

clinician's update™

MAKING CLINICAL SENSE

CKD and secondary
hyperparathyroidism



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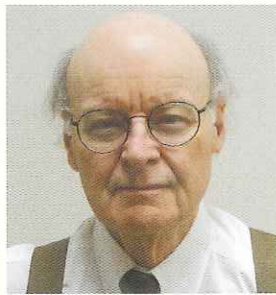
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Making clinical sense

CKD AND SECONDARY HYPERPARATHYROIDISM



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Consequences of renal secondary hyperparathyroidism

- Anemia
- Metabolic acidosis
- Pruritus
- Hypertension
- Cardiac/vascular calcification
- Dystrophic mineralization
- Neurologic dysfunction
- Renal osteodystrophy

Hyperphosphatemia and subsequent renal secondary hyperparathyroidism are recognized as serious complications of chronic kidney disease (CKD). Management of the rise in phosphorus can dramatically suppress disease progression. Studies in cats have shown that control of PTH extended life by almost 3 fold.¹

PROGRESSION OF CKD

An important factor in the progression of CKD, the rise of parathyroid hormone (PTH) is seen as a trade-off for maintenance of initial (albeit transient) hyperphosphatemia and hypocalcemia (see **CKD & Hyperphosphatemia** on page 3).^{2,3} Eventual exhaustion of greater than 75% to 80% of the functional nephron population leads to sustained hyperphosphatemia, direct stimulation of PTH synthesis and secretion, and altered vitamin D metabolism. PTH is also directly damaging to the kidneys.⁴

THE ROLE OF VITAMIN D AND CALCITRIOL

Reduced nephron population mass contributes to decreased production of vitamin D to an active form, calcitriol (1,25-dihydroxycholecalciferol D3). Lack of calcitriol leads to parathyroid hyperplasia, nodular formation, and sequential aggressive synthesis and secretion of PTH. Reduced calcitriol also leads to reduced gut absorption and kidney reabsorption of calcium, contributing to lowered ionized calcium concentration, PTH elevation, and graduated hyperparathyroidism. Increased phosphorus binds remaining calcium, further driving down ionized calcium.⁵

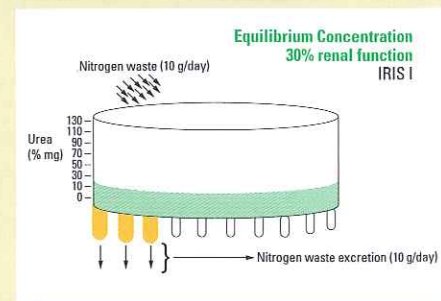
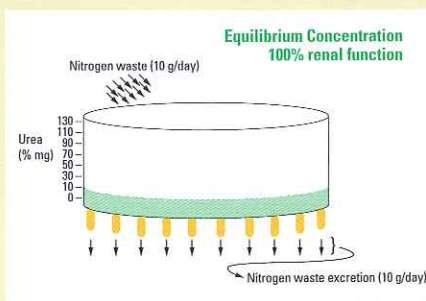
STAGING AND MANAGEMENT OF SECONDARY HYPERPARATHYROIDISM

CKD may be staged to facilitate appropriate therapy and monitoring using the IRIS CKD Staging System on page 3. Initial staging is based on fasting plasma creatinine and substages are based on accelerated plasma creatinine levels, along with serum phosphorus, protein spillage, and systemic blood pressure values. Along with application of low-phosphate diets and phosphate binders (our group initiates Epakitin® at IRIS Stage I), several management strategies are available for maintaining proper blood chemistry (see chart on page 4).^{6,7,8} Except for advanced renal osteodystrophy (see Case Study on page 3), therapeutic dietary and medical management can often be rewarding in correcting the consequences of secondary hyperparathyroidism. When medical management fails, subtotal parathyroidectomy may be indicated.⁹

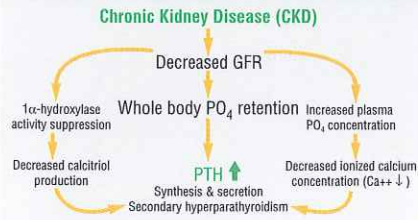
Intact nephron hypothesis

The kidneys eliminate metabolic wastes from the body and maintain electrolyte and acid–base balance, blood pressure regulation, and hormone synthesis. The nephron is the functional unit. Although the intact nephron hypothesis states that each nephron is either a fully functional unit or does not function, surviving nephrons can undergo hypertrophy to increase their functional capacity. When nephrons are destroyed as in progressive CKD, the kidney's capacity to accommodate diminishes over time.

