diagnosis.

In conclusion, we observed that alterations of bone mineral metabolism in patients with chronic kidney disease are frequent and progressive as re-

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nal dysfunction progresses, and their management in many cases is inadequate with the risk that this entails. Our Results were similar to those of other published cohorts and give rise to management and follow-up studies to evaluate the quality and effectiveness of the services provided to patients.

Conflict of interest

The authors do not have possible conflicts of interest.

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Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent

The authors declare that patient data do not appear in this article

Contribution of the authors

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Co-researchers: Johanna Acevedo, Sebastián Gómez, José Cañas, David Santander, José Ustariz.

Research Group Director; Adviser: Joaquín Rodelo.

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