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Original Article

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Mineral metabolism parameters throughout chronic kidney disease stages 1–5—achievement of K/DOQI target ranges

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Abstract

Background. Dialysis Outcomes and Practice Patterns Study has shown that the proportion of haemodialysis patients with adequate mineral metabolism parameters according to the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines is very low. The adequacy of such parameters in relation to the recommended ranges in patients with different chronic kidney disease (CKD) stages has not been reported. The objective of this study is to provide an in-depth description of mineral metabolism in the early stages of CKD in a European population, and to compare it with current recommendations for stages 3–5 (K/DOQI guidelines).

Methods. A total of 1836 patients were classified into stages 1–5 according to K/DOQI guidelines. The following clinical and biochemical data were recorded: age, gender, CKD aetiology, presence of diabetes, serum creatinine, creatinine clearance, serum phosphate, calcium, Ca × P product and intact parathyroid hormone (PTH).

Results. A decrease in 1,25-dihydroxyvitamin D and an increase in PTH are the earliest mineral metabolism alterations in CKD, while serum calcium and phosphate are altered later in the course of CKD. The percentages of patients with serum levels within the recommended K/DOQI guidelines for stages 3, 4 and 5 were as follows: serum calcium: 90.7, 85.6 and 55; serum phosphate: 90.9, 77.1 and 70.3; iPTH 42.4, 24.6 and 46.8 and Ca × P product 99.9, 99.6 and 83.8, respectively. The percentages of patients who had all four parameters within the recommended ranges were 34.9, 18.4 and 21.6 for stages 3, 4 and 5, respectively.

Conclusion. Mineral metabolism disturbances start early in the course of CKD. The first alterations to take place are a 1,25-dihydroxyvitamin D decrease, a 24 h urine phosphate decrease and a PTH elevation, which show significant level variation when the glomerular filtration rate falls below 60 ml/min. K/DOQI recommended levels for mineral metabolism parameters are difficult to accomplish, in particular for PTH levels.

Keywords: adequacy; calcium; chronic renal disease; guidelines; hyperparathyroidism; mineral metabolism; parathyroid; phosphate

Introduction

Chronic kidney disease (CKD) is a highly prevalent condition with increasing incidence in recent years. Patients with CKD have high morbidity and mortality rates when they are compared with a matched general population [1,2]. Over many years, numerous investigations have established a clear link between some of the comorbid conditions associated with CKD and mortality in haemodialysis (HD) patients, mostly in relation to cardiovascular events [3–7]. However, other investigations have also shown that most of the CKD patients will be affected by this morbidity and mortality excess before they reach end-stage renal failure and start on a chronic kidney replacement therapy programme. In fact, more patients will die prior to needing dialysis than reach end-stage renal disease, in spite of being under specialist care [8]. Among the conditions that occur in CKD, mineral metabolism disturbances have shown an association with the development of cardiovascular diseases and this association has been supported in numerous publications [3–7]. Based on these data, the European Best Practice Guidelines Working Group published the European Best Practice Guidelines [9] and, more recently, the National Kidney Foundation, published the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines [10] in an effort to summarize all data available, and established evidence-based

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recommendations for follow-up and treatment of disturbances of mineral metabolism in HD patients. However, the widespread recommendation of prevention strategies has been inhibited by the lack of interventional studies to confirm the influence of mineral metabolism optimization on cardiovascular mortality. In addition, data on CKD patients before dialysis are scarce, and therefore such recommendations do not exist for stages 1 and 2, and for stages 3, 4 and 5 they are more often based on expert opinion than evidence. Thus, before making specific recommendations for such stages, large descriptional studies are necessary to determine the mineral metabolism situation of CKD patients in different populations, and then, to study possible associations with mortality. Kestenbaum *et al*. [11] have recently made an interesting contribution, describing an association between phosphate levels and mortality in American patients with CKD, although the patients were not categorized into CKD stages. Yet, as can often be the case with CKD patients, data on the American population may not apply to European populations due to differences in social, ethnic and health system characteristics as well as in nutritional habits.

