


See related article, “The Genetic Landscape of Renal Complications in Type 1 Diabetes,” on pages 557–574.

The Pas de Trois of Vitamin D, FGF23, and PTH

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There is a remarkable interaction among the factors that increase fibroblast growth factor 23 (FGF23) transcription in the osteocyte and osteoblast, where they are individually and collectively essential for the fine tuning of FGF23 expression and secretion. Serum levels of the three hormones, PTH, 1,25(OH)2D, and FGF23, that regulate mineral and bone metabolism are all markedly changed in chronic uremia and are all associated with the systemic side effects of uremia. These hormones all interact one with the other. FGF23 expression is regulated by factors, such as calcium, phosphate-to-pyrophosphate ratio, acidosis, and other local and systemic factors, such as estrogen, interleukins, leptin, iron, FGFs, cleaved Klotho, 1,25(OH)2D, and PTH.1 PTH activates the renal enzyme, CYP27B1, that codes for the 25-hydroxyvitamin D 1α-hydroxylase to convert 25-hydroxyvitamin D to its active form 1,25(OH)2D in the kidney. In contrast, FGF23 and 1,25(OH)2D both inhibit the enzyme. 1,25(OH)2D increases serum FGF23 levels and decreases PTH. Both of these actions of 1,25(OH)2D are at the transcriptional level. FGF23 itself acts on the parathyroid FGFRI-Klotho receptor to decrease PTH expression and parathyroid cell proliferation, but in CKD, there is downregulation of the parathyroid FGFRI-Klotho receptor and FGF23 no longer decreases PTH.2,3 In CKD, the high PTH levels of secondary hyperparathyroidism, the reduced serum 1,25(OH)2D levels, and the exuberant FGF23 levels are all associated with and may exert systemic pathologic effects on target organs, such as bone, neutrophils, the liver, and the cardiovascular system. Both PTH and FGF23 act on the kidney to cause phosphaturia and regulate renal calcium reabsorption.

1,25(OH)2D acts on the osteocyte to increase FGF23 transcription by increasing the binding of the 1,25(OH)2D/vitamin D receptor (VDR) to a defined vitamin D–responsive element (VDRE) in the FGF23 promoter.4 PTH potently increases FGF23 transcription in vivo and in vitro.5 Therefore, PTH and vitamin D both act to increase FGF23 levels. Nguyen-Yamamoto et al.6 in this issue of the Journal of the American Society of Nephrology have now discovered another level of the interactions of vitamin D and FGF23. They show that local osteoblastic conversion of 25-hydroxyvitamin D to 1,25(OH)2D is an important positive regulator of FGF23 production, particularly in uremia. To do this, they compared serum FGF23 levels in wild-type mice with those in mice with conditional osteoblastic deletion of CYP27B1. Serum FGF23 levels were lower in the conditional CYP27B1 knockout mice compared with wild-type mice, despite normal circulating levels of vitamin D metabolites. In experimental uremia, there was a modest increase in serum FGF23 in mice with osteoblastic deletion of CYP27B1 compared with the marked increase in uremic wild-type mice and no change in FGF23 mRNA levels. These results show the role of local osteoblastic synthesis of 1,25(OH)2D in the enhanced FGF23 production in uremia. This is consistent with the findings in the work by Somjen et al.,7 which showed that both 1,25(OH)2D and PTH increased CYP27B1 expression in cultured human osteoblasts.

Mice with constitutive activation of PTH receptor signaling in osteocytes exhibited increased bone mass and remodeling,
two of the recognized skeletal actions of PTH. Similar to PTH administration, these mice had decreased expression of the osteocyte–derived Wnt antagonist Sost/sclerostin.\textsuperscript{8,9} Lavi-Moshayoff et al.\textsuperscript{9} showed that PTH acts on bone to increase FGF23 expression. PTH receptor activation \textit{in vivo} and \textit{in vitro} increased FGF23 expression through cAMP- and Wnt-dependent mechanisms. Parathyroidectomy both prevented and corrected the increase in FGF23 levels in rats with adenine high phosphorus–induced early renal failure.\textsuperscript{9} Therefore, in uremia, at least in this model, the high FGF23 levels are dependent on the high PTH levels. In patients with advanced secondary hyperparathyroidism, total parathyroidectomy reduced circulating FGF23 levels as in experimental models.\textsuperscript{9,10} PTH (1–34) infusion for 3 days to mice with normal renal function increased serum FGF23 and calvaria FGF23 mRNA levels, even when serum calcium was maintained in the normal range. PTH also increased FGF23 expression in rat osteoblast-like UMR106 cells by activating the protein kinase A and Wnt pathways.\textsuperscript{9} Therefore, PTH increases FGF23 expression, which in turn, decreases serum PTH, thus completing a bone-parathyroid endocrine feedback loop.\textsuperscript{1}

