Unawareness of the K/DOQI™ guidelines for bone and mineral metbolism in predialysis chronic kidney disease: resultas of the «OSERCE» spanish multicenter-study survey

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Nefrología 2008; 28 **(6)** 637-643

SUMMARY

Since its publication in 2003, the K/DOQI™ clinical practice guidelines for bone metabolism and disease in chronic kidney disease (CKD) have become a worldwide reference. The aim of this study was to analyze the observance to these guidelines in patients with a glomerular filtration rate < 60 ml/min/1.73m² not yet included in dialysis in a Spanish multicenter cohort. A questionnaire by investigator/centre was completed by 32 different nephrologists participating in the OSERCE study and representing the overall Spanish public health net. We observed that biochemical parameters were measured less frequently than recommended, except in CKD stage 3. The therapeutic goals for intact PTH were not properly reported by 59% of the consulted nephrologists for stages 3 and 4, whereas only 22% did not report them properly for stage 5. The goals for phosphorus were not adequately reported in 50% of cases (stages 3 y 4) and 60% (stage 5). For calcium, these values were 70 %, 73.3% and 65.5% for stages 3, 4 and 5, respectively. A corrected plasma calcium between 9.5 and 10.2 mg/dl is still considered adequate for 31%. As much as 87% nephrologists stated that they did not sistematically measure calcidiol plasma levels. In general, these results demonstrate that there is a great degree of unawareness of K/DOQITM predialysis guidelines. Thus, their poor implementation is probably not only due to the lower availability of approved therapeutic agents, the difficult achievement of goals or the disbelief on current recommendations. It would be desirable that forthcoming guidelines such as the KDIGO could also consider the need of educational efforts for CKD-Mineral and Bone Disorder.

Key words: *Osteodystrophy. K/DOQI. Guidelines. Chronic kidney disease. Mineral metabolism. CKD-MDB. Phosphorous. Vitamin D. Calcification.*

RESUMEN

Desde su publicación en el 2003, las guías K/DOQI™ sobre metabolismo y enfermedad ósea en la enfermedad renal crónica (ERC) han sido referencia internacional. El objetivo de este estudio fue analizar el grado de conocimiento de las mismas en pacientes con ERC estadios 3, 4 y 5 no en diálisis mediante una encuesta a 32 nefrólogos españoles que participaron en el estudio OSERCE. De este análisis se deduce que la frecuencia teórica de medición de parámetros bioquímicos es habitualmente menor a la recomendada, excepto en el estadio 3. Los objetivos terapéuticos para la PTH intacta fueron inadecuadamente reportados por el 59% de los nefrólogos encuestados para estadios 3 y 4, mientras que para el estadio 5 sólo por el 22%. Los objetivos para el fósforo fueron inadecuadamente reportados en el 50 % de los casos (estadios 3 y 4) y 60% (estadio 5). Para el calcio fueron del 70%, 73,3% y 65,5% en los estadios 3, 4 y 5 respectivamente. Un calcio plasmático corregido entre 9,5 y 10,2 mg/dl fue todavía considerado apropiado en el 31% de las respuestas. Hasta un 87% de los nefrólogos consultados manifestaron no medir sistemáticamente los niveles plasmáticos de calcidiol. En general, estos resultados demuestran que existe un alto grado de desconocimiento de las guías K/DOQITM en los pacientes con ERC no en diálisis. Por consiguiente, la falta de implementación de las mismas no sólo ha sido debido a la menor disponibilidad de agentes terapéuticos prediálisis, la dificultad de cumplimiento de objetivos o la propia incertidumbre de las guías sino también a su desconocimiento. Sería pues recomendable que próximas guías como las K-DIGO vinieran acompañadas también de intervenciones de carácter educativo en el diagnóstico y tratamiento precoz de las alteraciones del metabolismo óseo-mineral asociado a la ERC.

Palabras clave: Osteodistrofia. Guías. K/DOQI. Enfermedad renal crónica. Metabolismo mineral. CKD-MBD. PTH. Fósforo. Vitamina D. Calcificación.

