MINERAL AND BONE DISORDERS

Targeting CYP24A1

Disturbed phosphate homeostasis is a common feature of chronic kidney disease (CKD). High serum levels of FGF-23 are associated with adverse effects on bone metabolism. New findings suggest that inhibition of the vitamin D-inactivating enzyme, CYP24A1, might present a new therapeutic opportunity for the treatment of mineral abnormalities associated with high FGF-23 levels.

FGF-23 regulates mineral metabolism through a series of complex pathways. Its effects on vitamin D are twofold: it inhibits the production of active $1,25[\text{OH}]_2\text{D}$ by downregulating CYP27B1, the enzyme responsible for $1,25[\text{OH}]_2\text{D}$ production, while promoting the catabolism of active $1,25[\text{OH}]_2\text{D}$ by upregulating CYP24A1.

The high levels of CYP24A1 in association with high FGF-23 expression led Andrew Karaplis and his team to investigate whether increased CYP24A1 expression contributes to the pathogenesis of renal phosphate-wasting disorders associated with excess FGF-23. The researchers investigated the effects of CYP24A1 deletion in two strains of genetically modified mice with different aetiologies of high FGF-23 expression: *Hyp* mice — a murine model of X-linked hypophosphataemia — and *FGF23^{R176Q}* mice, which express a mutant form of FGF-23 described in patients with autosomal dominant hypophosphataemic rickets. Deletion of CYP24A1 by crossing these strains with *Cyp24a1^{-/-}* mice ameliorated the rachitic bone abnormalities associated with FGF-23 overexpression. This improvement occurred in the absence of improvements in the serum biochemical profile. The researchers also demonstrated that pharmacologic inhibition of CYP24A1 ameliorated the bone abnormalities of *Hyp* and *FGF23^{R176Q}* mice. “These findings implicate the extrarenal synthesis of bioactive vitamin D in osteoblasts and chondrocytes, acting in an intracrine and/or autocrine manner in these cells, in the amelioration of bone abnormalities,” says Karaplis. “Moreover, by inhibiting the inactivating enzyme, the amount of active vitamin D required to elicit beneficial effects in patients could potentially be reduced, thereby preventing adverse effects.”

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