Thus, the aim of the present study is to provide an in-depth description of the mineral metabolism situation of European CKD patients, and compare it with current recommended target ranges for stages 3–5 (K/DOQI guidelines).

Material and methods

Study population

This is a cross-sectional study comprising all CKD patients attending two nephrology out-patient clinics with similar treatment policies ($n = 2610$). They were classified in stages 1–5 according to K/DOQI guidelines [12]. After excluding those patients with primary hyperparathyroidism, previous parathyroidectomy, neoplasias, osteoporosis under treatment with biphosphonates or calcitonin, and those with missing data ($n = 472$), the remaining population consisted of 1836 patients. The characteristics of the patients with missing data did not differ from those of the remaining population. None of them had started haemodialysis. Most of the patients at stages 4 and 5 and some of those at stages 1–3 were advised to limit their intake of protein and phosphate by an experienced nephrologist and a nephrology nurse. None of the patients was on 25-vitamin D supplements.

The following clinical and biochemical data were also recorded: age, gender, CKD aetiology, presence of diabetes, serum creatinine, creatinine clearance, serum phosphate, calcium, Ca × P product and intact parathyroid hormone (iPTH). The iPTH concentrations were measured by a two-site electrochemiluminometric immunoassay (Cobast®, Roche Diagnostics GmbH) (normal range 1.2–6.9 pmol/l). The recommended ranges for each stage are described in K/DOKI Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease. For serum calcium at stages 3–4, reference values were those considered as normal by our laboratory (8.5–10.2 mg/dl) following the K/DOQI guidelines indications [10]. Treatment with calcium salts and/or calcitriol was also recorded. Treatment with calcitriol was given when PTH was >20 pmol/l (CKD 3) or >25 pmol/l (CKD 4 and CKD5 without dialysis) provided that P and Ca levels were under the aforementioned limits. The reason for not administering calcitriol to patients with lower levels of PTH was to avoid adynamic bone disease [13]. In addition, calcitriol use was avoided in patients with vascular or soft tissue calcifications even when PTH levels were above the desired range.

There was a subgroup of patients with data on serum 25-hydroxyvitamin D [$25(OH)D_3$] ($n = 205$), 1,25-dihydroxyvitamin [$1,25(OH)_2D_3$] ($n = 522$), 24 h urine calcium ($n = 319$) and 24 h urine phosphate ($n = 317$). Most serum $25(OH)D_3$ samples were collected in December, the rest of them during late autumn and winter months (October–February) and determined with radioimmunoassay (Biosource®, normal range 12–80 ng/ml, inter-assay coefficient of variation 20%). The mean value for the healthy population in Spain during winter–spring time is 13.7 ng/ml. Serum levels of $1,25(OH)_2D_3$ were determined using a radioreceptor assay (Gamma-B dihydroxyvitamin D, IDS Hybritec®; normal range 18–78 pg/ml, intra-assay and interassay coefficients of variation were 9.6 and 14%, respectively). The creatinine clearance was calculated with the Cockcroft–Gault equation [14].

Statistical analysis

Epidemiological and clinical data are presented as mean ± SD or percentage. To determine the differences between means in CKD groups, we used a one-way analysis of variance (ANOVA). To determine when particular means started to show significant variations, Student's *t*-values weres used in order to compare stages in pairs (CKD1 *vs* CKD2, CKD2 *vs* CKD3, CKD3 *vs* CKD4 and CKD4 *vs* CKD5). Results were considered statistically significant at the level of 5%. Data were analysed using the Statistical Package for the Social Sciences (SPSS) software package (11.0) for Windows (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows epidemiological and clinical data of the 1836 subjects, and comparisons of parameters between the different CKD groups. Significant differences among CKD stages were obtained in gender, age, serum creatinine, creatinine clearance, calcium and phosphate, Ca × P product, iPTH, treatment with calcium salts and/or calcitriol and $1,25(OH)_2D_3$. No significant differences were found in CKD aetiology, diabetes and $25(OH)D_3$ levels.

