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PROLONGING LIFE AND KIDNEY FUNCTION

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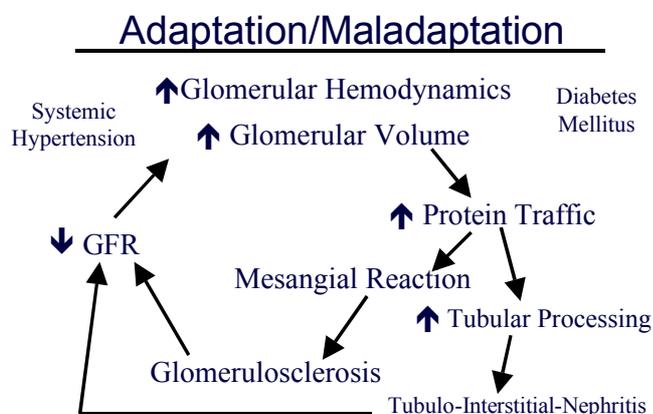
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Nature of Progression – A Unifying Hypothesis

CRF is clinically characterized in dogs and cats by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. Progressive loss of various renal functions seems inevitable in most patients with advanced stages of chronic renal disease. Progression will occur if the underlying renal insult cannot be treated (e.g. glomerulonephritis due to an unidentified antigen, amyloidosis) but can also progress at times when the cause of the initial injury has been removed. The “inexorable progression of chronic renal failure” only occurs however after substantial loss of renal mass has already occurred regardless of the original inciting injury. A variety of interventions (diet and drugs) can slow the progression of the renal disease, improve the quality of life for the patient, and/or extend the quantity of life.

"Super-nephrons" that result from hypertrophy of renal function and increased glomerular volume in remaining viable nephrons may result in their eventual demise. Hemodynamic adaptations in remnant nephrons cause increased single nephron GFR, glomerular plasma flow, and increased transglomerular capillary hydraulic pressure that are initially adaptive to maintain excretory function and total kidney GFR at higher levels that would be otherwise. Ongoing intraglomerular hypertension and increased glomerular volume eventually harm glomeruli. Tubular hypermetabolism, hyperammoniogenesis, renal mineralization, secondary hyperparathyroidism, systemic arterial hypertension, intrarenal coagulation, and immune mechanisms may also contribute to chronic progressive renal injury. It is not possible to predict the rate of this progression in experimental or clinical animals. Compensatory increases (so called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in some instances as shown in this figure.



Early Diagnosis of Progressive Renal Disease

BUN and serum creatinine concentrations are used as surrogates to estimate GFR but do not become increased until at least 75% of the nephron mass is non-functioning. Dogs and cats with advancing chronic renal disease often show no clinical signs until at least 50 to 67% of renal mass is lost with polyuria and polydipsia developing before the onset of azotemia. The ability to produce maximally concentrated urine is progressively lost as renal mass declines from 50 % until the region of isosthenuria (1.007-1.017 urinary specific gravity) is reached when 67% or more of renal mass has been lost. The development of clinical signs, sub-maximally concentrated urine, and azotemia occur following loss of substantial functional renal mass.

The range for normal serum creatinine concentrations is large for when groups of dogs or cats are considered but is much narrower for an individual animal. The International Renal Interest Society (IRIS) has recommended that the upper limit for normal serum creatinine in the dog to be less than 1.4 mg/dl and less than 1.6 mg/dl for cats. These upper limits are substantially less than those noted for most commercial laboratories. When these values are used, more animals with renal disease will be detected earlier but also some normal animals will be included in this group based on magnitude of serum creatinine alone. With the increasing attention to wellness and geriatric examinations that include laboratory testing, individual trends for change in serum creatinine can be detected IF the same laboratory is used that determines the creatinine measurement. Analysis of serum creatinine concentration by the same lab on the same sample is usually quite closely repeatable whereas there can be greater variance when samples are measured by different laboratories. Sequential increase in serum creatinine still within the normal range can suggest progressive loss of renal mass.

Observations of changes in the degree of maximal urinary concentration can provide early clues that nephron mass is decreasing. First morning urine samples (before eating and drinking) usually have the highest urinary specific gravity (USG) in dogs, often with USG greater than 1.040. Substantial variation of the USG occurs in dogs throughout the day depending on timing following eating, drinking, and exercise. Less variability in USG occurs throughout the day in cats. Cats with normal kidneys that eat mostly dry food usually make urine with a USG of greater than 1.035. A USG cut-off of 1.040 is recommended as less-likely to have substantial renal disease in those with borderline azotemia; the cut-off in dogs is 1.030. Sequential UA that reveal decreasing USG provide concern that renal mass could be decreasing.