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INTRODUCTION

After publication of the European guidelines,[1] the American National Kidney Foundation published its own clinical practice guidelines (*K/DOQI™ or Kidney Disease Outcome Quality Initiative)* for bone metabolism and disease in chronic kidney disease (CKD) in 2003, which became the worldwide referen-

ce used for many years.[1] Although they were always disputed because of the high degree of «expert opinion» contained in their recommendations, it is clear that they are not only a worldwide reference but also very popular, well-known and extensively followed in the management of dialysis patients.[3-5]. However, the condition previously known as «renal osteodystrophy»[6] and now generically called chronic kidney disease-mineral and bone disorder[7-9] starts long before the need for dialysis,[10] and early control of biochemical parameters is also recommended in CKD stages 3-5 predialysis.[2] The aim of this study was to analyze adherence to the K/DOQI™ guidelines for bone and mineral metabolism disorders in patients with CKD stages 3-5 predialysis in a survey of Spanish nephrologists participating in the OSERCE study, three years after publication of the K/DOQI™ guidelines.

PATIENTS AND METHODS

OSERCE is the Spanish acronym for «Epidemiological Study of Bone Disease in Chronic Kidney Disease in Spain». It is was a cross-sectional multicenter study, whose aim was to analyze the clinical and biochemical characteristics and the therapeutic management of mineral and bone disorders in CKD (CKD-MBD) in adult patients > 18 years of age with an estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 not yet included in dialysis (CKD stages 3, 4 and 5). The patients included were from the outpatient clinics of different nephrology department in Spain and gave their informed consent to participate in the study. The primary aims of the OSERCE study were to analyze the percentage of patients with intact parathyroid hormone (iPTH) levels outside the values recommended by the K/DOQI™ guidelines,[11,12] and to determine the percentage of patients in whom PTH was measured routinely. Each investigator completed a questionnaire before starting the study. The results of this questionnaire are reported in the present paper.

Questionnaire

The study included a questionnaire completed by each investigator/center on their clinical practice in CKD-MBM requesting both the frequency of measurements of bone metabolism parameters (calcium, phosphorus, intact PTH and calcidiol) and the target ranges considered as treatment goals in this population in the different stages of CKD. Practices related to the measurement of plasma bicarbonate and the performance of imaging tests to assess the presence of calcifications were also analyzed. The study was carried out from April to May 2006 and completed in 32 centers.

We considered «inadequate» responses as those outside the ranges recommended in the K/DOQI™ clinical practice guidelines for CKD patients not on dialysis and shown in table I. Hypercalcemia was defined as corrected calcium values exceeding 10.2 mg/dl in accordance with the guidelines.[2]

The results are expressed as the mean (mean percentage) and 95% confidence intervals (CI) (95% CI, lower limit-upper limit).

RESULTS

The questionnaires were answered by the 32 investigators participating in the OSERCE study, all of whom were nephrologists treating patients with CKD not on dialysis. The polled nephrologists were 16 women and 16 men with a mean age of 44.6 ± 9.1 years, median age of 44 years (range: 27-60) (95% CI: 41-48), and a mean of 17 ± 6 years working in nephrology (95% CI: 14-21).

Frequency of measurement of recommended biochemical parameters

Table II shows the frequency of measurement of the most important biochemical parameters and their comparison with the follow-up recommended by the K/DOQI™ guidelines.[2] As much as 87.5% of polled nephrologists stated that they did not systematically measure calcidiol plasma levels despite of these recommendations. Among polled nephrologists, 50% never performed this measurement (95% CI, 33-66), 37.5% performed it sometimes (95% CI, 22-54) and only five investigators (12.5%) always performed it (95% CI, 5-29).

Treatment goals for iPTH, calcium, phosphorus and calcium-phosphorus product

Tables III, IV, V and VI show the percentage reported as the treatment goal for plasma levels of intact PTH, phosphorus, calcium and calcium x phosphorus product, respectively. Table 3 shows that treatment goals for intact PTH were adequately reported for patients in stage 3 by only 41% of polled nephrologists (95% CI, 24-57). They were adequately reported by 36% (95% CI, 21-54) in stage 4 and by 78% (95% CI, 59-89) in stage 5.

