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# Are the K/DOQI objectives for bone mineral alterations in stage 3-5 chronic kidney disease patients unreachable or inadequate?

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Since its inception in the 1970s, dialysis has allowed for the survival of thousands of patients. In later years, a series of initiatives were put into place to reduce mortality and morbidity rates and to improve patient quality of life and the efficacy of treatment for patients with chronic kidney disease (CKD). In this context, in 1994, the National Kidney Foundation of America held a consensus conference that established the need for elaborating a series of clinical practice guidelines, which led to the Dialysis Outcomes Quality Initiative (DOQI) in 1995. In 1999, the need to expand the spectrum of these initiatives to include situations of earlier stages of CKD was reflected in the change of the significance of "D": from "dialysis" to "disease", thus giving way to the new name "Kidney Disease Outcomes Quality Initiative" (K/DOQI). However, it was not until 2003 that the clinical practice guidelines for bone metabolism and disease in chronic kidney disease were published under the direction of Massry and Coburn.[1] This label reflects the central objective of the report: bone disease in CKD. This document included 104 recommendations, but only 15% of these were based on published evidence; however, they are well founded on an exhaustive literature review, debates among working groups composed of international experts, and later revisions of the final draft. This document provided a substantial contribution for the unification of recommendations for diagnostic procedures and treatments, based on the best available evidence at the time.

In 2000, the European guidelines (clinical algorithms on renal osteodystrophy) appeared in the format of clinical algorithms. These guidelines were elaborated by the working group led by Cannata-Andia, and were published in a supplement of the journal *Nephrology Dialysis and Transplantation*.[2] These guidelines also covered the evidence available to date regarding mineral metabolism in a series of articles by recognised experts in the field. Silver[3] explained the molecular foundations that lead to hyperparathyroidism in CKD; Cannata-Andia[4] emphasised the increased prevalence of low turnover bone disease and the elevated risk this implies for soft tissue calcification; Ritz et al[5,6] introduced the concept of the need for correcting vitamin D deficits in CKD patients and updated the available knowledge regarding treatment with calcitriol and the potential role of active vitamin D analogues and calcimimetics; Drueke[7] reviewed the different phosphate binders available and referred to sevelamer as a promising treatment tool; and Cunningham[8] drew attention to the importance of monitoring calcium concentrations in dialysate. This European initiative was a pioneer in establishing recommendations for the field of bone mineral metabolism in CKD.

However, the K/DOQI guidelines published three years later became the universal reference for the treatment of CKD.[1] The scenario under which these guidelines were elaborated differed from the current situation in terms of patient profiles, our understanding of factors related to bone mineral metabolism, and treatment possibilities. At the time the guidelines were written, calcimimetics were not available (which is reflected in the elevated rates of parathyroidectomies), and the use of aluminium-based phosphate binders maintained osteomalacia within the spectrum of bone diseases.[4] The progressive loss during renal failure of vitamin D receptors and calcium sensors in the parathyroid tissues justified the use of elevated doses of calcitriol (chemical parathyroidectomy) and calcium, with the objective of slowing down hyperparathyroidism.[9,10] The role of phosphorous on glandular function and growth, along with its impacts on mortality rates, was understood, but this parameter was difficult to control given the need to avoid aluminium-base compounds, which were later

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replaced with calcium-based medications.[11,12] These practices, along with the commonplace use of dialysate with calcium concentrations of 3-3.5mEq/l, increased the risk of hypercalcaemia and calcification of soft tissues. Intact parathyroid hormone (PTH) had already been established as a valuable diagnostic tool. In this context, the K/DOQI guidelines were elaborated to address this risk, establishing a calcium x phosphorous product threshold level of >55mg$^2$/dl$^2$ as a safety limit, along with limiting calcium intake to 2000mg/day and lowering the calcium concentration in dialysate for patients with hypercalcaemia. A vitamin D treatment regimen was also established in the form of a primary strategy of modified dietary intake, along with supplements with active vitamin D (calcitriol or paricalcitol), according to baseline PTH levels. Despite this progress towards prudence in prescriptions, the nephrological community was faced with a dilemma with no obvious solution: increasing the risk of failure in the treatment of hyperparathyroidism by providing prudent treatment with calcium and vitamin D supplements, or increasing the risk of vascular calcifications and adynamic bone disease by providing more aggressive treatment for hyperparathyroidism.

Through the application of the K/DOQI guidelines, soft tissue calcifications (calciphylaxis, tumoural calcinosis, etc.) started to lose perceived relevance and there was a surge in literature references regarding the role of bone mineral abnormalities in vascular calcifications and the impacts of these on renal patient mortality and morbidity rates.[13-15]

Fortunately, the therapeutic arsenal for treating these disorders was expanded by the introduction of i.v. paricalcitol (2004) and calcimimetics (2004) in Spain, which improved the expectations for patients on dialysis. However, these tools do not facilitate early action.