Figure 1 shows the mean values of calcium (A), phosphorus (B), Ca × P product (C) and iPTH (D). Panels E and F show $25(OH)D_3$ and $1,25(OH)_2D_3$ values in the subgroup of patients in whom such data were available. Inter-group significance (ANOVA) and comparisons between each stage (Student's *t*) are specified in each graph. Serum calcium levels increase from stages 1 to 2 and decrease afterwards.

Table 1. Characteristics of study population

Characteristic	Stage					*P*-value
	CKD1 ($n=174$)	CKD2 ($n=341$)	CKD3 ($n=856$)	CKD4 ($n=354$)	CKD5 ($n=111$)	
Male/Female (*n*)	76/98	218/123	517/339	247/107	67/44	0.000
Age (years)	49 ± 15	60 ± 14	72 ± 12	75 ± 12	74 ± 15	0.000
Cause of CKD% (*n*)						0.000
DM	24.7 (43)	18.5 (63)	16.5 (141)	19.2 (68)	19.8 (22)	
Chronic glomerulonephritis	29.9 (52)	14.1 (48)	7.8 (67)	11.3 (40)	5.4 (6)	
Chronic pyelonephritis	14.4 (25)	17.9 (61)	21.1 (181)	16.9 (60)	13.5 (15)	
Polycystic kidney disease	8.6 (15)	7.0 (24)	3.7 (32)	4.8 (17)	8.1 (9)	
Nephrosclerosis	10.9 (19)	23.8 (81)	24.3 (208)	23.2 (82)	24.3 (27)	
Other	1.1 (2)	1.2 (4)	0.4 (3)	0.8 (3)	0.9 (1)	
Unknown	10.3 (18)	17.6 (60)	26.2 (224)	23.7 (84)	27.9 (31)	
Diabetes mellitus% (*n*)	34.5 (60)	30.2 (103)	27.7 (237)	28.8 (102)	27.0 (30)	0.446
Laboratory data, mean						
Serum creatinine (mg/dl)	0.97 ± 0.2	1.23 ± 0.2	1.69 ± 0.5	2.78 ± 0.9	5.01 ± 1.8	0.000
Creatinine clearance (ml/min)	112.5 ± 18	72.1 ± 8.5	44.3 ± 8.4	23.1 ± 4.2	11.5 ± 2.3	0.000
Calcium (mg/dl)	9.49 ± 0.38	9.57 ± 0.39	9.57 ± 0.46	9.35 ± 0.58	9.6 ± 0.76	0.000
Phosphate (mg/dl)	3.69 ± 0.62	3.54 ± 0.6	3.59 ± 0.55	3.92 ± 0.78	4.89 ± 1.23	0.000
Product Ca × P (mg/dl^2)	35.15 ± 6.2	33.96 ± 5.9	34.38 ± 5.6	36.62 ± 7.2	44.63 ± 10.4	0.000
iPTH (pmol/l)	4.86 ± 2.44	5.97 ± 3.05	8.96 ± 5.84	16.47 ± 13.02	24.29 ± 13.66	0.000
25(OH)vitamin D (ng/ml)		24.7 ± 17.8	29.6 ± 20.7	26.2 ± 17.9	23.4 ± 24.3	0.393
1,25(OD)vitamin D (pg/ml)	33.4 ± 13.3	33.9 ± 14.5	25.7 ± 11.6	16.8 ± 8.8	13.2 ± 7.8	0.000
Medication use% (*n*)						
Oral calcium	1.1 (2)	1.2 (4)	2.5 (21)	19.8 (70)	51.4 (57)	0.000
Oral calcitriol			0.6 (5)	7.9 (28)	27.0 (30)	0.000

Demographic, clinical and biochemical data of the population.
Percentage with absolute numbers in brackets and significance with chi-square for categorical variables and mean ± SD for non-categorical variables.
Conversion factor to SI units: Creatinine (×88.4), Calcium (×0.25), Phosphate (×0.32), iPTH (×9.09).