Proteinuria in the absence of an active urinary sediment is an early marker of many generalized progressive renal diseases. The development of renal proteinuria usually precedes the development of dilute urine and azotemia. Proteinuria detected by dipstrip measurement can be falsely positive due to effects in highly concentrated urine and can be falsely negative in those with dilute urine. Dipstrip methods measure mostly urinary albumin and become positive when there is more than 20 or 30 mg/dl present. A positive dipstrip reading for protein assumes more importance to indicate relevant proteinuria when the urine is less concentrated. Urine protein to creatinine ratio (UPC) measurement removes the confounding effect of urinary concentration or

dilution on the concentration of measured protein since urinary creatinine serves as a maker to neutralize this ; this is a unitless measurement. Measured protein includes both albumin and globulins. Normal UPC is less than 0.4: this cut-off allows for early detection of renal proteinuria. UPC is useful to monitor therapy also. The magnitude of the urine protein/creatinine ratio is roughly correlated with type of glomerular disease present. Microalbuminuria (MA) uses dog and cat specific ELISA capture methods to measure urinary albumin. MA is designed to detect urinary albumin from 1-30 mg/dl; urine is diluted to a standardized 1.010 USG before measurement. MA in normal dogs and cats is less than 2 mg/dl and is reported as not detectable. MA can be run in-house and reported as negative or positive; mild, moderate, and high positive is further defined based on depth of color reaction. MA sent to referral labs can provide albumin in mg/dl that is more precise. In progressive generalized renal diseases, MA is the first marker of proteinuria to become positive followed by UPC and then dipstrip. MA is very sensitive in the detection of proteinuria at early stages of renal disease but its presence does not necessarily mean that the animal will have progressive renal injury and eventual development of renal failure.

Dietary Management

Recently, evidence based medicine studies of clinical dogs and cats with chronic renal failure have emerged showing salutary effects of dietary modification. "Renal-friendly" veterinary diets are generally restricted in protein, phosphorus, calcium, and sodium while supplemented with carbohydrates, sources of alkali (potassium citrate), and polyunsaturated fatty acids in a favorable ratio of omega-6:omega-3 fatty acids. Compared to the average grocery or pet store foods, the renal friendly veterinary diets are restricted in protein by about 1/3 to 1/2, while phosphorus is restricted by 70 to 80%. Canned foods are generally more restricted in phosphorus than their dry counterparts and substantial differences exist amongst the available products. Dry but not canned food for cats is supplemented with potassium at about twice the level of maintenance foods apparently in an effort to avoid kaliopenic nephropathy. Comparison of nutrient intake on a mg/100 kcal energy intake basis for dogs and cats fed veterinary diets is available from the Nutrition Support Services web site maintained at The Ohio State University CVM (<http://www.nssvet.org/>).

Protein restriction should be considered when moderate to severe azotemia persists in the well-hydrated state. The clinician should strike a balance between reducing protein intake and the animal's willingness to eat. Maintenance of stable body weight and serum albumin concentration suggests adequate intake of calories and protein whereas progressive declines in body weight and serum albumin concentration suggest malnutrition or progression of disease and are indications to increase the amount of protein fed. If possible, the animal should be acclimated to the new diet while its appetite is still reasonably good. Recent studies have shown a beneficial effect of feeding commercially-available modified renal diets to dogs and cats with CRF to increase survival to at least twice that achieved with maintenance diet and to reduce the number or uremic crisis episodes.

Patients with CRF are less flexible in adjusting to changes in dietary sodium load, and many commercial pet foods provide more sodium than needed (often about 1%). Commercial products marketed for dogs and cats with CRF provide about 0.2-0.3% sodium. Gradually switching an animal to a renal diet will result in gradual sodium restriction. Excessive sodium restriction in cats with reduced renal mass may result in reduced glomerular filtration rate, inappropriate kaliuresis, and activation of the renin-angiotensin-aldosterone system without beneficial effect on systemic blood pressure. The degree of sodium-restriction in renal diets may warrant reconsideration in some cases.