Table IV shows that treatment goals for plasma phosphorus were adequately reported only in 50% of patients in stage 3 (95% CI, 33-67) and 50% in stage 4 (95% CI, 33-67), and in

Table I. Summary of biochemical values recommended by K/DOKI™ (Kidney Disease Outcomes Quality Initiative) guidelines for patients with chronic kidney disease stages 3, 4 and 5

CKD stage	GFR ml/min/1.73 m^2	Frequency of iPTH measurement	Frequency of Ca and P measurement	Calcium mg/dl	Phosphorus mg/dl	iPTH pg/ml	Ca x P product
3	30-59	12 months	12 months	8.4-9.5	2.7-4.6	35-70	< 55
4	15-29	3 months	3 months	8.4-9.5	2.7-4.6	70-110	< 55
5	< 15	3 months	1 month	8.4-9.5	3.5-5.5	150-300	< 55

CKD: Chronic kidney disease. GFR: Glomerular filtration rate. iPTH: Intact PTH. Ca: Ca Corrected plasma calcium. P: Phosphorus.

Table II. Percentages of frequency of measurement of the parameters recommended by K/DOQI™ (Kidney Disease Outcomes Quality Initiative) guidelines in nephrology outpatient clinics in Spain. Comparison between results of the survey and guideline recommendations. Results are expressed as the mean and 95% confidence interval with upper and lower limits

	Stage 3		Stage 4		Stage 5	
	Survey (%) (95% CI low-upp)	Guidelines**	Survey (%) (95% CI low-upp)	Guidelines**	Survey (%) (95% CI low-upp)	Guidelines**
iPTH	60% half-yearly (43-75) 30% yearly (17-47)	yearly	69% quarterly (51-82) 21% half-yearly (10-38)	quarterly	50% quarterly (33-67) 33% monthly (19-51)	quarterly
Calcium	67% half-yearly (49-80) 27% quarterly (14-44)	yearly	77% quarterly (59-88) 10% half-yearly (4-25)	quarterly	73% monthly (56-87) 27% quarterly (14-44)	monthly
Phosphorus	63% half-yearly (46-78) 30% quarterly (17-48)	yearly	83% quarterly (66-92) 7% half-yearly (2-21)	quarterly	70% monthly (52-83) 27% quarterly (14-44)	monthly

* Results of survey. ** K/DOQI™ guidelines recommendations.
iPTH: Intact PTH.

53% of patients in stage 5 (95% CI, 36-69). The most frequent discrepancy was to consider adequate phosphorus levels between 3.5 and 5.5 mg/dl in stages 3 and 4, which are usually recommended in stage 5 in dialysis patients. Table V shows that treatment goals for calcium were inadequately reported by only 30-35% of polled nephrologists, but goals between 9.5 and 10.2 mg/dl were still considered adequate in 31% of the responses (95% CI, 17-49). Hypercalcemia was defined as corrected calcium levels greater than 9.5, 10.2 and 10.5 mg/dl by 10% (95% CI, 4-26), 52% (95% CI, 35-68) and 38% (95% CI, 23-56) of nephrologists, respectively. Table V shows that at least 90% of polled nephrologists was knowledgeable of the recommended values for the Ca x P product (< 55 mg/dl) in the different stages of CKD.

Other aspects of the questionnaire

We finally note that 93% of polled nephrologists stated that they did not regularly measure bicarbonate levels (95% CI, 78-98). A target level of 22-25 mEq/l was considered adequate by 76% (95% CI, 58-87), 17% (95% CI, 8-34) accepted a certain degree of acidosis (18-21 mEq/l) and the rest considered adequate levels between 26-28 mEq/l. In addition, 72% of nephrologists (95% CI, 54-85) performed imaging tests to evaluate the presence of calcifications (mainly plain chest or abdominal X-rays or echocardiograms in approximately 50% of cases), while bone densitometry was performed in 39% of cases (95% CI, 24-57).

