# UNDERSTANDING FELINE CKD: MINERAL AND BONE DISORDER

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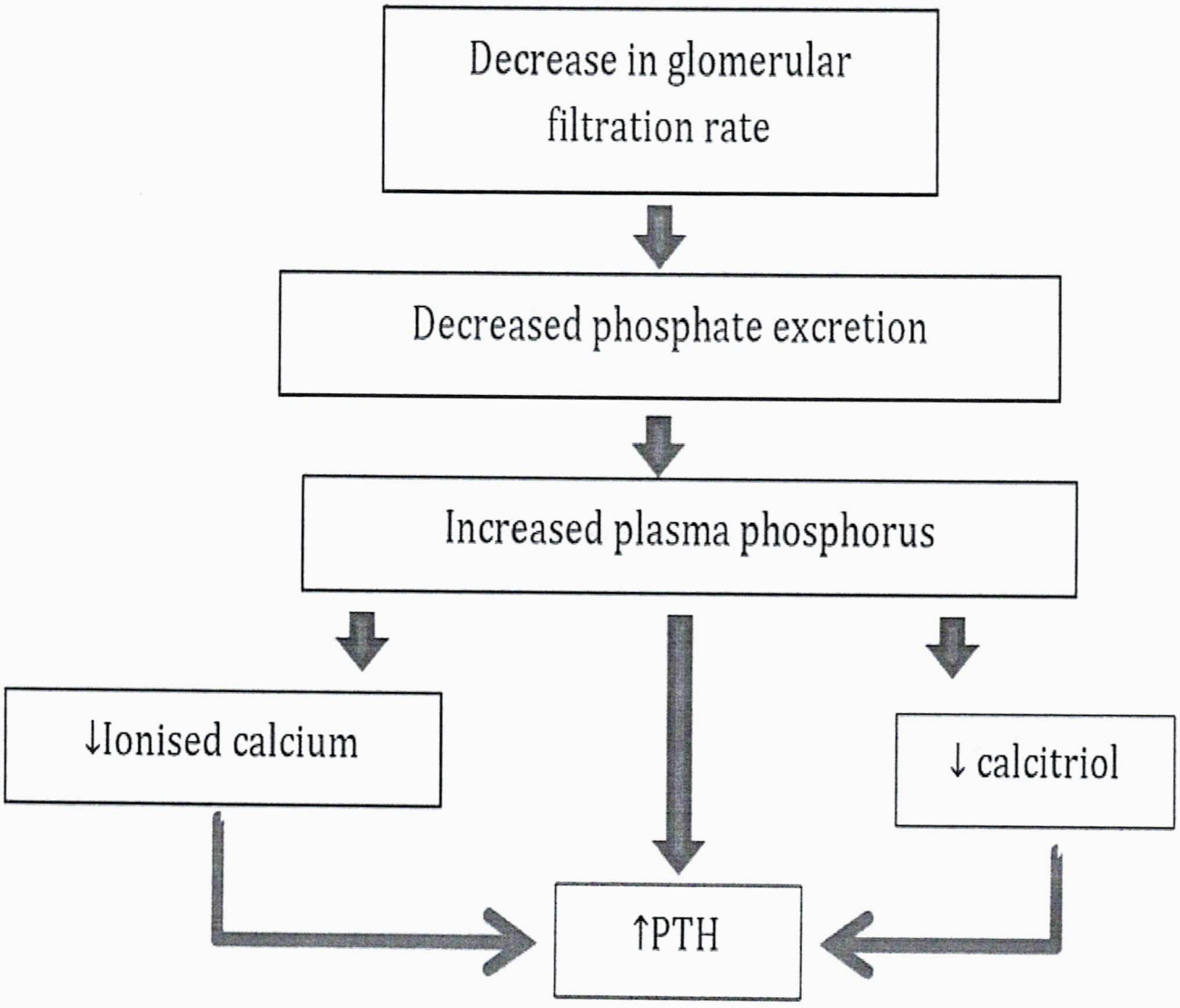
Introduction