Renal Secondary Hyperparathyroidism (2°-HPTH)

Renal secondary hyperparathyroidism occurs when PTH synthesis and secretion become excessive as a result of kidney disease. Excess PTH is a major uremic toxin but lack of adequate calcitriol stimulation of the vitamin D receptor in many tissues also contributes to the syndrome as there are calcitriol receptors in most tissues. Increased secretion of PTH by each parathyroid cell as well as increased number of cells due to parathyroid hyperplasia leads to increased circulating PTH. A calcitriol deficit in uremic patients is the most important factor leading to the uncontrolled secretion of PTH. In renal disease, there are fewer healthy proximal tubule cells containing the mitochondrial 1α -hydroxylase enzyme system necessary to form calcitriol from precursor 25-hydroxyvitamin D. Nephron loss during CRF is estimated most commonly by the magnitude of increased serum creatinine. An association of increasing serum creatinine with diminished serum calcitriol in dogs has been shown. Decreased blood calcitriol lowers intestinal calcium absorption leading to hypocalcemia. As iCa concentration falls, the secretion of PTH is stimulated. In early CRF, a modified version of the calcitriol "trade-off" hypothesis emphasizes the role of deficits of calcitriol caused mostly by phosphorus inhibition of calcitriol synthesis. The increased PTH concentration can restore calcitriol and iCa in early stages of CRF when enough proximal tubular cells remain that are capable of calcitriol synthesis.

As glomerular filtration rate is further reduced in late chronic renal failure, greater increases of serum phosphorus occur, so that mass law interactions contribute to a decrease of iCa , stimulating further PTH production. A greater reduction in the activity of the 1α -hydroxylase responsible for calcitriol synthesis occurs as a consequence of the markedly increased serum phosphorus. In addition, the absolute loss of most of the proximal tubular cells makes adequate synthesis of calcitriol no longer possible. At this point, the markedly elevated PTH concentration that ensues is no longer able to restore calcitriol concentrations to normal.

Phosphorus Restriction and Intestinal Phosphate Binders Treatment of renal 2°-HPTH

Dietary phosphorus restriction for dogs and cats with CRF has been shown in to blunt or reverse renal secondary hyperparathyroidism. When CRF is diagnosed, phosphorus restriction is initiated by feeding a low-phosphorus,

low-protein diet. Dietary phosphorus restriction alone may be capable of lowering serum phosphorus and PTH levels in some dogs and cats with chronic renal disease or early renal failure. Decreased PTH is achieved by decreasing the catabolism and increasing the synthesis of calcitriol. Currently there are no diets available that are restricted in phosphate alone, so restriction of dietary phosphate is typically accomplished by restricting animal-source proteins.

Those with greater loss of renal function will require addition of a phosphorus binder given with the food to enable enough phosphorus restriction proportionate to the loss of renal mass. Phosphorus-binding agents should be given with meals or within 2 hours of feeding to maximize their binding of dietary phosphorus. Commonly employed oral phosphorus binders include aluminum hydroxide, calcium carbonate, and calcium acetate. The starting dosage of these phosphorus binders is approximately 90 mg/kg/day and the dosage should be adjusted by periodic evaluation of the serum phosphorus concentration in a blood sample obtained after a 12-hour fast. Aluminium salts have been the intestinal phosphate binder used most extensively in veterinary medicine. Aluminium salts are good binders of luminal phosphate, but aluminium exposure is known to be toxic in humans with renal failure and in some experimental animal studies. Calcium salts provide an alternative to the use of aluminum salts, but they don't bind intestinal phosphate as well as that by the aluminium salts and they pose the potential problem for the development of ionized hypercalcemia. Calcium acetate is a better binder of phosphorus than calcium carbonate and the frequency of hypercalcemia is lower with this salt. Calcium salts may be superior to other intestinal phosphate binders if ionized calcium is moderately to severely decreased. Animals should be monitored for development of hypercalcemia whenever phosphorus binders containing calcium are used, especially if calcitriol is being administered concurrently. Sevelamer hydrochloride is an organic polymer designed as a non-aluminium non-calcium containing compound to bind intestinal phosphate. This compound has the possibility to bind vitamins at higher doses so vitamin supplementation has been recommended. We have safely and effectively used sevelamer in a small number of dogs and cats with renal failure. Lanthanum carbonate is a new generation intestinal phosphate binder in human medicine that does not contain calcium or aluminum. No reports of its clinical use in dogs and cats are yet available. A nutritional supplement extracted from shrimp and crab shells called Epakitin® contains chitosan and calcium carbonate and has been recommended for use as a phosphorus binder in dogs and cats; it may also exert non-selective adsorbent properties.