PTH increases FGF23 transcription by activating the orphan nuclear receptor Nuclear receptor–related 1 (Nurr1) protein.\textsuperscript{5} PTH also stimulates Nurr1 to increase osteopontin and osteocalcin gene expression both \textit{in vivo} and \textit{in vitro}. In UMR106 cells, Nurr1 overexpression or knockdown experiments showed that Nurr1 is essential for the PTH–mediated increase in FGF23.\textsuperscript{5} Nurr1 binds to the FGF23 promoter at an Nurr1-responsive element. \textit{In vivo}, Nurr1 mRNA and protein levels were increased in calvaria from rats with experimental CKD together with high PTH and FGF23 expression. Calcimimetics decrease not only PTH but also, FGF23 levels in patients with CKD.\textsuperscript{11} Importantly, in rats with experimental CKD, the calcimimetic R568 decreased PTH expression, calvaria Nurr1 mRNA and protein levels, and FGF23 mRNA.\textsuperscript{5} Thus, the effect of PTH to increase FGF23 transcription is mediated by Nurr1 \textit{in vitro} and \textit{in vivo}. In CKD, the decrease in serum PTH by calcimimetics leads to a decrease in Nurr1 and consequently, FGF23.\textsuperscript{5}

\textit{Parathyroid hormone receptor} (PTH1R) gene deletion in mice resulted in decreased FGF23 expression.\textsuperscript{12} Intermittent PTH (1–34) injections increased Nurr1 and FGF23 mRNA levels and serum FGF23 in wild-type mice but not in mice with PTH1R deletion.\textsuperscript{12} Therefore, PTH activates PTH1R signaling to induce FGF23 gene expression and secretion. Of interest, the Nurr1-responsive element in the FGF23 promoter is contiguous to the VHRE site.\textsuperscript{13} Therefore, PTH and 1,25(OH)\textsubscript{2}D may act together on the FGF23 promoter to increase FGF23 transcription.

FGFR signaling in the osteocyte also stimulates FGF23 expression.\textsuperscript{14} The FGF2 gene produces 18-kD low–molecular mass FGF2 and 22- to 34-kD high–molecular mass FGF2 isoforms. PTH increases FGF2 and FGFR1 expression in neonatal mouse calvarial organ cultures, suggesting that some effects of PTH on bone remodeling may be mediated by regulation of FGF2 and FGFR expression in osteoblastic cells.\textsuperscript{15} Activation of FGFRs by an activating antibody leads to an increase in serum FGF23, and inhibition of FGFRs both pharmacologically and by gene deletion leads to a decrease in FGF23 transcription in bone cells \textit{in vitro}.\textsuperscript{14,16} Despite the fact that 1,25(OH)\textsubscript{2}D and PTH increase FGF23 levels and parathyroidectomy prevents the high FGF23 mRNA levels of experimental uremia, blockade of FGFR itself is sufficient to prevent the increase in FGF23 in uremia.\textsuperscript{17} Inhibition of the FGFR prevented the increase in serum FGF23 in folic acid–induced AKI as well as in adenine high phosphorus–induced uremia.\textsuperscript{17} These contrasting results suggest that there is an interdependence of the signaling of the PTH receptor, VDR, and FGFR on the FGF23 promoter. Low–molecular mass FGF2 acts through NFAT and a transcription factor that cooperates with the VDR ETS1. High–molecular mass FGF2 acts through cAMP and CREB binding to a cAMP response element site in the FGF23 promoter.\textsuperscript{18} 1,25(OH)\textsubscript{2}D upregulates ETS1, which cooperates with the VDR.\textsuperscript{13} An ETS1–VDRE/Nurr1 composite conserved element has recently been defined in the FGF23 promoter.\textsuperscript{13} The proximity of these elements may allow interactions among the FGFR through ETS1 and cAMP response element, PTH1R, acting on Nurr1 and VDR through the VDRE/ETS1.

The study by Nguyen-Yamamoto et al.\textsuperscript{6} now shows that local osteoblastic conversion of 25-hydroxyvitamin D to 1,25(OH)\textsubscript{2}D is central to the increase in FGF23 production, mainly in uremia, where circulating levels of 1,25(OH)\textsubscript{2}D are low. Serum FGF23 levels are regulated by many local and systemic factors. It is remarkable that blockade of some single regulators, such as PTH and FGFR, prevents the increase in FGF23 in uremia, suggesting synchronization at the level of the bone cell. This contribution adds another level of control of FGF23 expression by endogenous and exogenous 1,25(OH)\textsubscript{2}D production of particular relevance to uremia.

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DISCLOSURES

None.

REFERENCES

Successful treatment of ESRD with maintenance hemodialysis is inextricably dependent on a reliable access to the bloodstream several times every week. Indeed, although the principles of extracorporeal treatment had been developed earlier, it was only with the introduction of the arteriovenous shunt by Belding Scribner and Wayne Quinton that made long-term treatment of uremia with hemodialysis feasible.1 With improved understanding and innovations over the ensuing five decades, there are now primarily three choices for vascular access—arteriovenous fistula (AVF), arteriovenous graft, and central venous catheter. However, each vascular access type imposes unique risks to the health of patients and further increases health care utilization. Hence, determining the access type associated with the lowest health risk and health care utilization is of great interest to patients, physicians, and health care providers, as well as payers of health services.

Although no randomized, controlled trials have been completed to date, a large number of cohort studies have examined the differences in health outcomes among patients with different types of vascular access. In a meta-analysis of 62 cohort studies with 586,337 participants, compared with patients with an AVF, those with central venous catheters had higher risks for...