Diagnostic update

IDEXX FGF-23 Test

FGF-23 is a renal management biomarker. In cats with early CKD (IRIS† CKD Stages 1 and 2), the IDEXX FGF-23 Test provides an evidence-based approach to recommend phosphate reduction therapy.

Background

Chronic kidney disease (CKD) affects an increasing percentage of cats as they age, reported as 0.1% of cats less than 9 years old but 30%–40% of cats above age 10, and as high as 80% of cats over the age of 15.[1–3] CKD causes significant morbidity and mortality in the older cat population.[4] Kidneys are essential in phosphate homeostasis. As CKD develops and there is a decline in glomerular filtration rate (GFR), phosphorus concentrations increase, causing an imbalance in phosphate-calcium homeostasis.[5] This is labeled chronic kidney disease–metabolic bone disease (CKD-MBD; also referred to as mineral bone disorder) and describes a complex syndrome that involves fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), 1,25-dihydroxy vitamin D_3 (1,25 vitamin D_3, calcitriol), calcium, and phosphorus (figure 1).[6] CKD-MBD leads to chronically elevated FGF-23 levels in most patients. There is strong clinical evidence from both human and veterinary literature that FGF-23 often identifies mineral disruption and phosphorus overload (CKD-MBD) earlier than total serum phosphorus and is a valuable tool in the management of CKD in cats.[7–10]

FGF-23 has been shown to increase with CKD severity in humans and cats.[9–11] However, FGF-23 does not consistently precede persistent increases in kidney biomarkers (SDMA, creatinine, urea).

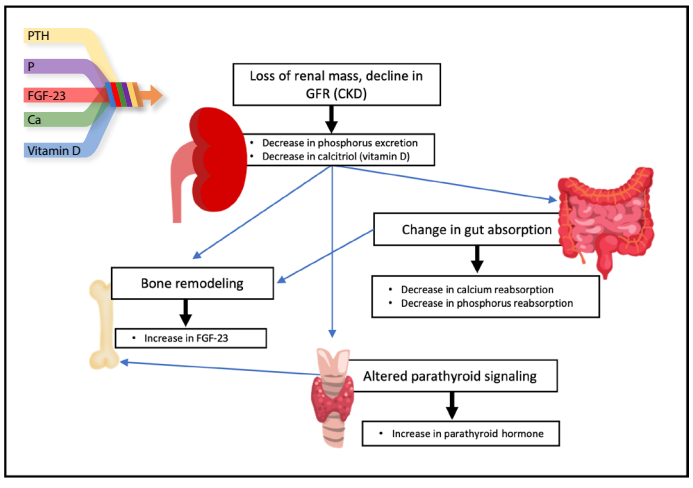

Figure 1. Simplified diagram of physiology of FGF-23 in CKD. Loss of GFR leads to a decline in phosphorus excretion, α-Klotho expression, and calcitriol production, leading to bone remodeling and increases in circulating FGF-23. These mineral imbalances, specifically calcium and phosphorus, alter gut metabolism and reabsorption, further propagating the metabolic bone disease. Due to the effect on signaling directly related to calcium reduction, a secondary increase is eventually seen in PTH, and labeled secondary renal hyperparathyroidism.

FGF-23 is not intended to be used as a core diagnostic tool to diagnose cats with CKD, but rather it serves as a useful indicator of the need for therapeutic intervention and potentially in prognosis.[10,12,13] The variability in FGF-23 levels in early CKD in cats is likely due to a combination of elements that include aetiology of CKD and the complexity of MBD beyond phosphate metabolism. Phosphate metabolism has been shown to be exceptionally important in cats with all stages of CKD. Prescription renal care diets have been shown to improve quality of life and increase lifespan when fed consistently and started at early stages of CKD in cats.[3,4,14] Veterinarians are in the midst of an extensive conversation regarding the timing of diet initiation, the nature of composition of diets, and inclusion or restriction of ingredients for cats diagnosed with CKD. Further research is required to better define the specific pros and cons of therapeutic kidney diets.[8,21,29] FGF-23 offers some clarity by signaling CKD-MBD and potential phosphate overload in early-stage CKD.[15] An increased FGF-23 after diagnosis of CKD supports the use of phosphate reduction therapy, the most accessible being dietary phosphate restriction. Plasma FGF-23 has been correlated to prognosis in human CKD patients, and research from veterinary literature suggests that a higher initial FGF-23 level may be a negative prognostic indicator for cats with CKD.[8,16] It is likely that FGF-23 will provide similar diagnostic information about renal management in dogs, but further research is needed to confirm this.[17–19]

