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Editorial Comment

Cinacalcet: the chemical parathyroidectomy?

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The existing body of evidence suggests that cinacalcet is an effective drug for secondary hyperparathyroidism (SHPT) control in patients undergoing maintenance dialysis (CKD-5D) [1–10]. Indeed, available evidence suggests that by modulating the parathyroid calcium-sensing receptor affinity to serum calcium, cinacalcet lowers by 40–50% (250–350 pg/mL) serum parathyroid hormone (PTH) (Table 1). A consensual reduction in calcium [∼0.5–0.8 mg/dL (0.125–0.200 mmol/L); 5–8%] (Table 1) is also reported and expected due to the calcium-PTH set point change induced by this drug [11, 12]. However, some, albeit not all, reports (Table 1) have described a consensual reduction in serum phosphorus, which is more complicated to explain and often confounded by the concomitant use of other agents such as vitamin D and phosphate binders that significantly affect phosphorous metabolism [13, 14].

Serum phosphorous represents a minimal part (∼1%) of the total body pool and is regulated by the net amount absorbed in the intestine, the quota excreted by the kidneys and the net amount exchanged by the bones in the time unit [13]. Notably, serum phosphorous does not always closely mirror the total body pool and phosphorous balance in CKD, since different hormones regulate renal tubular (i.e. FGF-23, FGF-7, PTH) and bone (i.e. PTH) phosphate handling to avoid excessive fluctuations of serum phosphorous concentration [13–15]. However, in CKD-5D patients the amount excreted by the kidneys is minimal if not absent. Hence, the reported tendency of cinacalcet to reduce serum phosphorous cannot be explained by a 'renal compensation', but rather by the PTH effect on bones.

We read with interest the manuscript by Zitt *et al.* [16]. The aim of their study was to elucidate the mechanisms by which cinacalcet may lower serum phosphorous. In this observational study (ECHO study) [16], the authors report an overall tendency towards phosphate reduction (median change −9.1%, interquartile range: −25% to +10%), after 12 months of cinacalcet therapy [16]. Each 10% serum PTH reduction correlates with a 3% decrease in serum phosphorous in the ECHO study cohort [16]. However, at least 25% of the study population experienced an increase in serum phosphorous (median change −9.1%, interquartile range: −25% to +10%) [16] in spite of the treatment with cinacalcet. The use of other compounds such as vitamin D or phosphate binders as well as the lack of diet control might explain why not all patients treated with cinacalcet exhibit a consensual serum phosphorous reduction, but authors document that among 45% of patients in which serum phosphorous decreases [defined as a change of at least 0.1 mg/dL (0.0323 mmol/L)], the use of concomitant medications cannot explain this trend (vitamin D either increased or remained unchanged and phosphate binders were either reduced or left unchanged during follow-up). Finally, the lack of association between cinacalcet dose and serum phosphorous corroborates the hypothesis that bone metabolism may play a role at least in some patients who experience a phosphate reduction while on cinacalcet treatment, similarly to what was seen after surgical parathyroidectomy [17]. The role of bone metabolism could also be hypothesized by the multivariable-adjusted and sensitivity analyses. Adjustment for factors associated with serum phosphorus in CKD-5D patients documents that baseline serum phosphorous, dialysis vintage and PTH change from baseline to month 12 are the major determinants of phosphorus reduction at follow-up [16]. However, sensitivity analyses document that a significant serum phosphate reduction is noted in all but the lowest baseline PTH quartile and PTH change at Month 12 [17], suggesting that the quota of phosphate removed from the bone is relevant among subjects with severe SHPT or among patients with parathyroid gland tissue still responsive to a calcimimetic drug (i.e. greater PTH reduction).

The findings reported by Zitt *et al*. are consistent with previous reports (Table 1). Though all studies recruited subjects with on average a poorly controlled PTH (in the range of 500–700 pg/mL), not all patients experienced a decrease in serum phosphate. However, no study has controlled the use of phosphate binders and vitamin D changes during follow-up. In this regard, Zitt *et al.* further expand the body of knowledge showing this trend among patients who did not decrease vitamin D or increase phosphate binder usage at follow-up. Nonetheless, the observational nature and the potential of imbalance among different groups (data not reported) and the lack of phosphate intake evaluation at baseline and during follow-up, caution against definitive conclusions about the role of PTH and the generalizability of the authors' results.

