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LETTER TO THE EDITOR

Management of mineral metabolism in haemodialysis patients: need for new strategies

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We read with great interest the paper by Collinson *et al.*[1] recently published in the *European Journal of Clinical Nutrition*.

The authors investigated the reasons for the high failure rate in preventing hyperphosphataemia in haemodialysis patients (HD).

The intriguing conclusion of the study was that none of the expected culprits—for example, drug insufficiency, limited dietary information or advice, and dialysis dose or method—was actually related with the problem. Hence, the suggestion to move to an innovative education-based strategy. Two years ago, NephroCare Medical Direction, a private organization accredited by the Italian Public Health System that delivers dialysis treatment to >2000 patients in Italy, identified control of mineral bone disease (MBD) as the topic of a clinical audit to be performed in all affiliated centres. Two of the authors (ADC and PE) were asked to organize the audit and take part in the procedure as external auditors after an agreement with the public institution where they operate as part of the full-time medical staff.

From July 2011 to September 2012 we recorded on an individual anonymous chart: the demographic information, clinical history, dialysis parameters (adequacy expressed as single-pool KT/V—spKT/V), patient compliance, biochemical examinations and data on pharmacological therapy.

Comorbidity was scored according to the Charlson comorbidity index (CCI).[2]

The audit was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent before data collection and analysis.

The clinical outcome indicators were taken from international guidelines, but considering that the consensus on some MBD therapeutic targets is not generalized[3] we let each dialysis centre choose between the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) and the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[4,5] and declare the choice before the beginning of the audit. Compliance with prescribed treatments was evaluated by administration of the Simplified Medication Adherence Questionnaire (SMAQ) to each patient, a tool that has been previously validated in haemodialysis patients,[6] whereas compliance with dietary advice was evaluated after administration of individual questionnaires by attending physicians.

A total of 170 patients from 18 centres were audited. Patient characteristics are summarized in Table 1: 45 patients (30%) were diabetic, whereas 16 (9.4%) had received previous kidney transplantation and 7 (4%) had undergone parathyroidectomy. In all, 153 (90%) patients underwent online haemodiafiltration three times weekly; the mean spKT/V was 1.64 ± 0.37 and dialysate calcium content was 1.5 mmol/l in 85.8% of the patients.

As shown in Table 1, the average phosphate and calcium plasma levels were 1.38 ± 0.38 and 2.28 ± 0.21 mmol/l, achieving therapeutic targets (for phosphate: 1.13–1.78 mmol/l and for calcium: 2.1–2.37 mmol/l) in 59.4% and 68.2% of the cases, respectively.

The mean intact parathyroid hormone (iPTH) levels were 32.8 ± 35.1 pmol/l; the overall rate of patients achieving therapeutic target was 38.2% and this percentage increased to 64% in centres adopting the KDIGO guidelines (3/18 centres). In all, 28 patients (16.4%) achieved the calcium, phosphate and iPTH targets simultaneously.

Phosphate plasma levels were inversely correlated with age and spKT/V (r^2 0.07, $P < 0.001$ and r^2 0.05, $P < 0.005$, respectively), whereas they were directly related to iPTH levels (r^2 0.05, $P < 0.005$).

Moreover, phosphate was significantly higher in patients referring low adherence to diet compared with the more compliant subjects (1.48 ± 0.38 vs 1.28 ± 0.32 pmol/l, $P < 0.005$).

As shown in Table 2, there was a strong correlation between compliance with medications and achievement of phosphate therapeutic targets, although phosphate control was not significantly associated with the P binders prescribed. Similarly, achievement of PTH target was not related with any particular drug prescribed to control hyperparathyroidism, and patients taking calcimimetics were less likely to have calcium levels within the recommended target.

Levels of MBD biochemical indicators were not related with the presence of diabetes, CCI, compliance to diet or dialysis-related factors.

Interestingly, not elderly patients ($n = 62$), when compared with patients $\geqslant 65$ years ($n = 108$), presented significantly higher phosphate and iPTH levels (1.48 ± 0.42 vs 1.27 ± 0.34 mmol/l, $P < 0.05$ and 38.8 ± 35.41 vs 29.58 ± 35.09 pmol/l, $P < 0.05$, respectively) and lower levels of CCI (3.5 ± 1.8 vs 4.3 ± 2.3, $P < 0.05$). Moreover, these patients presented a lower grade of compliance with treatments (Fisher's exact test, $P = 0.006$) and a reduced probability to achieve an adequate phosphate control (Table 2).

