The hypothesis that bone turnover influences FGF23 secretion

To the Editor: Fibroblast growth factor 23 (FGF23) regulates serum phosphate (Pi) levels. Isakova et al. commented on a blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. In this review, Isakova et al. revealed that Pi levels were normal to high in secondary syndromes of FGF23 excess, such as kidney disease; however, the levels were low in 'primary' syndromes of FGF23 excess, such as the hereditary diseases (X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets), and tumor-induced osteomalacia. With decrease in renal function, the serum FGF23 level is elevated; however, the phosphorus excretion decreases. Osteitis fibrosa progresses at the same time. FGF23 was secreted by osteocytes. Therefore, we drew up the hypothesis that bone turnover influences FGF23 secretion. We had reported previously the response of phosphorus load to osteoprotegerin (OPG) knockout (KO) mice (Figure 1). FGF-23 expression was significantly increased by a high-phosphate diet in wild-type (WT) mice, but not in OPG KO mice. NaPi2a messenger RNA expression in kidney was suppressed in WT mice receiving a high-phosphate diet, but suppression was less marked in OPG KO mice. Therefore, OPG may have a key role in mediating the response of FGF-23 to an oral phosphate load in bone cells. When we evaluate the metabolism of FGF23, it is necessary to consider the structural change in the osteitis fibrosa.


Figure 1 | Percentage tubular reabsorption of phosphate (%TRP). Percentage TRP levels of the wild-type (WT)/high-phosphate diet group are significantly lower than those of the WT/normal-diet group. In the osteoprotegerin/high-phosphate (OPG KO/high-P) group, they are significantly lower than in the OPG KO/normal-diet group, but the reduction rate is significantly lower in OPG KO mice than in WT mice.

The Authors Reply: We agree with Ohkido et al. that osteocytes likely have a critical role in fibroblast growth factor (FGF)23 regulation in chronic kidney disease (CKD). In addition to the supportive findings from their animal studies outlined in 'The hypothesis that bone turnover influences FGF23 secretion,' recent human studies have shown that FGF23 expression in bone is already elevated in the early stages of CKD. Moreover, emerging data on the structure and function of osteocytes, their dendritic processes, and surrounding capillary networks have provided further support for the existence of a bone–kidney axis. Future explorations of this hypothesis are likely to yield significant new insights into bone physiology and regulation of phosphorus metabolism and, ideally, the discovery of novel therapeutic targets for various bone and mineral illnesses. However, assessments of bone disease with bone biopsies in the large-scale randomized trials we propose would increase the complexity of trial design and diminish feasibility, and