Return of serum phosphorus to normal does not guarantee that PTH levels will return to normal, as phosphorus restriction only works in those that have enough active tubular machinery capable of calcitriol synthesis once the inhibitory effects of excess phosphorus are removed. Return of serum phosphorus to within the normal range is an initial goal, but achieving concentrations in the lower to mid range for normal serum phosphorus provides additional benefits in control of PTH.

Calcitriol as Treatment for Renal 2-HPTH

Calcitriol treatments help to decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. This occurs mostly by genomic effects to block PTH synthesis in addition to a mild calcemic effect and antiproliferative effect that prevents parathyroid gland hyperplasia. During treatment of CRF patients with calcitriol, simultaneous monitoring of serum ionized calcium, serum phosphorus and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism. Reformulation by a compounding pharmacy may be necessary to provide accurate dosing.

Calcitriol should not be administered until hyperphosphatemia has been controlled. If the $\text{Ca} \times \text{P}$ solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization. The beneficial effects of calcitriol are also lessened within the parathyroid gland when ionized calcium remains low. Phosphorus restriction relieves phosphate-mediated inhibition of the renal 1α -hydroxylase system, resulting in enhanced endogenous synthesis of calcitriol and subsequent inhibition of PTH synthesis. The effectiveness of calcitriol in control of hyperparathyroidism has been noted to increase in patients in whom serum phosphate was lowered.

Supplementation with calcitriol in CRF was initially designed as a daily therapy for life in veterinary patients as long as serum phosphorus remains within the normal range and serum calcium does not become increased. The majority of clinical patients with early CRF and creatinine concentrations between 2 and 2.5 mg/dL will have hyperparathyroidism effectively reversed or prevented by doses of calcitriol between 2.5 and 3.5 ng/kg/day. Doses lower than 2.5 ng/kg are rarely used, and occasionally a dose as high as 6 ng/kg/day is used when lower doses do not succeed in lowering PTH. After receiving the initial dose for 2 months, a recheck of serum PTH concentration will indicate if an incremental calcitriol dosage increase is necessary. A salutary effect of calcitriol treatment of CRF was recently shown in a placebo-controlled study of 37 dogs. The dose of calcitriol was adjusted according to serial ionized calcium and PTH determinations, and ranged from 0.75 to 5.0 ng/kg/day. Over the course of 1 year, there was a significant reduction in mortality rate in the group of dogs receiving calcitriol (28%) as compared to the placebo group (63% mortality). In dogs receiving calcitriol, the median survival time was 365 days, as compared to a median survival time of 250 days in those receiving a placebo (Polzin 2005). Thus, calcitriol therapy appears to have clinical benefit in dogs with chronic kidney disease. Similar studies were done in cats by the same investigators who concluded that there is no advantage to calcitriol treatments in cats with CRF but the study followed cats for just one year. In order to show a difference in treatment effect if one exists, studies in cats with CRF must be conducted for at least 2 and possibly 3 years due to the inherently slow nature of the progression of chronic renal disease in this species.

Based on recent evidence based medicine studies from clinical patients, control of renal secondary hyperparathyroidism should become a standard of

care. Intermittent rather than daily dosing treatment protocols are likely to become the standard of care since less hypercalcemia occurs during this protocol.

ACE-Inhibitors to Reduce Progression of CRF

Angiotensin-II plays a pathophysiologic role in proteinuria and the progression of renal disease. It may play a role in the progression of non-proteinuric renal diseases too. Converting enzyme facilitates the generation of angiotensin-II from angiotensin-I either locally within the kidney via brush border of proximal tubules or via activity of systemic endothelium. Angiotensin-II activity within the kidney causes vasoconstriction of glomerular arterioles with a preferential effect exerted at the efferent arteriole compared to the afferent arteriole. Vasoconstriction of the efferent arteriole at a time of no change in the afferent arteriole increases intraglomerular capillary pressure. Progression of renal disease in remnant nephrons can be attributed in part to the persistence of intraglomerular hypertension, a process that is associated with increased trafficking of macromolecules into the mesangium, with resulting proliferation of mesangial cells and increased mesangial matrix (glomerulosclerosis). Angiotensin-II has nonhemodynamic effects that are potentially important since it can act as a growth factor and stimulate other growth factors that influence renal vascular and tubular growth.