The repercussions of bone mineral metabolism disorders on vascular calcification and patient mortality/morbidity rates spawned the need for including these devastating consequences within the spectrum of bone mineral metabolism disorders. This expanded conceptualisation was reflected in the results of a conference sponsored by the Kidney Disease Foundation: Improving Global Outcomes (KDIGO),* which led to the consensus of a new definition, evaluation protocol, and classification system for renal osteodystrophy, published in 2006,[16] which defined this entity as a systemic disease (chronic kidney disease-mineral and bone disorder [CKD-MBD]) that comprised not only bone disease, but also the associated mineral metabolism disorders and vascular calcifications. This development led to the need for establishing new guidelines in light of the new research results and treatment tools available. In contrast to the KDOQI guidelines, the 2009 KDIGO guidelines (headed by Moe and Drueke),[17] make only 21 recommendations that are less specific and allow for a greater range of freedom in terms of individual evaluations. Given the absence of trials testing the benefits of interventions on mortality rates, these guidelines establish a grading system for recommendations and suggestions, rather than providing concrete instructions (Recommendation, Assessment, Development, and Evaluation [GRADE System]).[18] This system introduced the concept of evaluating the tendency or progression of serum levels of these parameters, rather than a specific value. Under the auspices of the European Renal Best Practice (ERBP) council, a group of European nephrologists who had not participated in the KDIGO guidelines were invited to perform a critical analysis of these parameters, concluding that the KDIGO cannot be considered to be a true guideline in many aspects, and their position on this issue was published in the form of 18 areas of uncertainty that continued to be the subject of discrepancies.[19]

Again, the introduction of new drugs to the therapeutic arsenal made these guidelines obsolete in many ways. The availability of oral paricalcitol and non-calcium based phosphate binders in CKD stages prior to dialysis (sevelamer carbonate and lanthanum carbonate) now allows for early action.[20-22]

The updates to the Spanish Society of Nephrology (S.E.N.) guidelines in 2011 covered this knowledge gap and provided Spanish nephrologists with a reasonably adequate treatment protocol.[23] These guidelines covered 41 key points based on the current state of research results and the most up to date clinical evidence.

This introduction is an attempt to place the OSERCE I study (epidemiology of bone disease in chronic kidney disease in Spain) in the context of the period in which it was carried out, the results of which are published in this issue.[24] It is

* KDIGO, an independent non-profit foundation, is an international initiative with the mission of "improving the care and prognosis of kidney disease on a global scale, promoting coordination, collaboration, and integration of initiatives," through the development of clinical practice guidelines for CKD.

** The strength of each recommendation is stratified into 2 levels:

- "Recommendation": a piece of advice or warning: this implies that the action should be applied in the majority of patients (level 1).
- "Suggestion": the proposal of an idea to take under consideration. This implies that there are different possible choices and that the suggestion is a reasonable action (level 2).