Biology of FGF-23

FGF-23 is a phosphatonin and is likely the most important element in the control of phosphate metabolism. Primarily produced by osteocytes and osteoblasts and directed by α-Klotho expression at the level of the kidney, FGF-23 progressively rises with loss of GFR and before total serum or plasma phosphorus increases.[23] The relationship between FGF-23 and indirect markers, such as SDMA and creatinine (CREA), is less clear. CKD-MBD is likely related to aetiology of CKD, comorbidities, and current therapies, and onset varies from cat to cat (figure 2). As phosphorus levels rise due to decreased GFR, FGF-23 increases to maintain phosphorus balance. With its coreceptor α-Klotho, FGF-23 decreases phosphorus and calcitriol in three ways: (1) downregulating sodium-phosphorus cotransporters, (2) inhibiting renal 1α-hydroxylase activity, and finally, (3) increasing 24-hydroxylase activity.[24–26] In earlier-stage human CKD, FGF-23 promotes a reduction in PTH (figure 2), but in later stage disease, FGF-23 appears to contribute to renal secondary hyperparathyroidism (increasing PTH) due to decreasing levels of calcitriol and perhaps additional mechanisms yet recognised.[27,28] This same pattern seems to be represented in studies in cats.[7,9]

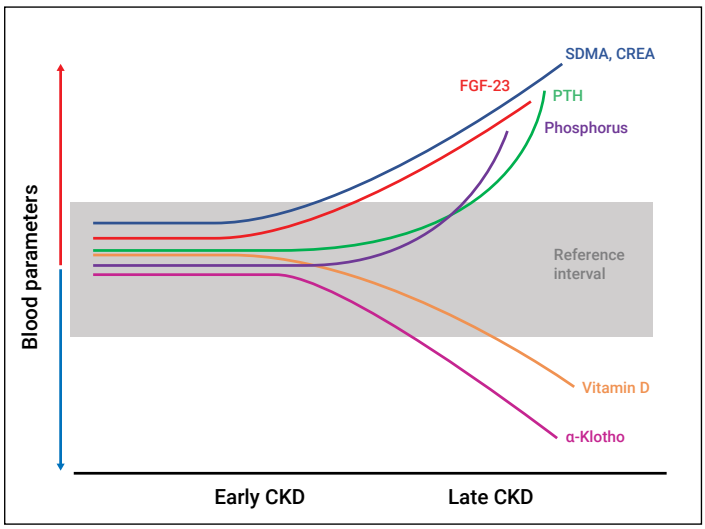

Figure 2. Diagram of relationship between FGF-23 and other important biomarkers and hormones in CKD in cats.

Clinical utility

FGF-23 should be measured in feline patients who have diagnosed, or have strongly suggested, CKD and are in earlier IRIS CKD stages (1 and 2) (figure 2).[20] FGF-23 is most helpful in delineating which IRIS CKD Stage 1 and Stage 2 cats will potentially benefit from phosphate reduction therapy, such as diet.[15] In later-stage kidney disease, FGF-23 may not prove as beneficial as a renal management tool as diet change is always recommended unless contraindicated due to other comorbidities. Additionally, at this level of disease FGF-23 levels are likely markedly elevated.[9]

FGF-23 is the only globally available renal management marker that often identifies phosphate overload (CKD-MBD) earlier than total serum phosphorus in cats with early-stage CKD. Knowing a cat's FGF-23 level gives an evidence-based approach to several clinician and client questions: When should diet be initiated? Is this lifelong diet change needed? While diet is often suggested for patients with IRIS CKD Stage 2, it can be dependent on patient needs and the client's ability to invest in a lifelong diet change. FGF-23 supports this decision with a value indicating the medical need and value of instituting and maintaining a therapeutic renal diet. For the client, it gives an objective representation of the disease they may not yet recognise in their cat and validates a decision to commit to care that may prolong their pet's lifespan. Although the timing and nature of therapy for cats with early CKD is complex, awareness that a cat has MBD encourages early therapy, such as diet change.[21] After all, MBD is known to contribute to kidney damage though mechanisms that include vascular calcification, secondary hyperparathyroidism, and derangement of the renin-angiotensin-aldosterone system (RAAS). Second, FGF-23 in early-stage CKD is a tangible piece of evidence to the owner that a diet or other therapeutic change is warranted.

FGF-23 and IDEXX SDMA testing

The IRIS staging guidelines for CKD include IDEXX SDMA testing and define IRIS CKD Stage 1 as SDMA levels < 18 µg/dL and IRIS CKD Stage 2 as SDMA levels between 18–25 µg/dL. In cats where persistent increases in SDMA and/or other evidence (creatinine, urine specific gravity [USG]) suggest CKD, increases in FGF-23 levels indicated the presence of CKD-MBD.[22] Using SDMA can allow for earlier diagnosis of CKD than traditional kidney biomarkers alone. FGF-23 as a renal management marker following earlier diagnosis can guide evidence-based decisions and validate care decisions for cats. It is possible that cats in early IRIS CKD stages will not yet have CKD-MBD and will have normal or borderline FGF-23 levels. In these cases, repeated monitoring of FGF-23, chemistry profile with IDEXX SDMA testing, and urinalysis is warranted every 3–6 months to understand when phosphate overload (CKD-MBD) has reached a level of clinical influence and phosphate reduction therapy is warranted.