Chronic kidney disease (CKD) is a common condition in both feline and canine medicine and the concept of secondary renal hyperparathyroidism (SRHP) is well recognised. However, phosphorus homeostasis and the pathophysiology of SRHP has been and remains incompletely understood. In recent years, the discovery of phosphatonins (a factor responsible for inhibition of renal tubular reabsorption of phosphorus) and in particular fibroblast growth factor 23 (FGF23) has revolutionised our understanding of the control of phosphorus and the changes that occur in phosphorus homeostasis during CKD. Based on the realisation that PTH is not the only player in the regulation of phosphorus and calcium homeostasis in CKD, the term secondary renal hyperparathyroidism in human medicine has largely been superseded by the term mineral and bone disorder. In the last 2–3 years, studies have begun to investigate the role that FGF23 may play in our veterinary patients.

Regulation of phosphorus is intrinsically linked to the regulation of calcium with both electrolytes being under the influence of parathyroid hormone (PTH) and calcitriol (1,25 dihydroxycholecalciferol). Calcitriol increases calcium and phosphorus absorption from the gastrointestinal tract whilst PTH increases calcium and phosphorus resorption from bone, increases calcium reabsorption, and decreases phosphorus reabsorption from the tubular filtrate in the kidney. For many decades we have widely accepted the 'trade off hypothesis.' Reduction in the number of functioning nephrons leads to a reduced capacity to excrete various solutes in the urine including phosphorus with resulting hyperphosphatemia. This retention of phosphorus, by the law of mass action, results in a relative decline in free calcium concentration. A combination of reduced free calcium and increased phosphorus concentration contributes to stimulating production of PTH (Figure 1). Simultaneously, increasing phosphorus concentrations have an inhibitory action on the production of calcitriol, which also has a stimulatory action on PTH production. As PTH inhibits reabsorption of phosphorus in the proximal tubules, increased PTH production serves to try and increase phosphorus excretion. At the same time increased PTH concentrations will also stimulate release of calcium and phosphorus from bone and increase production of calcitriol, which will increase absorption of both calcium and phosphorus from the small intestine. However, with continually declining renal function, phosphorus retention continues to occur such that the body becomes phosphorus loaded and the SRHP develops. The 'trade-off' for increasing phosphorus excretion by remaining functioning nephrons is therefore the gradual but persistent increase in PTH concentration.

Chronically increased PTH production can ultimately result in bone demineralization (renal osteodystrophy) and complex of phosphorus and calcium can result in dystrophic mineralisation of soft tissues. When this mineralisation occurs within the kidney, concern is raised that it can contribute to progressive renal injury.

***Figure 1***




The 'trade-off hypothesis' in the regulation of phosphorus in chronic kidney disease.

The prevalence of SRHP increases with advancing stage of CKD. An early study performed by Barber and Elliott in 80 cats indicated that 20% of cats with compensated CKD (mean [creatinine] 2.6 mg/dL), 49% of cats with uremic CKD (mean [creatinine] 3.6 mg/dL), and 100% of cats with endstage CKD (mean [creatinine] 10.3 mg/dL) demonstrated hyperphosphatemia, whilst 47%, 87%, and 100% of cats in those respective groups showed hyperparathyroidism.[1] Calcitriol concentrations were assessed in 31 cats and were found to be below the reference interval in 35%. The higher prevalence of hyperparathyroidism than hyperphosphatemia in cats adds support to the theory that increase in PTH concentrations occurs before the onset of hyperphosphatemia. This has also been seen in a group of non-azotemic cats > 9 years which were followed longitudinally until the development of azotemia. Those cats that went on to develop azotemia in a 12-month period had significantly increased PTH concentrations at entry to the study

than cats which remained non-azotemic over the same time period.[2] Hyperphosphatemia has been associated with reduced survival in cats.[3,4] Evidence from naturally occurring feline CKD also indicates that hyperphosphatemia is associated with progression of disease.[5] The management of hyperphosphatemia and SRHP with dietary manipulation and use of low-phosphorus diets can therefore have substantial impact on our patients with CKD.[6-10] Evidence supports that maintaining plasma phosphorus concentrations within the IRIS targets for each stage of CKD improves survival and can improve the clinical manifestations of SRHP.