The decrease reaches statistical significance between stages 3 and 4. Serum phosphate shows a mirror image with respect to calcium levels; there is a slight decrease at stages 2 and 3 with respect to stage 1 and a progressive increase afterwards. Significant differences are seen between stages 3 and 4 and between stages 4 and 5. The Ca × P product rises significantly after stage 3 (3 *vs* 4 and 4 *vs* 5). PTH starts to increase at stage 2 with respect to 1 and rises progressively and significantly until stage 5 (1 *vs* 2, 2 *vs* 3, 3 *vs* 4 and 4 *vs* 5).

The mean levels of $25(OH)D_3$ do not vary among stages. Panel F shows how $1,25(OH)_2D_3$ maintains similar levels at stages 1 and 2 and decreases progressively as CKD advances reaching statistical significance for stages 2 *vs* 3, 3 *vs* 4 and 4 *vs* 5. In addition, there was a negative correlation between $25(OH)D_3$ levels and iPTH ($r^2=0.283$, $P<0.01$) and between $1,25(OH)_2D_3$ levels and iPTH levels ($r^2=0.323$, $P<0.01$).

Figure 1 also shows the subgroup of patients with data for 24 h urine calcium (G), 24 h urine phosphate (H) and fractional excretion of phosphate (FEP) (I). Urine calcium and phosphate excretion decrease as renal function deteriorates ($P<0.05$; stage 2 *vs* 3 and 3 *vs* 4 for urine calcium and $P<0.05$; stage 2 *vs* 3 and 3 *vs* 4 for urine phosphate). Fractional excretion of phosphate increases gradually and significantly from stages 1 to 4 although significance was not obtained between stages 4 and 5 ($n=6$).

Figure 2 shows the percentage of patients who accomplish the K/DOQI target ranges for the different mineral metabolism parameters: serum calcium, phosphate, iPTH and Ca × P product for stages 3–5 without dialysis. The proportions of patients who achieve all mineral metabolism parameters recommendations are: 34.9, 18.4 and 21.6% for stages 3, 4 and 5 respectively.

Discussion

This study provides a complete description of mineral metabolism parameters throughout CKD evolution, from stages 1 to 5, in a large population. It shows how early some of the mineral metabolism parameters are altered. In particular, serum PTH and $1,25(OH)_2D_3$, and urine calcium and phosphate levels already vary from stage 1 to 2 and do so progressively until stage 5. These early alterations are likely to be implicated in the origin of hyperparathyroidism and yet, in clinical practice, these parameters are seldom followed at these stages, and therefore no recommendations are given for management and prevention.

The complexity of hyperparathyroidism physiopathology has often been a controversial subject. The early elevation of PTH levels has been considered a consequence of $1,25(OH)_2D_3$ deficit [15,16]. The present results are consistent with this hypothesis. Thus, from a physiopathological point of view,