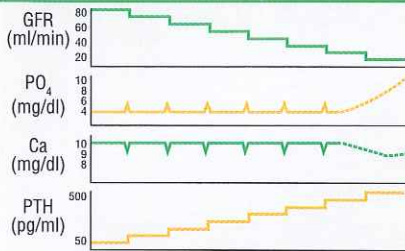
■ = Functional nephrons ○ = Nonfunctional nephrons



CKD & Hyperphosphatemia (PO₄↑)



Progression of CKD Relationship of Ca, PO₄, & PTH



Case study – Renal osteodystrophy

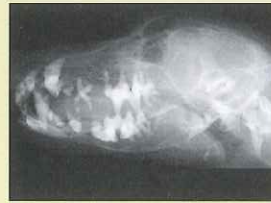


Murphy

West Highland white terrier
Male, 15 years old

Results

The low ionized calcium and extremely high PTH are classic indicators of secondary hyperparathyroidism. Both radiographs show decalcification of the jaw ("rubber jaw"). The most common cause would be CKD (late IRIS III).



Laboratory indicator	Value	Range
Intact parathyroid hormone	> 210.00 pmol/L	3.00 – 17.00 pmol/L
Ionized calcium	1.16 mmol/L	1.25 – 1.45 mmol/L
BUN	93 mg/dL	< 20 mg/dL
Creatinine	4.8 mg/dL	< 1.2 mg/dL
SpGr	1.008	1.007 – 1.047

BUN = Blood urea nitrogen
SpGr = Specific gravity

IRIS* CKD Staging System**

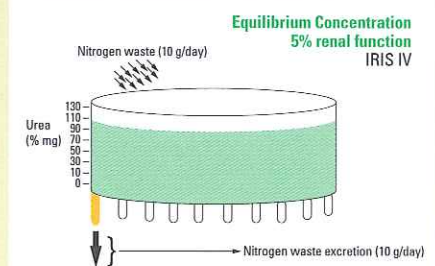
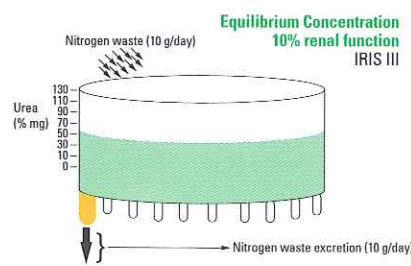
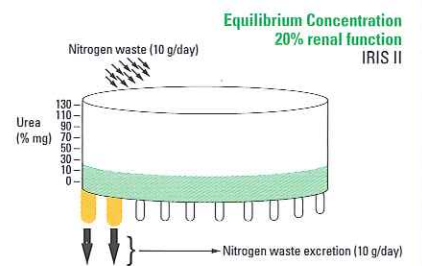
Stage	Remaining renal function	Canine plasma creatinine (mg/dL)	Feline plasma creatinine (mg/dL)	Comments†
I	30%	< 1.4	< 1.6	<ul style="list-style-type: none"> Hyperphosphatemia unlikely Hypertension possible Proteinuria possible
II	20%	1.4 – 2.0	1.6 – 2.8	<ul style="list-style-type: none"> Hyperphosphatemia possible Hypertension possible Proteinuria possible
III	10%	2.1 – 5.0	2.9 – 5.0	<ul style="list-style-type: none"> Hyperphosphatemia probable Hypertension possible Proteinuria possible
IV	< 5%	> 5.0	> 5.0	<ul style="list-style-type: none"> Hyperphosphatemia probable Hypertension possible Proteinuria possible

* The mission of the International Renal Interest Society (IRIS) is to help veterinary practitioners better diagnose, understand, and treat renal disease in dogs and cats. IRIS and the IRIS Staging System were created at the 8th Annual Congress of the European Society of Veterinary Internal Medicine in Vienna, Austria, in 1998. Visit iris-kidney.com for more information.