IDEXX test option and when to test

IDEXX now offers the IDEXX FGF-23 Test, a competitive ELISA that measures the FGF-23 biomarker. FGF-23 testing is indicated after diagnosis (or strong suspicion) of early CKD in cats, including IRIS CKD Stages 1 and 2. There are some comorbidities that research would suggest impact FGF-23 levels including uncontrolled hyperthyroidism, cardiac disease, moderate to severe systemic inflammation and/or neoplasia, lytic bone lesions, and profound anaemia.[3,30–32] Currently avoiding testing FGF-23 in patients with these disease patterns is recommended. Measuring FGF-23 is redundant in cats who already have total serum phosphorus above 1.5 mmol/L.

Interpretation of results

FGF-23 ≤ 299 pg/mL is within normal levels: No evidence of CKD-MBD. This is not an indication that CKD is not present, but only that FGF-23 has not increased out of the expected range for cats without CKD-MBD and that therapy to address phosphorus levels is likely not indicated at this time. If other indications exist, such as significant, stable increases in kidney biomarkers, proteinuria, or acid-base disturbance, intervention to support disease is likely still appropriate.

FGF-23 300–399 pg/mL is borderline: FGF-23 is higher than expected but not at a level that clearly indicates the need for targeted therapy. It is appropriate to institute CKD therapies indicated by other diagnostics or clinical context. Repeating FGF-23 testing in 3–6 months, alongside a chemistry profile with IDEXX SDMA testing and urinalysis, is recommended to monitor for progression and development of CKD-MBD, which would warrant intervention.

FGF-23 ≥ 400 pg/mL is increased: Targeted therapy to reduce phosphorus overload is warranted alongside all other indicated CKD therapies.

For cats with early-stage CKD and normal or borderline FGF-23 levels, repeating FGF-23 testing with semiannual to annual lab work is indicated. CKD-MBD is not always linearly related to functional kidney biomarkers, such as SDMA and creatinine, and increases in FGF-23 may occur without changes to kidney function. Therefore, it is important to monitor onset of phosphorus overload and treat accordingly.

Follow-up

Research would suggest that FGF-23 decreases after initiation of kidney appropriate diets and/or reduction in phosphorus intake. Including monitoring of FGF-23 on chemistry profiles and kidney recheck profiles of animals under therapy may prove advantageous in understanding response to therapy.[9]

Ordering information

Test name and contents	Code	Sample requirement	Turnaround time
IDEXX FGF-23 Test	FGF23	Plain Serum Tube	2–4 days
IDEXX FGF-23 Advantage	FGF23A	Plain Serum Tube	2–4 days
IRIS Renal Disease Grading (Standard) with IDEXX FGF-23 Test Urinalysis, UPC Ratio, Serum Creatinine, IDEXX SDMA* Test, Phosphate, Electrolytes and IDEXX FGF-23 Test	IRDGF	Plain Serum Tube, Urine	1 day; 2–4 days for FGF-23 results
IRIS Renal Profile (Comprehensive) with IDEXX FGF-23 Test Comprehensive IDEXX CBC*, Urea, Creatinine, ALP, ALT, AST, Bilirubin, GGT, Cholesterol, Creatine Kinase, Total Protein, Albumin, Globulin, Glucose, Calcium, Chloride, Sodium, Phosphate, Potassium, Bicarbonate, Anion Gap, IDEXX SDMA* Test, Urinalysis and Urine Culture, UPC Ratio and IDEXX FGF-23 Test	IRISF	Plain Serum Tube, EDTA Tube, Fluoride Oxalate Tube (optional), Blood Smear, Urine	1 day; 2–4 days for FGF-23 and urine culture results

Additional specimen requirements

Only domestic feline‡ serum specimens will be accepted for FGF-23 measurement. Specimen refrigeration is optimal; freezing is not necessary. See additional collection protocols available on VetConnect* PLUS.

Contacting IDEXX

Customer Support
If you have any questions regarding test codes, turnaround time, or pricing, please contact our Customer Support Team at 1 300 44 33 99.

Expert feedback when you need it
Our medical specialty consulting service is available for expert and complimentary consultation. Please call 1 300 44 33 99 if you have questions.

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†IRIS is International Renal Interest Society.
‡Domestic feline refers to domesticated species. FGF-23 has not been validated in wild felids.

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