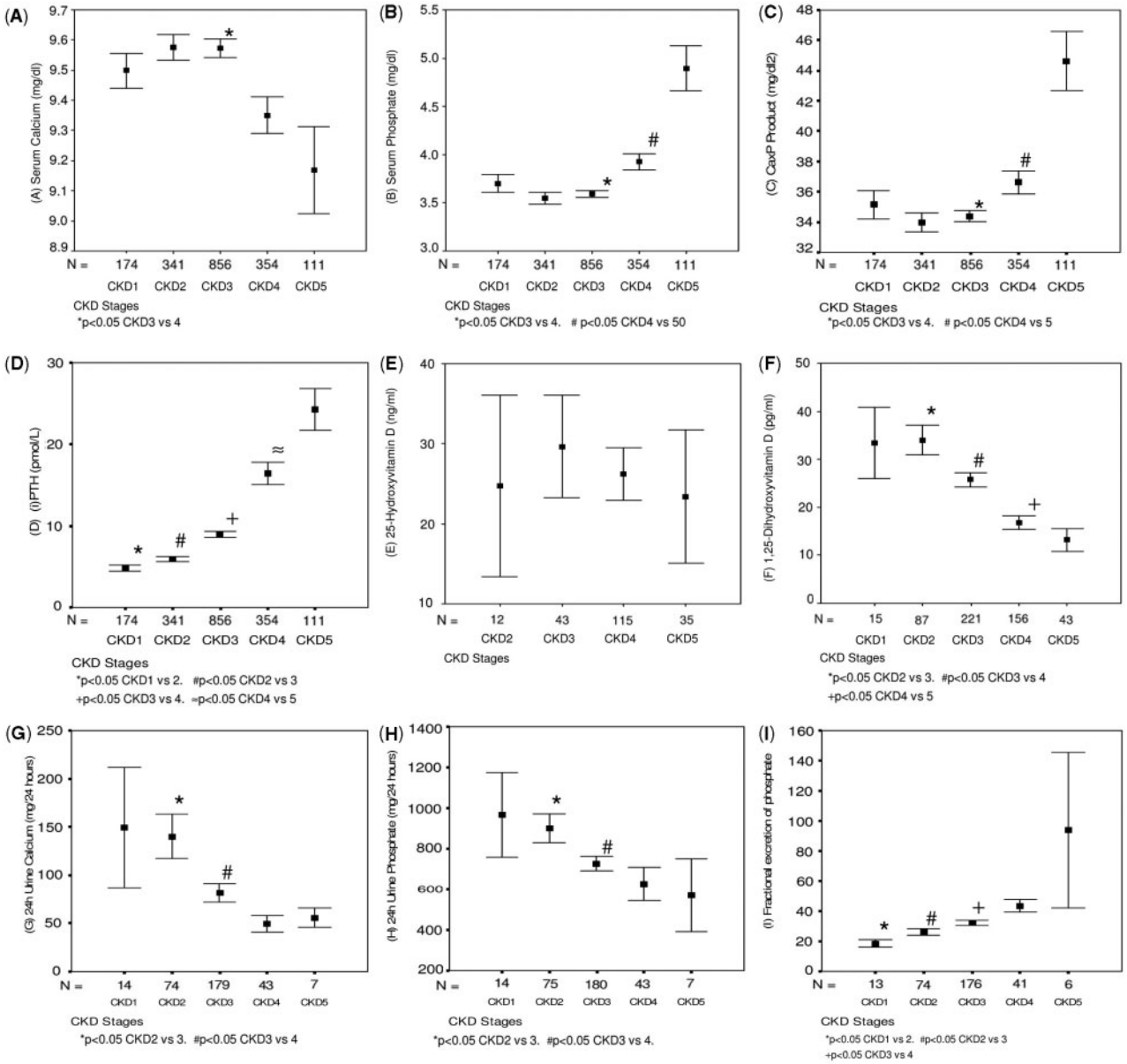

Fig. 1. Mean levels of serum calcium (**A**), phosphate (**B**), Ca × P product (**C**), iPTH (**D**), 25-Hydroxyvitamin D (**E**), 1,25-dihydroxyvitamin D (**F**), 24 h urine calcium (**G**), 24 h urine phosphate (**H**) and fractional excretion of phosphate (**I**) for each CKD stage and significance with ANOVA and Student's *t*.