Table 1. Control of laboratory parameters of mineral metabolism during cinacalcet treatment

Study	Study design	Study cohort	Follow-up	Main results
Urena *et al* [10]	Observational study (ECHO study)	*n* = 1865 Mean age 58 years Male 57% Dialysis modality HD 88% PD 12% Mean dialysis vintage HD 6.5 years PD 3.1 years Diabetes (NR) Hypertension (NR) Median baseline iPTH: 721 pg/mL	12 months	Increase in the proportion of patients achieving NKF-DOQI targets. Overall: 50% median iPTH reduction (∼300 pg/mL) 9% median phosphate reduction (∼0.2 mg/dL (0.065 mmol/L)) (NS) 6% median calcium reduction (∼0.5 mg/dL (0.125 mmol/L)) (NS) Unchanged vitamin D use; reduction in phosphate binder use
Moe *et al* [7]	RCT (polled analysis of three phase 3 RCT) [1, 5, 8]	*n* = 1136 26% >65 years Male 62% Dialysis modality HD 96% PD 4% Mean dialysis vintage (NR) Diabetes (NR) Hypertension (NR) Median baseline iPTH: ∼550 pg/mL	26 weeks	Increase in the proportion of patients achieving NKF-DOQI targets. Overall: 56% median iPTH reduction (∼338 pg/mL) 11% median phosphate reduction (∼ 0.7 mg/dL (0.27 mmol/L)) 8% median calcium reduction (∼0.8 mg/dL (0.2 mmol/L)) Change in vitamin D and phosphate binder use at follow-up
Cooper *et al* [3]	Pooled analyses of three phase 3 RCTs aimed at testing the relationship between iPTH and serum phosphorous	*n* = 1136 (665 allocated to cinacalcet) Mean age (NR) Male (NR) Dialysis modality (NR) Mean dialysis vintage (NR) Diabetes (NR) Hypertension (NR) Mean baseline iPTH: (NR)	26 weeks	Patients stratified according to baseline iPTH levels into 3 strata: 300–500 pg/mL; 501–800 pg/mL and >800 pg/mL. PTH reduction varied according to strata: 41% (mean reduction: 235 pg/mL), 48% (332 pg/mL) and 35% (838 pg/mL). Phosphorous reduction varied according to strata: 6%(mean reduction 0.49 mg/dL (0.16 mmol/L)), 8% (0.66 mg/dL (0.21 mmol/L)), 11% (0.86 mg/dL (0.28 mmol/L) Linear association between iPTH and phosphorous change ($r = 0.26$) Serum phosphorous decreased by 0.14 mg/dL (0.05 mmol/L) each 100 pg/mL iPTH decrease Increase in vitamin D use; increase in calcium-based phosphate binder use
Messa *et al* [6]	RCT (OPTIMA study)	*n* = 368 Mean age 58 years Male 64% Dialysis modality HD 97% PD 3% Mean dialysis vintage 5.8 years Diabetes (NR) Hypertension (NR) Mean baseline iPTH: 500 pg/mL	23 weeks	Increase in the proportion of patients achieving NKF-DOQI targets. Overall: 46% median iPTH reduction (∼250 pg/mL) 5% median phosphate reduction (∼0.4 mg/dL (0.13 mmol/L)) (NS) 7% median calcium reduction (∼0.7 mg/dL (0.18 mmol/L)) (NS) Increase in vitamin D use; increase in calcium-based phosphate binder use
Fishbane *et al* [4]	RCT (ACHIEVE study)	*n* = 173 Mean age 58 years Male 56% Dialysis modality HD 100% PD 0% Mean dialysis vintage 3.8 years Diabetes 63% Hypertension 96% Median baseline iPTH: 600 pg/mL	33 weeks	Increase in the proportion of patients achieving NKF-DOQI targets. Overall: 47% median iPTH reduction (∼270 pg/mL) 1.2% median phosphate decrease(∼0.1 mg/dL (0.032 mmol/L)) (NS) 7% median calcium reduction (∼0.7 mg/dL (0.175 mmol/L)) No substantial change in vitamin D or phosphate binder use during follow-up
Raggi *et al* [9]	RCT (ADVANCE study)	*n* = 360 Mean age 61.5 years Male 58% Dialysis modality HD 100% PD 0% Mean dialysis vintage 6.0 years Diabetes: 43% Hypertension: 94% Mean baseline iPTH: 426 pg/mL	52 weeks	Overall: ∼31% mean iPTH reduction (∼132 pg/mL) 14% mean phosphate reduction [∼0.9 mg/dL (0.29 mmol/L)] 5.0% mean calcium reduction [∼0.5 mg/dL (0.125 mmol/L)] Progressive increase in vitamin D; unchanged dosage of calcium-containing phosphate binders during follow-up.
Chertow *et al* [2]	RCT (EVOLVE study)	*n* = 3883 Median age 55 years Male 60% Dialysis modality HD 100% PD 0% Median dialysis vintage 3.8 years Diabetes: 33%	4 years	Overall: ∼42% median iPTH reduction (∼400 pg/mL) 16% median phosphate reduction (∼1.0 mg/dL (0.323 mmol/L)) 3% median calcium reduction (∼0.3 mg/dL (0.08 mmol/L)) No substantial change in vitamin D or phosphate binder use during follow-up.

