Mineral and bone metabolism in dialysis: towards unified patient care?

Solenne Pelletier and Denis Fouque

Department of Nephrology, Hôpital Edouard HERRIOT and Université de Lyon, Lyon, France

Correspondence and offprint requests to: Denis Fouque; E-mail: denis.fouque@chu-lyon.fr

Since the mid-1990s, a tremendous effort has been made to improve the mineral and bone metabolism abnormalities in patients with chronic kidney disease (CKD). In addition to the technological advances in dialysis, (high performance, larger and more biocompatible membranes, and water quality), as well as frequency and duration, many drugs were also launched in a very short span (Figure 1). International guidelines have also attracted the interest and addressed the concerns of physicians in charge of maintenance dialysis patients, and due to the frequent use of new software and informatization of dialysis care, mineral and bone disease management has been considerably improved. However, clinical trials have not been performed quick enough to allow the generation of robust end points such as mortality. It is noticeable that for most of the mineral and bone disorder medications currently being used, 5–15 years after becoming available on the market, no survival benefits have been clearly shown in quality clinical trials. We only rely then on epidemiological reports from which a large number do not present a good methodological structure (retrospective design, missing values, confounding factors, selection biases, etc.). That said, however, from a biological point of view, serum phosphate control has considerably improved these past years. Whereas the first large retrospective studies were published in 1998 analysing data from 1995 [1,2], year for year thereafter, studies showed that the mean serum phosphate had improved from 2.0 to ~1.5 mmol/L in 2008 [2–5]. The December 2009 cross-sectional serum phosphate median value in 9500 French maintenance haemodialysis patients was 1.47 mmol/L, crossing below, for the first time, the symbolic level of 1.50 mmol/L (annual meeting of the Société de Néphrologie and the Société Francophone de Dialyse, Bruxelles, Belgium, 30 September 2010). This fact cannot be ignored, and improving any laboratory abnormality by 25% in less than 15 years is a success story in the medical field. As in other fields (hypertension, coronary artery disease, lipid control, etc.), and in response to a continuous improvement of serum abnormalities towards normal values, it will be more and more difficult to show survival benefits of new drugs, and future trials will have to enrol a much larger number of patients.

Mendelssohn and colleagues [5] address four interesting issues in this field: first, they analyze how daily practice can affect laboratory results on a day to day basis level; second, they evaluate medication prescription at the country level, and compare it to prescription in other countries; third, they analyse the role of healthcare budget restriction in patients’ conformity to current guidelines; and fourth, they challenge guidelines if the gap between theory and practice does not improve substantially over time or with the use of new treatments.

Numerous kinds of software have been created in order to help physicians gather laboratory data and allow automatic analyses and warnings. Among them, the Photograph™ software [3] allows the generation of an instant picture of the dialysis unit after entering serum values of phosphate, calcium, parathyroid hormone and phosphocalcic product, among other dialysis and nutritional parameters (see Figure 1 in the paper of Mendelssohn et al. [5]). If the data are entered regularly, e.g. every 3, 6 or 12 months, it allows the physician to compare the unit compliance to the guideline targets and check for improvement over time. This scheme allows self-control of medication prescription, since every physician would want their patients to come closer to the recommendations, and most prospective reports show a continuous improvement in reaching targets (see Figure 2 in the paper of Mendelssohn et al). What would be of additional interest is to see how phosphate and calcium parameters behave in centres which did not use the Photograph™ software.

The second point is the variability in patient care when independent local administrative rules apply. Mendelssohn et al. analysed serum values of mineral metabolism according to the possibility of prescribing drugs with more or less restriction in Canada, and showed that patients were better controlled when less restrictions applied. These variations were associated with differences in prescriptions: serum phosphate was more ‘on target’ when sevelamer was prescribed to more patients (40% in less restricted vs 14% in more restricted areas), whereas this did not have an influence on serum calcium or parathyroid hormone. Cinacalcet, although prescribed in <3% of patients in Canada, may have also had an impact on these results if heterogeneously administered between regions [6]. This report is not really surprising since heterogeneity in drug prescription is high in CKD–MBD: in the recent ECHO
study performed in 1865 MHD patients among 12 countries in Europe [7], the mineral and bone disease medication spectrum varied greatly: administration of vitamin D from 39% of patients (France) to 75% (UK), and active vitamin D derivatives from 1.4 (France) to 2.2 μg/week (Italy). The mean daily cinacalcet dose ranged from 44 (Italy) to 54 mg (Austria). Twenty percent of patients with hyperparathyroidism in Italy received a mean of 1800 mg calcium per day compared with 52% in France, and 53% of patients in Austria were prescribed sevelamer compared with 72% in Nordic countries [7]. These differences may be accounted for by restrictions in the healthcare budget but also by different food intake, sun exposure and metabolic patterns, since vitamin D compounds or calcium-based binders are relatively inexpensive and not limited in most countries. It is also interesting to note that the medication regimen differed not only by reimbursement policy but also, in the more restricted regions, patients were younger and had a shorter dialysis vintage [5]. Thus, a more restricted policy might also have an impact on general care.