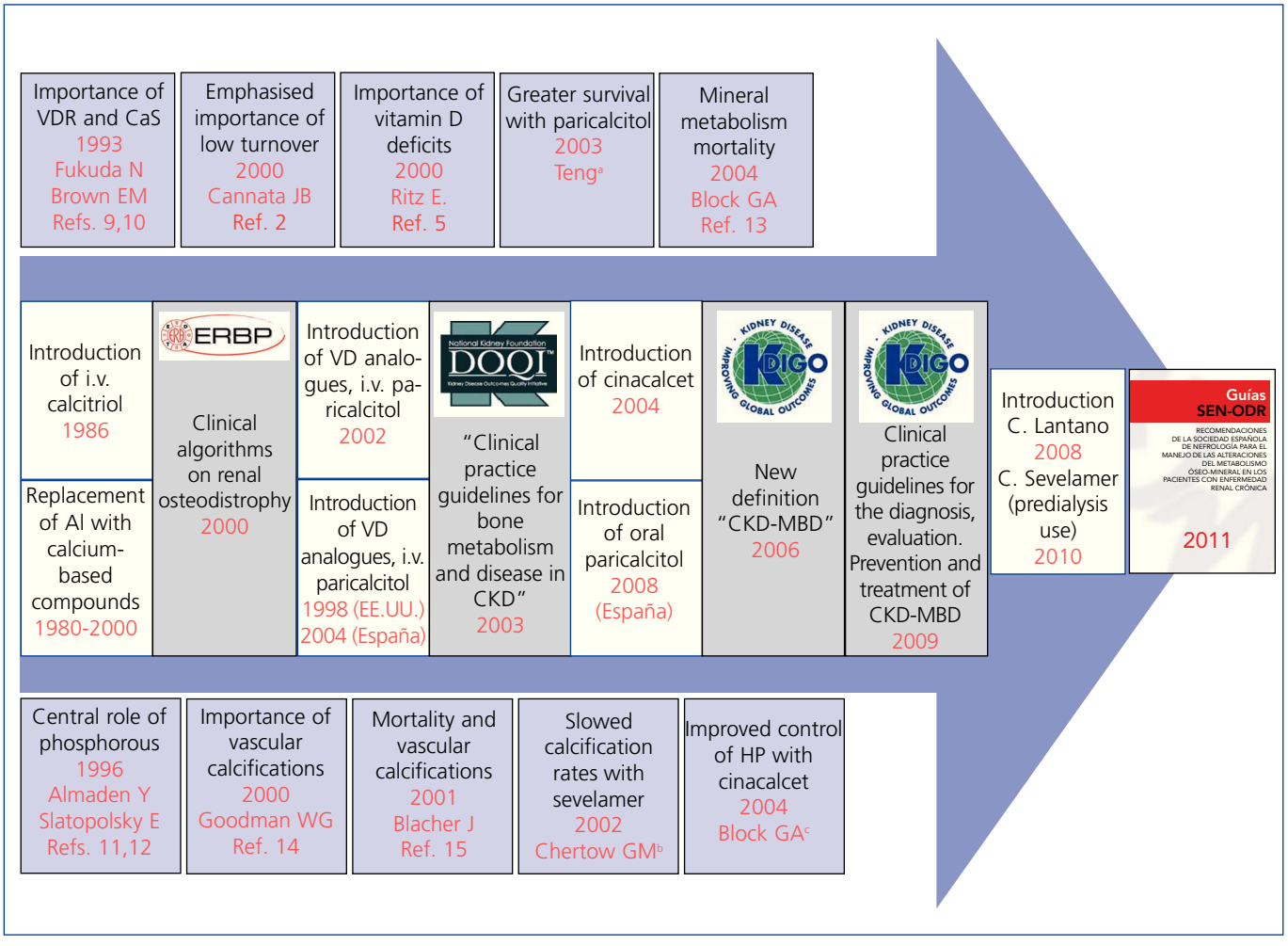


**Figure 1.** Chronological timeline of relevant published data and the introduction of treatment tools that have marked changes to treatment policies reflected in clinical practice guidelines.

Data approved by author. Al: aluminium; CaS: calcium sensor; CKD-MBD: chronic kidney disease-mineral and bone disorder; HP: hyperparathyroidism; VDR: vitamin D receptor

[a] Teng M, et al. Survival of patients undergoing haemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003;349(5): 349-56. [b] Chertow GM, et al. Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62(1):245-52. [c] Block GA, et al. Cinacalcet for secondary hyperparathyroidism.

important to recall that oral paricalcitol, sevelamer carbonate, and lanthanum carbonate were not available for use prior to dialysis in the period during which this study was carried out.

Several studies have examined the level of compliance with K/DOQI guidelines and its beneficial impact on the prognosis of patients on dialysis.[25,26] However, only three articles have been designed for evaluating the level of compliance with K/DOQI objectives in patients with CKD prior to entry into dialysis.[24,27,28] Two of these were carried out in Spain during the same time period: the first, which unified the results from two centres with similar treatment criteria, and the OSERCE I study, which covered a population of patients from 32 nephrology departments, and as such, provided a representative sample of the current clinical situation in Spain. This study provides methodological strengths that deserve mention: samples from a sub-group of patients were sent for a centralised laboratory analysis, which yielded good correlation with the results obtained at each individual health centre. This was also a study involving consecutive patients that sought treatment at each nephrology department during a 2-month period (April and May). This condition eliminates the variability that can occur in treatment policies and the fluctuating vitamin D levels determined by seasonal changes.