DISCUSSION

Although the European guidelines were published previously,[1] the American National Kidney Foundation published shortly afterwards its own K/DOQI™ clinical practice guidelines for bone metabolism and disease in CKD.[2] It was also in these same K/DOQI™ guidelines that the current concept of CKD was first defined, and which has been recently adopted with minor changes by the KDIGO (Kidney Disease Improving Global Outcomes) international initiative.[13,14] It is clear that the K/DOQI™ guidelines have become the worldwide reference used in most countries and studies, and they were a common standard of definitions and treatment goals for many years. Although the guidelines for bone metabolism and disease were always disputed because of the high degree of «expert opinion» contained in their recommendations,[2] it is clear that they have been a unifying element that has permitted all nephrologists to use the same language and to compare uniformly the results of different studies, and thus they have been very popular, well-known and extensively followed in the management of dialysis patients.[3-5]

Recently, and coinciding with the growing importance of early diagnosis of CKD and cardiovascular risk factors associated with CKD in clinical practice,[13-19] several articles have demonstrated the association between mortality and serum levels of different biochemical parameters related to mineral metabolism.[20-22] So much so that the KDIGO international guidelines have introduced a new broader concept (CKD-MBD, or Chronic Kidney Disease-Mineral and Bone Disorder) which emphasizes the importance of control of bone and mineral disorders associated with CKD beyond mere control of bone disease to achieve a systemic dimension,[7] but only a draft version for discussion showing their guidelines in this area has been published. It is for this reason that the K/DOQI™ guidelines are still the worldwide reference, especially in dialysis patients, at least until forthcoming publication of the next version of the KDIGO guidelines.

However, CKD-MBD starts long before the need for dialysis,[10,23,24] so the K/DOQI™ guidelines also included target recommendations for predialysis CKD patients.[2] In this study, it can be clearly seen that the degree of knowledge of predialysis guidelines is very poor among the Spanish nephrologists working in the outpatient clinics of the different centers participating in the OSERCE study.

First, it is notable that the different biochemical parameters were measured less frequently than recommended by current guidelines except in patients with CKD stage 3 and measure-

Tables III, IV, V y VI. Percentage of responses on levels considered adequate for plasma levels of intact PTH (iPTH), phosphorus, calcium and calcium-phosphorus product in patients with Chronic kidney disease stages 3, 4 and 5. The boxes in gray show the % of agreement between the opinion of the polled nephrologists and the recommendations of the K/DOQI™ (Kidney Disease Outcomes Quality Initiative) guidelines in each stage of chronic kidney disease. The column on the right show a summary of the percentage of agreement in all stages in each of the tables, expressed as percentage and 95% confidence interval with lower and upper limits

Table III. iPTH

iPTH (pg/ml)	35-70	70-110	110-150	150-300	% of agreement with guidelines % (95% CI)
Stage 3	**41%**	26%	22%	11%	41% (24-57)
Stage 4	0	**36%**	46%	18%	36% (21-54)
Stage 5	0	0	22%	**78%**	78% (59-89)

Table IV. Phosphorus

Serum phosphorus (mg/dl)	2.5-5.5	3.5-5.5	2.7-46	% of agreement with guidelines % (95% CI)
Stage 3	13.3	36.7	**50%**	50% (33-67)
Stage 4	10	40%	**50%**	50% (33-67)
Stage 5	6.7	**53,3**	40%	53% (36-69)

Table V. Calcium

Serum calcium (mg/dl)	8-8.4	8.4-9.5	9.5-10.2	% of agreement with guidelines % (95% CI)
Stage 3	3.3%	**70%**	26.7%	70% (52-83)
Stage 4	0%	**73,3%**	26.7%	73.3% (56-86)
Stage 5	3.4%	**65,6%**	31%	65.5% (47-80)