(*continued*)

Table 1. Continued

Study	Study design	Study cohort	Follow-up	Main results
		Hypertension: 92% Mean baseline iPTH: 690 pg/mL		

NS, not significant; RCT, randomized clinical trial; HD, haemodialysis; PD, peritoneal dialysis; NR, not reported; iPTH, intact parathyroid hormone.

Similarly to what was reported by Cooper *et al.* [3], current results [16] suggest that higher PTH at baseline and the degree of PTH changes are linearly associated with serum phosphate reduction. In keeping with the existing body of evidence, these results might be explained by the low PTH discriminating accuracy in detecting different types of high- vs low-bone turnover renal osteodystrophy diseases [18]. In a series of 101 bone biopsies, low- and high-bone turnover diseases were found, respectively, in 64% and 6% of CKD-5D patients with PTH in the suggested range (150–300 pg/mL) by the Kidney Disease Outcomes Quality Initiative guidelines [19]. Albeit not ideal, PTH accuracy increases with extreme values (i.e. below two and above nine times of the reference range) of PTH [20, 21]. It is plausible that in spite of the high PTH levels [median (interquartile range): 721 pg/mL (506–1050)] at study entry, a minority of the patients recruited in the ECHO study had a low-bone turnover characterized by high serum phosphorous levels and likely worsened by a calcimimetic treatment. In a recent series of 163 iliac crest bone biopsies of CKD-5D individuals, it was observed that serum phosphorus trends towards higher levels in both low- and high-bone turnover disease [21]. While a low or adynamic bone disease is characterized by a low capacity of the bones to accommodate the phosphorous load coming from the diet, high-bone turnover disease is characterized by a substantial removal of minerals from the bones. The latter may potentially explain why patients with higher PTH tend to experience a greater serum phosphorous reduction.

These results are limited by a substantial loss of patients to follow-up and by the lack of information on phosphate intake at baseline and at study conclusion. Indeed, low serum albumin, a marker of malnutrition, was associated with low serum phosphate in the ECHO study [16]. Nonetheless, the authors suggest that at least in patients with a considerable phosphorous removal from the bone, treatment with a calcimimetic may be beneficial to normalize bone metabolism through PTH reduction.

The clinical impact of serum phosphorous reduction on the relevant outcome is far from being established, especially in light of the recently published results of the EVOLVE trial [2], and future studies should address whether high-bone turnover attenuation increases survival among CKD-5D subjects.

Conflict of interest statement. None declared.

(See related article by Zitt *et al.* Serum phosphorus reduction in dialysis patients treated with cinacalcet for secondary hyperparathyroidism results mainly from parathyroid hormone reduction. *Clin Kidney J* 2013; 6: 287–294)

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