The level of compliance with the objectives established by the K/DOQI guidelines are shown in Table 1 for the three studies mentioned, based on stage. For the most part, the proportion of patients that fell within the recommended range

**Table 1.** Percentage of biochemical parameters that fall within the K/DOQI-2003 Guideline recommended ranges

| | PTH | Ca | *P* | Calcidiol | Calcium compounds | Calcitriol |
|---|---|---|---|---|---|---|
| **Craver L et al. (ref. 27) (2007)** | | | | | | |
| **N=1836[a]** | | | | | | |
| **ERC 3:856** | 42.4 | 90.7 | 90.9 | 9.2 | 2.5 | 0.6 |
| **ERC 4:354** | 24.6 | 85.6 | 77.1 | 20.4 | 19.8 | 7.9 |
| **ERC 5:111** | 46.8 | 55 | 70.3 | 3.9 | 51.4 | 27 |
| **Hoy T et al. (ref. 28) (2007)** | | | | | | |
| **N=793** | | | | | | |
| **424** | 61.3 | 98.7 | 87.6 | | | |
| **212** | 78.4 | 96.5 | 88.5 | - | - | - |
| **157** | 75 | 80.1 | 72.6 | | | |
| **OSERCE I (ref. 24) (2013)** | | | | [b] | | |
| **N=634** | | | | | | |
| **210** | 37 | 45 | 24 | 17 | 10.4 | 17.9 |
| **287** | 23 | 52 | 47 | 20 | 23 | 31.8 |
| **135** | 39 | 57 | 29 | 19 | 48.5 | 46.2 |

Ca: calcium; CKD: chronic kidney disease; P: phosphorous; PTH: parathyroid hormone.
[a] Total: includes patients with stage 1 and 2 chronic kidney disease. b In the OSERCE I study the sample for determining calcidiol and calcitriol was 339 patients.

was less than 50%, reflecting treatment policies based on calcium compounds and calcitriol. The biochemical values for calcium and phosphorous must be analysed with caution, since these do not reflect body overload, and normal plasma levels do not necessarily imply an absence of risk.

The most notable result was that only 1.8% of all patients simultaneously had all four parameters (serum calcium, serum phosphorous, calcium x phosphorous product, and PTH) within normal ranges, which serves as an indication that the K/DOQI guideline objectives for these stages of CKD are not feasibly reached in normal clinical practice. These results coincide with those reported in other countries.[29,30] As such, the question remains whether or not the stated objectives are appropriate. Taking into account the large body of evidence available regarding the risks implied by calcium, phosphorous, and PTH values that fall outside of the recommended ranges, little doubt remains regarding the effects of the values for these parameters on patient prognosis; however, it is difficult to maintain levels within the recommended ranges in clinical practice in a large proportion of patients. The following is a description of the probable causes that have produced this difficulty in adjusting biochemical parameters to the values recommended in the guidelines:

1. The vast majority of patients with CKD are in stages prior to the need for dialysis, in which implementing the objectives set out in clinical practice guidelines is more difficult, given late referral of these patients to nephrology departments (which differs between countries, provinces, and even rural vs urban areas).

2. Nephrology departments comprise nephrologists with varying areas of expertise who do not universally or homogeneously master the management of mineral metabolism disorders. The OSERCE working group analysed this variability among Spanish nephrologists through a survey, concluding that there is a widespread level of unfamiliarity, and that biochemical parameters are in general measured at a frequency far below the recommended rate.[31]

3. The possibility did not exist for treating patients in these stages of CKD with non-calcium based phosphate binders or oral paricalcitol.

4. There may be a lack of motivation on the part of nephrologists due to the absence of studies examining the impacts of interventions on morbidity/mortality rates.

## CONCLUSIONS

This situation has led to the conclusion that the values recommended in the guidelines are appropriate, yet in the context in which the study was carried out, unreachable.

Although these results may appear disheartening, they do not undermine the effort put into elaborating the clinical practice guidelines for the treatment of bone mineral metabolism that would guarantee providing the best possible treatment to our patients.

It is unrealistic to imagine that the physicians involved in treating these patients can process and apply every piece of information generated in the field of nephrology, and guidelines facilitate making decisions in the clinical setting. However, this does not absolve the physician from his/her responsibility for being updated on the most current pathophysiological information available, so that these advancements can be applied in the treatment of each individual patient.

In the same manner that changes in legislation come more slowly than social changes, scientific advancements and the introduction of new medications leave guidelines seemingly obsolete, and we cannot deprive our patients from the possible benefits of newer, more updated information.

The value of the OSERCE I study, although it was published almost a decade after the K/DOQI guidelines, is of current relevance because the objectives set out in the K/DOQI guidelines remain pertinent and are very similar to those established in the KDIGO guidelines (2009) and S.E.N. guidelines (2011). In addition, this study demonstrates the difficulty in reaching appropriate biochemical values, and yet again highlights the importance of early action.

With this in mind, the future challenges we face in the field of bone mineral metabolism in CKD patients lie in establishing earlier physiological markers (FGF23 [fibroblast growth factor 23], calciuria, phosphaturia, etc.), elaborating specific guidelines for action in early stages of CKD (stages 1 and 2), and reaching a greater level of compliance with treatment guidelines in the context of primary care.

## Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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