

## FGF-23: a new player in the regulation of phosphate (2015)

Jonathan Elliott, Royal Veterinary College, University of London, UK

Kidneys are central to phosphate homeostasis. When functional renal mass is reduced in chronic kidney disease (CKD) phosphate is retained, because phosphate excretion is limited by glomerular filtration rate (GFR). The kidney is unable to **secrete** phosphate into the filtrate – it is **excreted** by an overflow mechanism that depends on the capacity of proximal tubules to reabsorb it. The familiar action of parathyroid hormone (PTH) on proximal tubules is to reduce expression of sodium-linked phosphate transporters and thereby increase elimination of phosphate in urine. In CKD, PTH secretion increases as an (mal)adaptive response to aid phosphate excretion by diseased kidneys. But PTH is secreted primarily in response to changes in plasma ionised calcium concentration, so it has long been assumed that other hormones play a direct role in phosphate regulation. Over the last 15 years much basic research has occurred to identify these 'phosphotonins', endocrine mediators that regulate phosphate.

### What is FGF-23?

FGF-23 is a 30 kD protein secreted by osteocytes and osteoblasts. It was discovered in 2000 as a circulating factor found in excess in hypophosphataemic patients with tumour-induced osteomalacia.

### What stimulates FGF-23 secretion?

Increases in plasma phosphate and calcitriol both stimulate FGF-23 secretion, but how cells producing FGF-23 sense and respond to changes in phosphate concentration is not understood at present.

### What does FGF-23 do?

This low molecular weight polypeptide hormone is involved in phosphate and calcitriol homeostasis. It binds to FGF Receptor 1, expressed on renal tubular epithelium and in parathyroid and pituitary glands. It requires the co-factor  $\alpha$ -klotho to activate these receptors. In kidneys it inhibits synthesis of sodium-linked phosphate transporters and so has a phosphaturic effect similar to PTH. It also inhibits  $1\alpha$ -hydroxylation of 25-hydroxycholecalciferol by tubular epithelium and favours 24-hydroxylation to produce 24,25-dihydroxycholecalciferol, an inactive metabolite. In parathyroid glands, FGF-23 inhibits PTH synthesis and secretion. Knockout mice that lack FGF-23 are hyperphosphataemic, with increased tubular reabsorption of phosphate, increased plasma concentrations of calcitriol and reduced plasma concentrations of PTH. Recombinant FGF-23 caused hypophosphataemia and increased renal phosphate clearance when injected into mice. Both these findings provide evidence for the physiological actions of FGF-23.

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### Can FGF-23 be measured in the cat?

A sandwich ELISA has been validated for use in cats. The absolute accuracy of the assay is not known but the reference interval is 56 – 700 pg/ml, considerably higher than in human plasma (8.2 – 54.3 pg/ml).

### What factors influence plasma FGF-23?

As a low molecular weight protein FGF-23 is excreted from plasma via glomerular filtration. Hence, FGF-23 can be used as a surrogate marker of GFR and has been shown to increase in proportion with reduction in GFR in the cat (Finch *et al.*, 2013) and to be significantly higher with each IRIS stage of CKD (Stages 1 to 4) (Geddes *et al.*, 2013a). However, there is clear evidence that plasma phosphate also influences plasma FGF-23 concentrations in the cat, as hyperphosphataemic cats have higher plasma FGF-23 within a given IRIS CKD stage than normophosphataemic cats (Geddes *et al.*, 2013a). Furthermore, dietary phosphate restriction leads to reduced plasma FGF-23 concentration (Geddes *et al.*, 2013b). Preliminary data show that in cats with CKD and hypercalcaemia, plasma FGF-23 concentrations are increased, suggesting that calcium stimulates FGF-23 secretion.

### What might be the clinical value of measuring plasma FGF-23 concentration?

Plasma FGF-23 is correlated with survival in human patients with CKD and the same appears to be true in the cat – so FGF-23 might be a useful prognostic indicator in cats at first diagnosis of CKD (Geddes *et al.*, 2015). Studies have shown that plasma FGF-23 is a predictor of the onset of azotaemia in cats (Finch *et al.*, 2013). In addition, dietary phosphate restriction of cats where plasma phosphate concentrations were within the IRIS target range for phosphate still led to reduction in plasma FGF-23 concentration, whereas PTH concentrations and plasma phosphate concentrations did not change significantly (Geddes *et al.*, 2013b). Thus, it is possible that plasma FGF-23 concentrations might indicate the need for dietary phosphate restriction due to whole body phosphate overload where plasma phosphate concentrations have not yet increased.

### Conclusion

FGF-23 is a novel phosphaturic hormone, knowledge of which is in its infancy in veterinary species. It is clearly involved in phosphate regulation in the cat. Measurement of this protein in the blood may be of diagnostic and prognostic utility and could prove useful for guiding treatment.

### References

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