The hypothesis that bone turnover influences FGF23 secretion

To the Editor: Fibroblast growth factor 23 (FGF23) regulates serum phosphate (Pi) levels. Isakova et al.1 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. FGF-23 was secreted by osteocytes.2 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.3 When we evaluate the metabolism of FGF23, it is necessary to consider the structural change in the osteitis fibrosa.


Ichiro Ohkido1, Keitaro Yokoyama1, Shino Kagami1 and Tatsuo Hosoya1

1Department of Internal Medicine, Division of Kidney and Hypertension, The Jikei University School of Medicine, Tokyo, Japan

Correspondence: Ichiro Ohkido, Department of Internal Medicine, Division of Kidney and Hypertension, The Jikei University School of Medicine, 3-25-8 Nishi-Shinbashı, Minato-ku, Tokyo 105-8471, Japan.
E-mail: iohkido@jikei.ac.jp

Kidney International (2010) 77, 743; doi:10.1038/ki.2009.534

The Authors Reply: We agree with Ohkido et al.1 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.2 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.3 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

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.
Assessment of acid–base disorders

To the Editor: Adrogue et al.\(^1\) give an overview of the three distinct approaches that are currently used in assessing acid–base disorders. In contrast to their assumption that the chloride level is normal in high anion gap acidosis (Table 2), there is often a low plasma chloride level because the plasma chloride level is normal in high anion gap acidosis (Table 2),\(^2\) and therefore these measurements were not included in the blueprint.\(^4\)


The Authors Reply: We respectfully disagree with the comments made by Dr Berend.\(^1\) The study he quoted to counter our ‘assumption that the chloride level is normal in high anion gap acidosis’ failed to detect absolute hypochloremia in patients with this condition.\(^2\) Thus, normochloremic acidosis is an appropriate and standard term for high anion gap acidosis. This term allows differentiation of high anion gap acidosis from the normal anion gap acidosis that features hyperchloremia.

The need to adjust the plasma anion gap for the anionic charge of plasma albumin, a simple computation performed routinely by clinicians, is unrelated to the proposed effect of albumin itself on acid–base status. As stated in our paper,\(^3\) there is no evidence that the body, and in particular, the liver, regulates albumin to maintain acid–base balance. A role of albumin itself in the regulation of acid-base status is accepted by neither the physiological nor the base-excess approach. Dr Berend claims that our assessment of example 2 is probably incorrect because we did not consider that a decrease in plasma albumin by 1 g/dl results in an increase in bicarbonate by 2.8 mmol/l. As this claim is based on a simple associative relationship,\(^4\) it provides no support for a cause-and-effect relationship of albumin to plasma bicarbonate.

Finally, the lack of definition of the secondary ventilatory response to metabolic acid-base disorders is indeed one of the limitations of the physicochemical approach, but certainly not its most serious drawback, as Dr Berend asserts.