PTH, FGF23, and calcium: it takes three to tango?

To the Editor: Regulation of the calcium and phosphate metabolism is complex. Various endocrine feedback loops are involved, which are difficult to disentangle. Lopez *et al.*,[1] in parathyroidectomized (PTX) rats, demonstrate that parathyroid hormone (PTH) replacement produces a dose-dependent increase in fibroblast growth factor 23 (FGF23) secretion. They postulate direct and indirect effects of PTH on FGF23, the latter through calcitriol.[1] Other investigators showed that correction of serum calcium in PTX rats only slightly attenuated the decrease of serum FGF23.[2] Several lines of evidence, however, indicate that calcium, rather than innocent bystander, may well be a direct regulator of FGF23 secretion. First, serum calcium levels are independently associated with FGF23 levels in dialysis patients, transplant recipients, and in patients with primary hyperparathyroidism. Second, in vitamin D receptor-null mice, dietary calcium supplementation significantly increases serum calcium levels, FGF23 messenger RNA abundance, and circulating FGF23 levels.[3] Finally, in patients with severe secondary and tertiary (persistent) hyperparathyroidism referred for PTX, postoperative changes of FGF23 are limited and related to changes of calcium instead of PTH.[4]

Reduced kidney function, hormone resistance, and altered bone turnover might modulate the bone parathyroid feedback loop and explain the apparent discrepancy. Additional calcium clamp studies in PTX rats with long-term kidney failure are required to define the independent roles of PTH and calcium in regulating FGF23 secretion in chronic kidney disease.

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The Authors Reply: We thank Dr Evenepoel, Dr Viaene, and Dr Meijers for their interest in our recently published article in which we investigated the effect of parathyroid hormone (PTH) on circulating levels of fibroblast growth factor 23 (FGF23). As Evenepoel *et al.*[1] point out, regulation of FGF23 secretion is complex and it is influenced by several factors that are closely related. In addition to the two traditional regulators, phosphate and calcitriol, our paper demonstrates that PTH has an important role on FGF23 secretion through both direct and indirect (mediated by calcitriol) effects. In fact our results show that the absence of PTH overrides the stimulatory effect of hyperphosphatemia—parathyroidectomized animals have very high plasma phosphate levels but low FGF23 concentrations.[2] These data provide support to previous observations on the effect of PTH on FGF23 in rats with renal failure.[3] Thus, we believe that now three major endocrine axes should be considered in the regulation of FGF23 secretion: phosphate, calcitriol, and PTH.

We agree with Evenepoel *et al.*[1] that calcium may have a role in this complex and interrelated regulatory system, and may represent a fourth endocrine feedback loop. Therefore, we believe that further studies are warranted to provide a more profound knowledge on this intricate subject.

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