### Discovery of Fibroblast Growth Factor 23 (FGF23)

In 1959, Prader and colleagues published a case report of an 11-year-old girl with a rib mass and acquired hypophosphatemia, renal phosphate wasting and rickets which resolved after surgical excision of the mass. At that time it was recognised that the mass lesion must have been secreting what was referred to as a 'rachitogenic substance' likely to be causing the electrolyte abnormalities. Today this condition would be referred to as tumor-induced osteomalacia (TIO) as a consequence of excess production of FGF23 by the neoplastic lesion. However, it was not until 2000 that the importance of FGF23 in phosphate homeostasis was recognised and implicated in multiple hypo- and hyperphosphatemic disorders.[11]

### FGF23, What Is It and What Does It Do?

FGF23 belongs to and shares structural similarity with other members of the fibroblast growth factor family. The protein has two functional domains: an N-terminal, which is common to all fibroblast growth factor proteins, and a C-terminal, which confers the specialised activity of FGF23.[11] FGF23 is predominantly produced by osteocytes and osteoblasts in the skeleton, although transcripts have also been identified in human heart, liver, and thyroid/parathyroid tissues.[12,13] Within the circulation FGF23 can either be detected as an intact form (iFGF23) or broken into N- or C-terminal fragments, but it is widely accepted that iFGF23 is responsible for the majority of biological action.

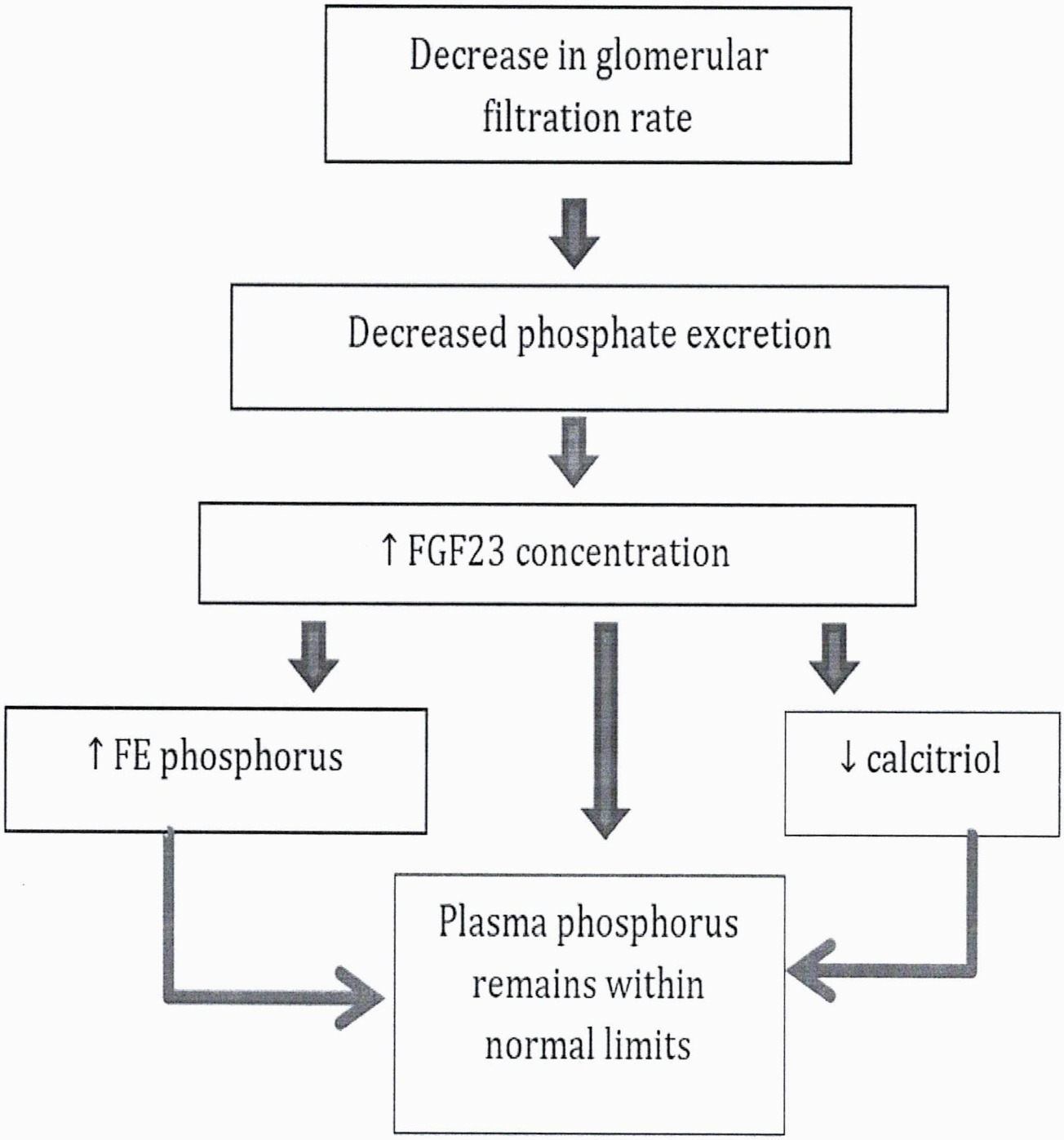
FGF23 interacts with cell surface membrane-bound receptors (FGFR1, 3c, 4) but also requires interaction with a co-receptor, α-klotho.[14,15] FGF23 binds more avidly to its specific receptors in the presence of α-klotho. Although FGFR are widely distributed throughout the body, the limited distribution of α-klotho confers tissue specificity to FGF23, focusing its actions within the parathyroid, kidney, and pituitary.[16] The primary physiological functions of FGF23 are to stimulate renal excretion of phosphate, to decrease production of calcitriol by inhibiting 1-α hydroxylase and stimulating the catabolic 24-hydroxylase, and to inhibit PTH secretion. Given the known function of FGF23 in the regulation of phosphorus, the primary site of action is believed to be the proximal tubular cells, where it regulates the transcription and translation of the NaPi-2a sodium phosphate cotransporter.[17]