In a 6 month study of dogs with modest azotemia and moderate to severe proteinuria, enalapril treatment (0.5 mg/kg PO q12-24h) reduced proteinuria (as assessed by urine protein/creatinine ratio), decreased blood pressure, and slowed progression of renal disease in dogs with biopsy-proven glomerulonephritis compared to treatment with placebo. Results from this study provided enough clinical evidence to make the use of ACE-inhibition standard of care for protein-losing nephropathy in dogs caused by glomerulonephritis.

Should ACE-inhibition be prescribed for dog that have tubulo-interstitial disease as the cause for their CRF? Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril, benazepril) may have protective effects in patients with chronic renal disease due to their ability to block adverse effects of angiotensin II. ACE-inhibition reduces glomerular capillary hydraulic pressure by decreasing postglomerular arteriolar resistance. Proteinuria is decreased secondary to decreased glomerular hydraulic forces and development of glomerulosclerosis is limited when protein trafficking across the glomerulus is decreased. Remnant nephrons in animals with CRF have glomerular hypertension that can benefit from reductions in transglomerular forces. An additional potential benefit from ACE-inhibition is improved control of systemic blood pressure. This beneficial effect must be balanced against their potential to worsen azotemia since glomerular pressure provides the driving force for GFR in the "super-nephron".

Benazepril is licensed for treatment of CRF in cats in the European Union [Fortekor®]. Average survival of benazepril treated cats of one study was 501 days vs 391 days for placebo treated cats but this effect did achieve statistical

significance. When a subset of cats in this study with proteinuria (UPC > 1.0) were considered, survival was significantly improved for those treated with benazepril (401 days in benazepril treated cats vs 126 days for control cats). Benazepril consistently reduces proteinuria in various stages of chronic kidney disease in cats and in another study stabilized cats in IRIS stage 2 and 3 more often than cats treated with placebo.

Hypertension

The prevalence of systemic hypertension in dogs and cats with CRF ranges from approximately 30 to 75% of affected patients; the prevalence of hypertension is higher in animals with glomerular disease and proteinuria. Systemic hypertension is a major risk factor for the progression of CRF in people and rats. Recent evidence suggests that is also true for dogs and cats with CRF. Perfusion pressure in remnant glomeruli during CRF is increased (vasodilatation of afferent arterioles due to the super-nephron phenomenon), and the fear is that increased systemic blood pressure will be transmitted to the glomerular vascular beds causing further damage. A clinical study of dogs showed that dogs with systemic hypertension at breakpoint high levels progressively lost renal function at greater rates than dogs with lower systemic blood pressure. More rapid progression occurred in dogs with initial blood pressure greater than 160 mm Hg though blood pressure remained increased despite antihypertensive treatments in 10 of 11 dogs. Those in the high blood pressure group had 3 times an increased risk for uremic crisis than dogs in lower pressure groups and had much greater risk for renal related death (Jacob 2003).

Patients with systolic blood pressure readings consistently above 165 mm Hg or those with abnormally high blood pressure readings that also have fundic lesions consistent with hypertensive retinopathy (e.g., retinal edema, intra-retinal serous exudation, retinal hemorrhages, arterial tortuosity, retinal detachment) are considered candidates for anti-hypertensive therapy. Single agent antihypertensive therapy using ACE-Inhibitors (ACE-I; enalapril, benazepril), calcium channel blockers (amlodipine), beta adrenergic antagonists (atenolol, propranolol), or alpha-1 adrenergic antagonist (prazosin) may lower blood pressure. Diuretics and dietary salt restriction are not effective treatment for severe hypertension. Enalapril (0.5 mg/kg PO q12h) is often recommended in dogs with renal disease and hypertension since intrarenal protection may be afforded in addition to lowering of systemic blood pressure. Renal origin hypertension may require much higher doses of ACE-I however and often times a second agent must be added on for effective treatment. Enalapril has not been very effective for treatment of hypertensive cats. The calcium channel blocker, amlodipine has been used successfully to manage hypertension in cats at a dosage 0.625 to 1.25 mg per cat given orally once per day. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine. Adverse effects (including hypotension) are very uncommon with the use of amlodipine in cats. In a recent study, amlodipine controlled hypertension in nearly 60% of CRF cats treated over a period of 3 months or more (Elliott 2001). Side-effects from antihypertensives include hypotension and reduced blood flow to

kidneys. In some animals, it appears that high systemic blood pressure is helping to drive GFR since when systemic hypertension is successfully treated, GRF falls and BUN and creatinine increase. In others, GFR actually increases as the level of systemic hypertension declines

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