Table VI. Calcium x Phosphorus Product

Ca x P product (mg^2/dl^2)	< 55	< 60	< 70	% of agreement with guidelines % (95% CI)
Stage 3	**93%**	7%	0	93% (79-96)
Stage 4	**97%**	3%	0	97% (83-99)
Stage 5	**90%**	10%	0	90% (75-96)

ment of intact PTH in patients with CKD stage 5. Intact PTH was measured more frequently in patients in stage 3 (PTH was measured yearly in about 30% of patients and two or more times a year in up to 70%) and in stage 5, where PTH was measured in 83% of patients with equal or greater frequency than recommended (33% of patients even had monthly measurement of intact PTH). This frequency was even higher for calcium and phosphorus in patients in stage 3, where more than 90% of patients had measurements in periods of less than 6 months. Obviously, it is well known that stage 3 encompasses a heterogeneous group of patients with kidney function ranging from the upper limit of the definition of CKD (60 ml/min/1.73 m^2) to glomerular filtration rates of 30 ml/min/1.73 m^2. Some have thus considered it appropriate to divide stage 3 in stage 3A (< 60-45 ml/min/1.73 m^2) and 3B (< 45-30 ml/min/1.73 m^2) to make this population more homogeneous for follow-up, referral to the specialist or even different therapeutic management.[17,25] It is then likely that this frequency of measurement will better match the real needs of these patients than the lax recommendation of the K/DOQI™ guidelines. In contrast, calcium and phosphorus levels were measured less frequently than recommended by current guidelines in CKD stages 4 and 5, probably better reflecting not only the different care realities, but also, especially in stage 5, the lack of division of stage 5 between patients on dialysis (current stage 5D where monthly measurement of patients is logistically feasible) and those who glomerular filtration rate is < 15 ml/min/1.73 m^2, but who are not yet in a dialysis program.

It is also notable that 87% of nephrologists did not measure systematically calcidiol levels in their predialysis patients despite the fact that measurement of calcidiol has been re-

commended since the implementation of the K/DOQI™ guidelines, at least for management of hyperparathyroidism in patients with CKD stages 3 and 4.[2] This fact has particular relevance if we consider that CKD patients frequently have vitamin D *deficiency* or *insufficiency*, sometimes severe,[11,23,24] even in our setting,[11,24] and that vitamin D is attributed multiple pleiotropic effects and effects on survival that go beyond bone metabolism.[26,27] In addition, different vitamin D receptor activators can have different effects on survival.[28] In Spain, the easy availability of cholecalciferol or ergocalciferol in the required doses, as well as the lack of comparative analyses between active forms and native vitamin D has no doubt influenced this observation. Only recently has an article appeared on an observation study analyzing the relationship between differences in early survival in dialysis patients and plasma vitamin D levels in patients treated or not with active forms of vitamin D.[29]

Of note regarding the K/DOQI™ guidelines was the extensive knowledge of treatment goals for PTH in stage 5, where 78% of polled nephrologists had target PTH values between 150-300 pg/ml considered with a grade of evidence in the K/DOQI™ guidelines,[2] although currently questioned.[8,30] In stages 3 and 4, only approximately 40% (36-41%) of nephrologists had the treatment goal for PTH recommended in the guidelines. This observation is important in that different studies have determined the difficulty in complying with K/DOQI™ guidelines and the need for new drugs to achieve treatment goals both in patients on dialysis[4,31,32] and in predialysis,[12,24,33,34,35] but our results provide the new information that not only is there a lack of approved and effective therapeutic agents in predialysis, but also a high degree of unawareness or disbelief of current recommendations. In fact, it can be seen in the analysis of the responses that the most frequent bias was to consider normal in stages 3 and 4 values that are more widely known and which are recommended in the K/DOQI™ guidelines for patients in stage 5 on dialysis (for example, phosphorus levels of 3.5-5.5 mg/dl). Strictly inadequate plasma calcium levels were reported by less than 4% of nephrologists. However , there was still nearly 30% of nephrologists whose treatment goal was calcium levels between 9.5-10.2 mg/dl (the limit between desirable calcium and the definition of hypercalcemia is poorly defined in the K/DOQI™ guidelines). Similarly, 38% of polled nephrologists considered hypercalcemia as values > 10.5 mg/dl, whereas only 10% defined hypercalcemia as values > 9.5 mg/dl, thus still reflecting the treatment trends maintained until not long ago.[6,36] This finding has recently been documented in the distribution of the results of the DOPPS (Dialysis Outcomes and Practice Patterns Study), where it can be seen that Spain, Germany and Sweden were the only countries in which plasma calcium did not decrease significantly in dialysis patients during its different phases (covering from 1996 to the present).[37] Curiously, 90% of nephrologists were knowledgeable of Ca x P recommended values, despite the fact that it is probably the least precise parameter in control of mineral metabolism, especially in predialysis.[12]