FGF23 production is regulated by both phosphorus concentrations and calcitriol. In health, high phosphorus intake results in increasing FGF23 concentrations and an increase in renal phosphorus excretion, although the mechanism by which phosphorus sensing occurs has not yet been determined.[18] Calcitriol stimulates FGF23 secretion and in a typical negative feedback loop FGF23 reduces calcitriol.[19,20] This sensing is believed to occur via the vitamin D receptor. FGF23

inhibits production of PTH and PTH stimulates FGF23 both directly and indirectly through PTH-mediated increases in calcitriol. An interesting current area of research is the role of iron and hypoxia-inducible factor (HIF) in the regulation of FGF23.[21,22]

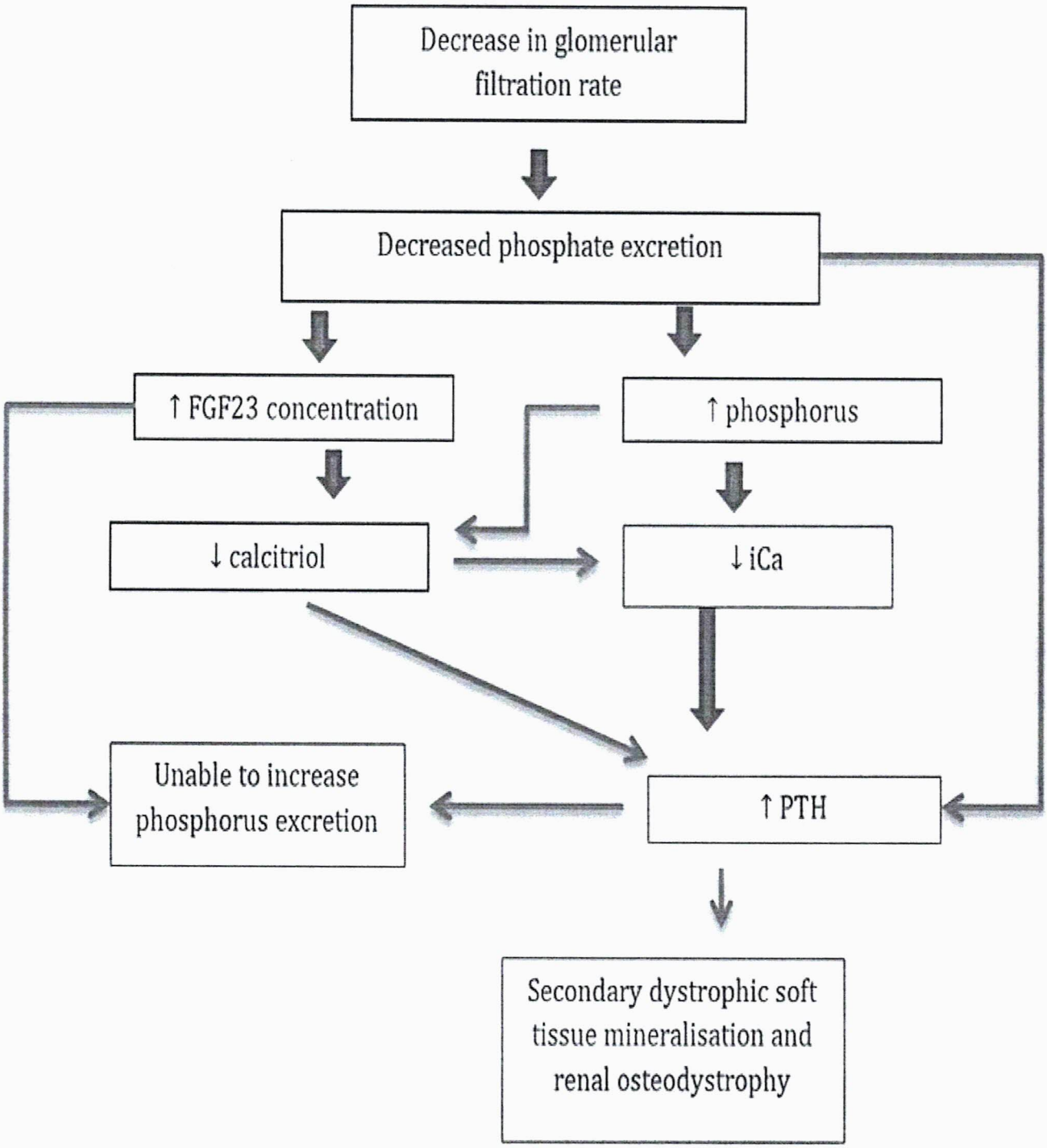
Circulating FGF23 concentrations are reported to increase with reducing renal function in human patients. iFGF23 appears to be the major form of detectable FGF23 in such patients and, although this is attributed to increased bone production, reduced renal excretion may also be contributing.[23,24] With advancing CKD, increasing FGF23 concentrations have been associated with higher serum phosphate, increased fractional excretion of phosphate, lower eGFR and reduced calcitriol concentrations.[25-27] The reduction in calcitriol concentrations is independent of reduction in GFR, suggesting that reduced calcitriol is predominantly the consequence of inhibition by FGF23, rather than reduction in renal mass. Studies suggest that FGF23 concentrations begin to increase early in the course of renal disease prior to evidence of hyperphosphatemia and SRHP and that therefore FGF23 may act as a sensitive screening test to identify patients which are developing mineral metabolism disorders in early CKD.[28] It has been proposed that FGF23 increases early in the course of CKD, either as a consequence of phosphate retention due to reduced renal excretion, or could be the consequence of decreased α-klotho expression in the kidney. Others suggest that early in the course of CKD there may be a primary FGF23 excess, perhaps as a consequence of change in bone metabolism, reducing plasma phosphorus, increasing phosphorus renal excretion, and decreasing α-klotho expression.[29] Nevertheless, based on the discovery of FGF23 an updated 'trade-off' hypothesis can be proposed (Figure 2a & b).