early calcitriol supplementation should be the treatment of choice. In practice, hypercalcaemia and hyperphosphataemia sometimes limit its use at the desired doses. Serum phosphate levels also contribute to PTH stimulation, but they seem to act at latter stages, since they do not begin to increase until stage 5 due to markedly diminished tubular excretion. However, there are a few considerations to be taken into account concerning the role of phosphate. First, its maintenance within 'normal' limits is not a physiological fact, because they are kept within these limits at the expense of a PTH increase, as described by Slatopolsky and Bricker [17]. This would explain the decrease of serum phosphate from stages 1 to 2. Second, alterations in serum levels are a late-stage consequence of a decrease in urinary total excretion as renal function declines, when this mechanism is no longer compensated by the increase of FEP induced by PTH. These early mechanisms are supported by previous literature data that demonstrate the efficacy of early phosphate restriction in hyperparathyroidism prevention (as soon as PTH levels are increased, without waiting for elevated phosphate levels) [18]. Serum calcium levels are also involved in hyperparathyroidism progression but are more likely to play an important role in advanced stages, when they begin to decrease. However, serum calcium levels are a poor reflection of calcium metabolism, and have little

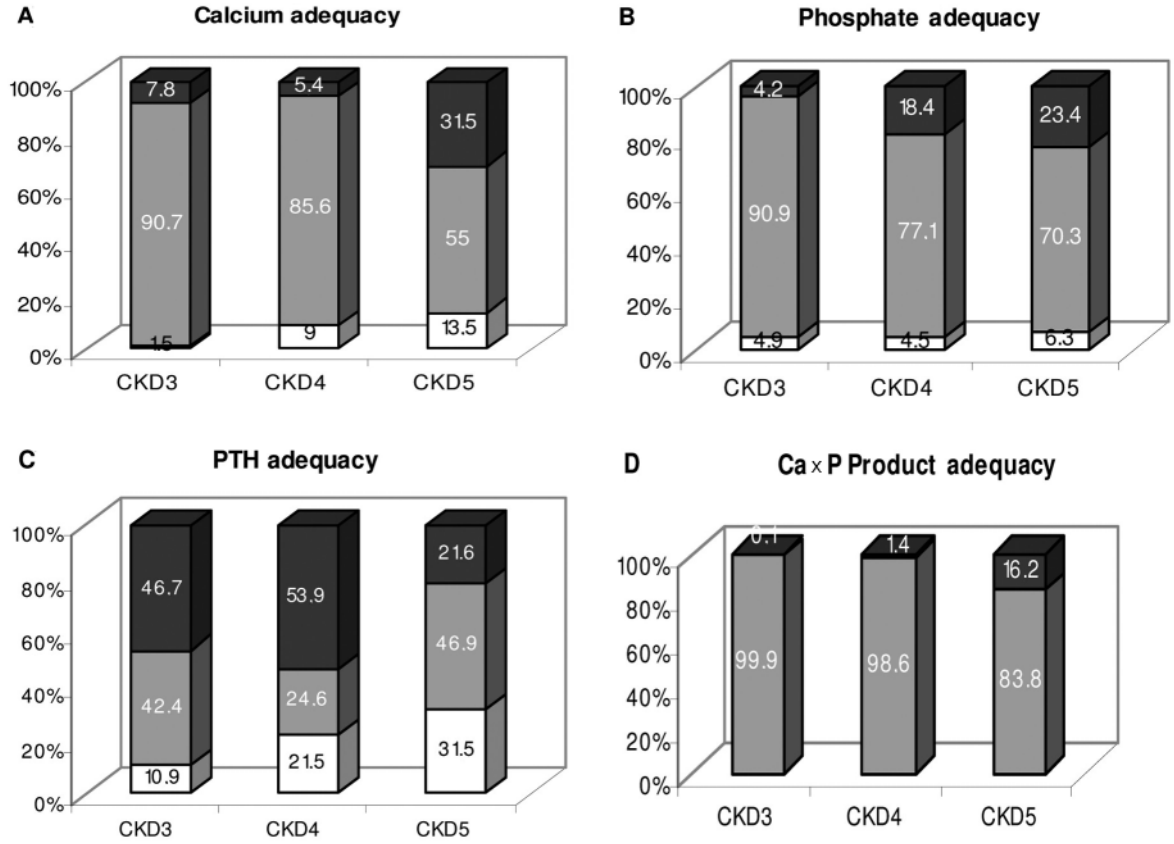

Fig. 2. Bars represent the percentage of patients with calcium (**A**), phosphate (**B**), iPTH (**C**) and Ca × P product (**D**) within (middle part of the bars, in grey),below (bottom part of the bars, in white) and above (upper part of the bars, in black) K/DOQI target recommendations for stages 3–5.

correlation with calcium overload. Thus, maintaining them within these limits is probably the best practice in the absence of further evidence supporting a different approach.