Overall, this observational study performed in Canada during 18 months in 2006 and 2007 reports that 25% of patients had a serum phosphate >1.78 mmol/l, 30% were within KDOQI target for PTH, and only 11.7% of patients were within all four parameters, although there was a trend for improvement as compared with DOPPS III. One cannot be satisfied with such limited results, and this fact questions the applicability of the KDOQI guidelines in the future. The new set of the KDIGO guidelines recently released [8] may not further improve understanding since they also carry some limitations [9–11].

In conclusion, Mendelssohn et al. should be acknowledged for producing recent epidemiological data and raising questions on medication availability and patient care. What is missing here is information on potential consequences of this on patient morbi-mortality. We have to increase production of good quality observational registers and should not only rely on numerous retrospective analyses, because care of patients can be very different worldwide, not only in response to reimbursement policies but also to dialysis techniques, food intake, social behaviour, medical education and marketing influence. In this regard, the management of mineral and bone disorder in CKD represents a challenging example of heterogeneity and seems to be far from being unified.

Conflict of interest statement. None declared.

(See related article by Lebner et al. Interprovincial differences in the achievement of K/DOQI targets of mineral metabolism in Canada. Nephrol Dial Transplant 2011; 26: 156–163.)

References
Efficient anticoagulation of the extracorporeal blood is a precondition for any renal replacement therapy. Heparin is the most frequently used anticoagulant in this regard. However, heparin is associated with a number of serious risks including life-threatening haemorrhages and the induction of a heparin-induced thrombocytopenia (HIT). In recent years, great efforts have been made towards the development of alternative anticoagulation strategies. Regional anticoagulation with citrate has been shown to be a valuable and efficient option. Its anticoagulatory effect is exclusively restricted to the extracorporeal circuit without any systemic bleeding risk, and it can be safely applied in HIT type II. This makes citrate an excellent anticoagulant for continuous renal replacement therapy (CRRT) devices in an intensive care unit.

Regional anticoagulation with citrate was proposed in 1983 for haemodialysis of patients with acute renal failure but was not widely accepted due to the occurrence of severe side effects including alkalosis [1], hypernatraemia and severe hypocalcaemia. A better understanding of the metabolic effects of citrate as well as technical progress in the bedside monitoring of the acid–base status and the systemic ionized calcium has helped to better control and overcome these threats. The development of metabolic alkalosis during citrate anticoagulation results from the metabolic conversion of citrate to bicarbonate. It usually occurs when CRRT replacement fluids with high buffer content are used. In these circumstances, citrate provides additional buffer equivalents on top of the bicarbonate or lactate buffer provided by the CRRT replacement fluid thus leading to metabolic alkalosis. Hypernatraemia is also an iatrogenic complication. Citrate is usually applied in the form of tri-sodium citrate which as a consequence can lead to an unphysiological high sodium load. Many citrate anticoagulation protocols therefore apply renal replacement fluids with a reduced sodium and buffer content to avoid the occurrence of hypernatraemia and metabolic alkalosis [2–5]. However, the most threatening side effect of citrate still remains the induction of hypocalcaemia. During citrate anticoagulation, calcium-free renal replacement fluids are commonly used in order to avoid a clotting of the haemofilter due to the calcium ions from the renal replacement fluids (either by calcium backfiltration during dialysate or calcium infusion during dialysis or haemofiltration). If the systemic ionized calcium is not adequately monitored and substituted, a negative calcium balance occurs which inevitably results in systemic hypocalcaemia, a phenomenon that often occurred in the early years of citrate anticoagulation where a bedside monitoring of the systemic ionized calcium was technically not available. The widespread