***Figure 2a***




A new 'trade-off' hypothesis for early CKD.
FE: Fractional excretion; FGF23: Fibroblast growth factor 23

***Figure 2b***




A new 'trade-off' hypothesis for late CKD.

In early CKD, an increase in phosphate retention will drive increase in FGF23 production. Increased FGF23 will inhibit transcription and translation of the NaPi-2a cotransporter in the proximal tubule of remaining functioning nephrons, limiting reabsorption of phosphorus and facilitating phosphorus excretion. Increased FGF23 in combination with increased phosphorus will inhibit 1α-hydroxylase activity, thereby decreasing calcitriol production and absorption of phosphorus and calcium from the gastrointestinal tract. In the parathyroid gland, increased FGF23 will directly inhibit the production of PTH, thereby limiting release of calcium and phosphorus from bone as a consequence of the action of PTH.

FGF23 As A Risk Factor in Humans

FGF23 has been associated with mortality in incident endstage renal disease (ESRD), in kidney transplant patients, and in patients with pre-dialysis CKD.[30-32] Studies have also associated FGF23 with progression of CKD and as a cardiovascular risk factor, although whether it is acting purely as a marker or is directly implicated in disease progression remains to be fully determined. Preliminary data indicate that dietary manipulation of phosphate intake will aid in modulating FGF23 concentrations both in healthy individuals and in those with CKD and that FGF23 concentrations are also lowered with administration of phosphate binders.[18,33-40]

### Evaluation of FGF23 in Cats

In the past 3 years, preliminary studies have been performed investigating the role of FGF23 in phosphorus homeostasis in cats with CKD. A commercially available human ELISA has been validated for quantification of FGF23 in feline EDTA plasma. In a study by Geddes and colleagues, FGF23 concentrations were found to significantly increase with advancing IRIS stage of CKD. Cats in IRIS stage 2 and 3 were subdivided according to whether they met the IRIS targets for phosphate regulation. Those cats that had plasma phosphate concentrations greater than the IRIS targets were found to have significantly higher FGF23 concentrations than those cats where phosphorus concentrations were within target.[41] A further study by Finch and colleagues evaluated FGF23 concentrations in non-azotemic cats > 9 years. These cats were followed longitudinally until the development of azotemia. Those cats that developed azotemia within a 12-month period, at baseline had significantly higher FGF23 concentrations than those cats which remained non-azotemic, suggesting that as in humans plasma FGF23 concentrations may be an early biomarker for alteration in renal phosphorus homeostasis and early non-azotemic CKD.[2] Finally, a study by Williams and colleagues has evaluated both PTH and FGF23 in cats with hyperthyroidism. This study aimed to determine whether either of these factors were associated with the development of azotemia after treatment of hyperthyroidism or survival in cats with treatment of hyperthyroidism. Unfortunately, neither were predictive of the development of azotemia in this setting but FGF23 concentrations were significantly associated with all-cause mortality.[42] Future study is warranted to investigate the role that dietary and phosphate binder manipulation has on FGF23 concentrations in the cat and whether modulation of FGF23 is beneficial in terms of survival of cats with CKD.

Later in the course of CKD, FGF23 concentrations will continue to increase as a consequence of declining GFR and increased production from osteocytes and osteoblasts. Plasma phosphorus concentrations will begin to increase with declining GFR and will further stimulate FGF23 production. End organ resistance to FGF23 develops due to reduced expression of the FGFR and α-klotho. This can result in FGF23 losing its direct inhibitory action on PTH production. Decreased calcitriol concentrations will reduce calcium absorption from the gastrointestinal tract, stimulating PTH production and will also increase PTH production due to loss of calcitriol-mediated inhibition at the parathyroid gland. PTH production will also be stimulated by increased plasma phosphorus concentrations. Therefore, although a combination of increased PTH and FGF23 initially compensate and increase phosphorus excretion, overt hyperphosphatemia ultimately develops with declining renal function.

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