** CKD can be further classified by presence or absence of proteinuria (P or Non-P) and presence or absence of systemic hypertension (H or Non-H); see comments column.

† Renal proteinuria defined as urine protein:creatinine ratio (dog > 0.5, cat > 0.4)

For the most part, consequences of secondary hyperparathyroidism are associated with uncontrolled and sustained PTH elevation along with hyperphosphatemia.



Management of renal secondary hyperparathyroidism

Reduce phosphorus in food

Several therapeutic foods are available that provide reduced levels of phosphorus to help slow the progression of kidney disease. They also have reduced levels of protein and may have some buffering capacity.

Bind phosphate

Agent	Mode of action	Dose	Comments
Nutraceutical - Epakitin®	<ul style="list-style-type: none"> Contains chitosan, calcium carbonate, lactose, and soy protein Binds PO₄ 	1 gm/5 kg Q 12 H with meals	<ul style="list-style-type: none"> Begin using in IRIS Stage I May need to be paired with additional PO₄ binders in IRIS Stages III and IV
Aluminum hydroxide	<ul style="list-style-type: none"> Forms insoluble aluminum phosphate Reduces PO₄ absorption 	40-45 mg/kg Q 12 H with meals	<ul style="list-style-type: none"> May be toxic¹⁰ May cause constipation, hypochromic microcytic anemia, myopathy, osteomalacia, progressive dementia
Calcium salts - Calcium carbonate - Calcium acetate	<ul style="list-style-type: none"> Bind PO₄ in alkaline pH of small bowel 	25-50 mg/kg elemental calcium Q 12 H with meals	<ul style="list-style-type: none"> May cause hypercalcemia, soft tissue calcification, cardiovascular mineralization; restrict availability of calcitriol Large volume demand as GFR decreases
Sevelamar HCl	<ul style="list-style-type: none"> Noncalcium, nonaluminum PO₄ binder Anion exchange resin trades Cl ions for PO₄ ions in small intestine 	25-40 mg/kg Q 12 H with meals	<ul style="list-style-type: none"> Potential to bind bicarbonate and cause metabolic acidosis Potential to bind vitamins and bile acids
Lanthanum carbonate	<ul style="list-style-type: none"> Noncalcium, nonaluminum PO₄ binder Rare earth element not absorbed well from GI tract 	40-50 mg/kg Q 12 H with meals	<ul style="list-style-type: none"> GI disturbance Cost

Upregulate vitamin D3*†

Cholecalciferol (vitamin D3)	<ul style="list-style-type: none"> Provides substrate stores for 25-hydroxycholecalciferol 	0.03 mg/kg/d for 2 days 0.02 mg/kg/d for 2 days then 0.01 mg/kg/d maintenance	<ul style="list-style-type: none"> Requires sequential liver and renal metabolism
Calcitriol	<ul style="list-style-type: none"> Inhibits synthesis and secretion of PTH Regulates calcium absorption from gut and reabsorption from kidney 	1.5-3.5 ng/kg/d orally	<ul style="list-style-type: none"> Hypercalcemia Soft tissue calcification

Partial parathyroidectomy

For resistant secondary hyperparathyroidism, removal of 3/4 of hyperplastic parathyroid gland and continuation of PO₄ binder therapy may be indicated.

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* Optimum dosage must be determined based on serial evaluation of PTH activities and serum Ca and PO₄ levels. Paricalcitol and doxercalciferol are similar to calcitriol and currently being used in human medicine.

† Calcimimetic agents such as Sensipar® (Amgen) are being evaluated in treatment of secondary hyperparathyroidism as add-on therapy to calcitriol and vitamin D analogs and dietary phosphate binders.

Epakitin® Highlights

By limiting the increase of phosphorus with the help of a low phosphorus diet and/or by adding a phosphate binder to the diet,¹ it is possible to slow down CKD and increase life expectancy. Contains a chitosan-based nutritional supplement (chitosan is a natural polysaccharide extracted from crab and shrimp shells).

- Binds phosphate
- Reduces uremia
- Improves general health of animals with CKD
- Demonstrated clinical efficacy



This summary is based on a presentation at the 2009 NAVC Conference and references cited. The opinions expressed do not necessarily reflect the view of the publisher or the sponsor.