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Editorial Comment

EDITORIAL COMMENT

CKD-MBD KDIGO guidelines: how difficult is reaching the 'target'?

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Abstract

Patients with chronic kidney disease (CKD) are affected by mineral and bone disorder (MBD), resulting in abnormalities in serum calcium (Ca), phosphorous (P) and parathyroid hormone (PTH). Changes in mineral metabolism have also been associated with higher rates of both all-cause and cardiovascular-related mortality. The majority of haemodialysis patients are also deficient in the endogenous hormone 1,25-dihydroxyvitamin D (calcitriol), often contributing to increased secondary hyperparathyroidism (SHPT) and consequently to abnormal levels of Ca, P and PTH. Thus P overload and SHPT are well-known targets of medical treatments, such as P binders, vitamin D and calcimimetics, although with still limited evidence-based advantages in terms of survival. The tough hedge that is still keeping nephrologists far from a conclusive and winning approach against CKD-MBD is reasonably related to the still partial comprehension of the molecular pathways involved in a complex, multifactorial and extreme process.

Key words: CKD-MBD, KDIGO, secondary hyperparathyroidism

Despite therapeutic advances, mortality rates remain high among patients with chronic kidney disease (CKD), particularly those undergoing haemodialysis (HD) [1]. The main cause of mortality in these patients is attributed to cardiovascular-related diseases [1]. However, patients with CKD are also affected by mineral and bone disorder (MBD), resulting in abnormalities in serum calcium (Ca), phosphorous (P) and parathyroid hormone (PTH) [2]. Changes in mineral metabolism have also been associated with higher rates of both all-cause and cardiovascular-related mortality [3–6].

In 2003, the US National Kidney Foundation implemented the Kidney Disease Outcomes Quality Initiative (KDOQI) international guidelines to establish target levels for serum PTH, Ca and P in an effort to help lower secondary hyperparathyroidism (SHPT)-related mortality [7]. Unfortunately, evidence suggests that these restrictive guidelines are difficult to achieve, especially over the long term [8]. Since these guidelines were implemented, there has been an increased awareness of SHPT in addition to the introduction of newer treatment options in clinical practice. Furthermore, clinical guidelines are available for optimal levels of serum markers of CKD-MBD, but target parameters are not achieved in many HD patients [9].

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Management of CKD-MBD was intended to assist clinicians in treating patients with CKD Stages 3–5 who are also on dialysis [10]. Very recently (July 2017), updated KDIGO guidelines confirm those targets for CKD-MBD biomarkers [11].

Although several studies have examined the association between mineral levels and the impact of achievement of CKD-MBD target ranges on mortality rates in HD patients [12, 13], only a few studies have been conducted to date on incident HD patients [14–16]. Furthermore, evidence indicates that in incident HD patients, mortality rates are higher in the early stages (first 3–4 months) of dialysis, warranting studies in this setting [16].

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In the present issue of *Clinical Kidney Journal*, Fouque *et al.* present data from the Photo-Graphe3 study in France [17]. This is a prospective, multicentre, observational study in 9010 incident HD patients followed for 32 months. Interestingly, authors observed that the proportion achieving the three KDIGO targets increased from 11% to 16% ($P < 0.0001$) over 24 months, remaining stable afterwards, with significant improvement in serum P and serum Ca levels, without any significant improvement in serum PTH levels [17].

Other studies were performed to investigate similar issues. In Italy, we performed the FARO-2 study. The aim of the FARO-2 study was to assess SHPT management and alignment with CKD-MBD guideline target ranges [15, 16] on mortality rates in a subgroup of incident HD patients from the FARO study [6, 12, 18]. In the FARO-2 study, we showed that mortality rates at 24 months are associated with a reduction by as much as 25% in patients who achieved target ranges for three of the bone and mineral parameters (Ca, P and PTH) according to KDOQI guidelines. Moreover, by attaining target ranges for the three parameters at least once over the survey, survival rates were still 20% greater than those never achieving the KDOQI targets. The findings from our survival analysis supported these previous studies and, more importantly, extend our knowledge by demonstrating that the achievement of KDOQI targets over time were associated with a significant improvement in survival. Furthermore, we performed a retrospective analysis to determine how patients fared in terms of achievement of target ranges according to the newer KDIGO guidelines [10, 11]. It is important to underline that while the target ranges for Stage 5 CKD HD patients for intact PTH concentrations are 150–300 pg/mL according to KDOQI guidelines [7], the newer KDIGO guidelines recommend maintaining PTH levels 2- to 9-fold the upper normal limit [10, 11], corresponding to a range of 130–600 pg/mL [18].

In the FARO-2 study, as we had expected, the number of patients on target was increased by following the KDIGO guidelines. While only 35.9% of patients were on target for PTH levels according to the KDOQI guidelines, this proportion increased to 63% when the KDIGO guidelines were adopted. Likewise, the proportion of patients with three biochemical parameters on target (tri-target) at least once was higher for the KDIGO (46%) compared with the KDOQI guidelines (30.1%) and in patients who attained tri-target for all six visits (25.8% for KDIGO versus 13.3% for KDOQI). Since the KDIGO guidelines are less restrictive, a greater proportion of patients will likely have more severe hyperparathyroidism. Therefore it was not surprising that our analysis also revealed a higher mortality rate in those patients who were never on target according to KDIGO ranges (46%) compared with KDOQI ranges (29.7%).

Going back to the French cohort, a prospective observational study was performed on 8377 prevalent patients receiving intermittent HD therapy that examined the association between mortality and serum concentrations of phosphate, Ca and PTH through KDIGO target ranges [19]. The authors described a 'grey zone' where the precise biochemical targets are difficult to define, with the exception of avoiding extreme values. The KDIGO guidelines did not recommend precise threshold values, but rather 'normal' laboratory values, which may differ from one PTH kit to another. This study also confirmed the relative risk of low intact PTH values, as proposed by the KDIGO recommendations [19].

Table 1 presents a summary of the present study [17] and the FARO-2 study [16] in incident HD patients.

Table 1. Comparison of the Photo-Graphe3 study and the FARO-2 study in incident HD patients

	Photo-Graphe3	FARO-2
Country	France	Italy
Number of patients	9010	610
Follow-up (months)	32	36
Percentage of achieving KDIGO tri-targets	16	25.8

One of the difficulties in achieving multiple CKD-MBD targets consistently is that the majority of treatment approaches reflect a compromise between controlling PTH and controlling Ca and P [20]. Although newer therapies, such as combined calcimimetic and active vitamin D therapy, have been shown to enhance the ability of patients to reach CKD-MBD target values for biochemical parameters [21], their long-term safety and efficacy, and ultimately mortality rates, still need to be verified in randomized controlled trials. Long-term randomized controlled trials are still needed to determine the extent that these therapies, administered in combination or as monotherapy, provide a survival benefit.

In conclusion, considering the limitations of this observational design, the benefit of achieving KDOQI targets and the more recent KDIGO targets on survival in incident HD patients remains to be confirmed in long-term prospective randomized clinical trials.

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