It is notable the high percentage of follow-up reported for bicarbonate levels in patients with CKD. Although the bicarbonate levels recommended by the guidelines are clearly defined as greater than or equal to 22 mEq/L, 17% of polled nephrologists accept a slight degree of acidosis. In view of current knowledge, it is likely that the degree of control of acidosis will require revision in the near future.[38,39] Finally, it is worth mentioning that a large percentage of nephrologists (72%) uses imaging tests to search for vascular calcification in the diagnosis of CKD-MBD,[7] generally tests of low complexity. However, although bone densitometry is not recommended in patients with CKD,[7] it is still used by 39% of nephrologists participating in this study.

Our study has several limitations, all related to the relatively small number of nephrologists who completed the questionnaire and the validity that can be given to the results of a questionnaire. To add a measurement of precision, the percentages are accompanied by their respective 95% confidence intervals. Nevertheless, the participants were professionals dedicated especially to CKD not on dialysis or predialysis units. In any case, the results obtained could have shown an even lower degree of knowledge of the K/DOQI™ guidelines if nephrologists dedicated to other areas of nephrology had been surveyed. The surveys were conducted in nephrologists from all areas of the Spanish territory, and although random sampling was not performed for selection of participants because the number of CKD or predialysis units is not significantly higher than that included, the data might be representative of the CKD population in Spain. Nevertheless, and with the consequent limitations, the information obtained is of great importance for knowing clinical practices in CKD-MBD.

In summary, these results demonstrate that there is a great degree of unawareness of K/DOQI™ predialysis guidelines. Thus, their poor implementation is probably not only due to the lower availability of approved therapeutic agents, but also to unawareness or disbelief of current recommendations. It would be desirable that the recently published new guidelines of the Spanish Society of Nephrology[8] or forthcoming international guidelines include not only well-defined information on predialysis patients but also educational efforts on the need for early diagnosis and treatment of CKD-MBD.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Medical Department of Abbott Laboratories S. A.

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M. D. Lorenzo (Hospital Juan Canalejo. A Coruña), V. Lorenzo Sellares/D. Luis (Hospital Univ. de Canarias), M. P. Marco (Hospital Arnau de Vilanova. Lleida), G. Martín-Reyes (Hospital Carlos Haya. Málaga), I. Martínez-Fdez (Hospital de Galdácano. Vizcaya), E. Morales Ruiz (Hospital Doce de Octubre. Madrid), M. A. Munar (Hospital Son Dureta. Palma Mallorca), J. Nieto (Hospital General de Ciudad Real), E. Novoa (Complejo Hospitalario de Orense), L. Orte (Hospital Ramón y Cajal. Madrid), M. C. Páez (Hospital Univ. V. Macarena. Sevilla), J. Pérez-Pérez (Hospital Miguel Servet. Zaragoza), C. Piñera/A. L. M. De Francisco (Hospital Univ. Marqués de Valdecilla. Santander), C. Ramos (Hospital Clinico Universitario Valencia), R. Ruiz-Calero (Hospital Infanta Cristina. Badajoz), A. Soldevilla (Hospital La Fe. Valencia), V. Torregrosa (Hospital Clinic. Barcelona), P. Vidau (Hospital General de Asturias).

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