Regarding the achievement of K/DOQI recommended target ranges, previous studies have only examined the situation of mineral metabolism in haemodialysis patients [5,7]. Ours is the first study to do so throughout all stages 3–5 of CKD in a large population. All previous studies coincide with the difficulty of achieving K/DOQI recommendations. In our case, the results reflect poor adequacy to K/DOQI guidelines concerning PTH levels, with a high proportion of patients having PTH levels that are too low or too high. These results are in line with previous histological data that describe the spectrum of bone disease in pre-dialysis patients as broad, and not limited to hyperparathyroidism, with only a small proportion of patients being free from bone disease [13]. PTH levels have been related to mortality. Both high and low levels are associated with poor survival rates in haemodialysis patients [4]. PTH itself is thought to cause increased cardiovascular risk and is associated with the loss of arterial elasticity and left ventricular hypertrophy [19]. It is believed that the relevant mechanism could be direct action on vascular and cardiac cells, which express PTH receptors [20]. However, the Ca × P product is also increased in secondary hyperparathyroidism. Thus, both mechanisms are likely to interact and contribute to cardiovascular damage. At the other extreme, low PTH levels are a marker of malnutrition, adynamic bone disease and other pathological conditions; representing a sample of haemodialysis patients with higher morbidity and mortality [21]. PTH is the parameter that shows the maximal deviation from K/DOQI guidelines in our population. In stages 3 and 4, this happens mainly because a significant proportion of the population has high levels of PTH, but as CKD progresses the proportion of patients having low levels increases, reaching 31.5% in stage 5. In addition, the proportion of patients with high PTH levels decreases from stages 4 to 5, although they have higher absolute mean values (stage 4: 16.47 pmol/l, stage 5: 24.29 pmol/l).

Our results potentially disclose an optimal degree of calcium, phosphate and Ca × P control for stage 3, when a high proportion of patients fall within the recommended target ranges. In stages 4 and 5, the proportion of patients with high phosphate and high calcium levels increases gradually, leading to a 16.2% of patients with high Ca × P product in stage 5. In spite of the limited information on mortality and

mineral metabolism in CKD patients before dialysis, when reviewing literature data on this topic, several things stand out. First, there is disparity in recommended phosphate threshold levels. There is evidence that phosphate levels well below those cited by the guidelines are associated with increased risk of cardiovascular events. In this respect, Kestenbaum *et al.* [11] found an association between phosphate levels >3 mg/dl and mortality, with the range between 2.5 mg/dl and 3 mg/dl being the reference value, whereas the K/DOQI guidelines recommend 2.7–4.6 mg/dl for stages 3–4. In fact, our own clinical observations are consistent with these results: while a high proportion of our patients in stages 3 and 4 achieve K/DOQI recommendations, they still show alarmingly high rates of death, suggesting that the recommended ranges might be too permissive. In addition, the fact that more patients achieve the Ca × P product target ranges than the Ca and P target ranges separately, suggests that Ca × P target ranges are too high. Prospective interventional studies to confirm that optimization of Ca and P levels reduces cardiovascular disease would be of great interest.

In summary, this is the first study to provide a complete description of the mineral metabolism parameters situation concerning in a large CKD population before dialysis. It shows that the PTH recommended levels are difficult to obtain with current treatment options, although new drugs, such as vitamin D analogues, calcimimetics and new phosphate binding agents will provide more options in future years.

Conflict of interest statement. None declared.

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