Although MBD in HD patients is the object of primary clinical and research interest, its prevention and treatment still remain unsatisfactory, and the rate of failure in controlling the disease is so high that it induces in care personnel some adaptive tolerance as if it were an unavoidable condition.[7] The results of the audit reported here confirm the high failure rate in the achievement of guideline targets, showing that only 16% of the evaluated patients presented with calcium, phosphate and PTH levels simultaneously controlled. Different reasons may account for the problem, including some differences in guidelines that depend on weak evidence and limited implementation.[8]

Current MBD management strategies imply the use of multiple drugs, such as phosphate binders, vitamin D compounds and calcimimetics, associated with an adequate dialysis prescription and dietary restrictions. Our results clearly show that this drug-centred approach is not sufficient to achieve therapeutic targets. In fact, our audit highlights the strong relationship between the achievement of therapeutic targets and the extent of compliance, especially in younger patients, as also noticed by Collinson.

Accordingly, educational interventions involving dieticians, dialysis nurses and patients have shown effectiveness in inducing significant reductions in serum phosphate levels.[9–11] We believe that all the stakeholders involved in the care of MBD should be aware of the scanty utility of pointing only to drug prescription (using new drugs, changing timing or dose and so on) as the key through which one can improve the control of MBD. By definition,

Table 1. Clinical characteristics and biochemical data of the HD patients evaluated in the audit

N	170
Male/female	104/66
Age, years	67.8 ± 13.7
Dialytic age, months, median (IQR)	52.5 (25–93)
Diabetic patients, *n* (%)	45 (30)
CCI, median (IQR)	4 (2–5)
spKT/V	1.64 ± 0.37
Calcium serum levels (mmol/l)	2.28 ± 0.21
Pts on calcium target, *n* (%)	116 (68.2)
Phosphorus serum levels (mmol/l)	1.38 ± 0.38
Pts on phosphorus target, *n* (%)	101 (59.4)
iPTH serum levels (pmol/l)	32.8 ± 35.1
Pts on iPTH target, *n* (%)[a]	65 (38.2)
Medications	
Phosphate binders, *n* (%)	105 (61.7)
Calcitriol (per os), *n* (%)	61 (35.8)
Paricalcitol, *n* (%)	37 (21.7)
Cinacalcet, *n* (%)	28 (16.4)
Compliance with medications, n *(%)*	
Nonadherent	73 (42.9)
Adherent	97 (57.1)
Compliance with diet, n *(%)*	
Nonadherent	82 (448.2)
Adherent	97 (51.8)

Abbreviations: CCI, Charlson comorbidity index; HD, haemodialysis patients; iPTH, intact parathyroid hormone; IQR, interquartile range; os, oral administration; pts, patients. Quantitative variables are expressed as mean (±s.d.) or median and interquartile range; qualitative ones by number and percentage. [a]PTH target was defined on the basis of guidelines chosen and declared before the beginning of audit (KDOQI:150–300 pg/ml or KDIGO: 2–9 upper limit of local laboratory).

Table 2. Analysis of the variables involved in the achievement of therapeutic targets

Variables		*OR*	*95% CI*	P
Phosphorus on target				
Compliance with drugs	No	1.0 (Reference)		
	Yes	2.38	1.23–4.59	0.01
Use of phosphate binders	No	1.0 (Reference)		
	Yes	1.63	0.86–3.1	0.14
Age < 65 years	No	1.0 (Reference)		
	Yes	0.48	0.25–0.92	0.03
PTH on target				
Compliance with drugs	No	1.0 (Reference)		
	Yes	0.93	0.49–1.76	0.8
Use of calcimimetics	No	1.0 (Reference)		
	Yes	1.66	0.76–3.65	0.22
Use of paricalcitol	No	1.0 (Reference)		
	Yes	0.48	0.19–1.03	0.08
Calcium on target				
Compliance with drugs	No	1.0 (Reference)		
	Yes	1.2	0.61–2.33	0.6
Use of calcimimetics	No	1.0 (Reference)		
	Yes	0.34	0.15–0.76	0.01

Abbreviations: CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone. Odds ratio and confidence intervals were calculated by the two-sided Fisher's exact test. $P < 0.05$ was considered statistically significant.

in fact, any therapy cannot be effective if it is refused or missed by the patient. Therefore, compliance has to be ranked as the first aim of therapeutic intervention and deserves to be treated as the objective of scientific research rather than a matter of good sense-based counselling. A trained multidisciplinary staff including physician, nurse, nutritionist, psychologist and professional education expert should be dedicated to increase the compliance in strict cooperation with family members. In addition, structured programmes should be designed to improve the compliance and their effectiveness should be tested in controlled prospective studies.

CONFLICT OF INTEREST

ADB, SS, DM and BC had financial relationships (employment) with NephroCare. The remaining authors declare no conflict of interest.

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