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Causes of Progression of Chronic Kidney Disease

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Patients with chronic kidney disease (CKD) have stable or slowly progressing azotemia as increasing numbers of nephrons become non-functional. Causes of progression of CKD may be due to the continuation of the initial cause. However there appears to be a point in the development of renal disease when the process becomes self-perpetuating. This appears to occur when serum creatinine is in the 2-4 mg/dl range.

Chronic kidney disease can be congenital, familial or acquired (**Table 1**). A high incidence of CKD has been observed in litters and lines of many breeds of dogs and cats and the list of breeds involved continues to get longer. This suggests that various forms of familial CKD may be possible in almost any breed given the right circumstances even though the series of events necessary to produce most forms of congenital and familial CKD is not understood at this time.

Table 1. Etiology of chronic renal failure

- Irreversible acute renal failure
- Congenital renal dysplasia and aplasia
    - IgA nephropathy (dogs)
    - Fanconi Syndrome
    - Polycystic kidney disease
- Glomerular disease
    - Glomerulonephropathy
    - Amyloidosis
- Tubulo-interstitial disease
    - Pyelonephritis
    - Idiopathic
- Chronic outflow obstruction
    - Trigonal tumor with ureteral obstruction
    - Renoliths (particularly if infected)
- Neoplasia

- Lymphosarcoma
- Feline infectious peritonitis
- Hypercalcemia
- Borreliosis

Many animals develop CKD after incomplete recovery from an episode of acute renal failure where the cause of the initial insult is known. In addition, there are several well defined primary initiating causes of CKD (Table 1). However, in most patients that are recognized to have the syndrome of CKD, owners have no knowledge of a primary insult.

Several factors make identification of the primary initiating insult difficult. Current hypotheses propose that an initiating insult begins the process of CKD and nephron dropout continues long after the initial insult has gone. Because patients do not show clinical signs associated with CKD until GFR is reduced to 25-30% of normal, the syndrome becomes apparent only after a prolonged period and after continued loss of a vast amount of functional tissue. Histologic features that may elucidate the nature of the primary insult are overwhelmed by non-specific tissue changes associated with chronic progression.

During the early clinically silent phase of CKD leading up to the point where GFR is reduced to 25-30 % of normal, the kidneys undergo a series of functional and anatomical adaptations. The histologic appearance of renal tissue from patients with CKD sometimes indicates primarily glomerular, tubular, or interstitial changes but this usually does not allow identification of a primary cause. However, the histologic appearance of the kidneys from most patients with advanced CKD tends to be similar regardless of the primary initiating cause because the kidney can only respond to injury and reduced functional renal mass with stereotypical structural and functional changes,

Animals with early CKD may have a variable outcome. Some patients seem to stabilize for a long period with no further reduction in renal function, some are stable for a while but tend to suffer intermittent periods of sudden further loss of function, and others continue to progress unrelentingly.

Causes of Progression

Dietary phosphorus

Phosphate is cleared by renally by glomerular filtration followed by active reabsorption of a proportion of the filtered load in the proximal tubule. Early in the course of CKD, as GFR declines, the filtered load of phosphorus (GFR x serum phosphorus) tends to decrease. However, daily phosphorus excretion is maintained at the same level by reduced tubular reabsorption. Reabsorption of phosphorus is under the control of parathyroid hormone (PTH), which inhibits active phosphorus reabsorption in the proximal tubule. As GFR continues to decline the concentration of PTH necessary to maintain normal phosphorus excretion increases. This PTH mediated tubular adaptation allows plasma phosphorus level to remain normal until GFR is reduced to 20% of normal. At that point, further decreases in GFR will cause plasma phosphorus levels to rise.

Hyperphosphatemia induces metastatic calcification when the total serum calcium concentration multiplied by the serum phosphorus concentration exceeds 70 according to the formula: [serum calcium (mmol/L) /0.25] x [serum inorganic phosphate (mmol/L)/0.32]. Metastatic calcification is most prominent in the stomach and kidney where it can induce rapid deterioration in renal function. However, many other organs are also affected.

It has been well understood for many years that normal phosphorus diets fed to patients with CKD will cause progression of renal disease and dietary phosphorus restriction tends to slow the decline in GFR. Low phosphorus diets prevent soft-tissue mineralization including mineralization of the kidney. Parathyroidectomy in dogs failed to show a beneficial effect in dogs in induced CKD beyond that anticipated by the effects of dietary phosphorus restriction.

Glomerular damage

Studies in many species including dogs and cats indicate that patients with CKD tend to develop increased intraglomerular capillary pressure in the remnant nephrons and there is considerable evidence that this adaptive change may be detrimental. Increased intraglomerular capillary pressure may be induced by systemic hypertension or local glomerular hemodynamic events.

In dogs with induced CKD subdivided according to their systemic blood pressure, those with systemic hypertension had increased protein: creatinine ratio (UPC) and increased mesangial matrix, tubular damage and interstitial cellular infiltrate and fibrosis.

Intraglomerular hypertension has been observed in both dogs and cats in models of induced CKD. In a 6 month study of dogs with CKD, treatment with enalapril did not change GFR compared with untreated controls but did reduce systemic blood pressure and UPC. Although glomerular hypertrophy was unaffected, tubulo-interstitial lesions decreased.

In cats with induced CKD, the ACE inhibitor benazepril given for 6.5 months decreased both systemic arterial blood pressure and intraglomerular capillary pressure and simultaneously increased GFR. No histologic differences were observed between the two groups. In another study in cats with induced CKD, amlodipine given for 36 days reduced systemic blood pressure and albuminuria.

Dietary lipids can have detrimental and sparing effects on the glomerulus in CKD. In dogs with induced CKD, diets high in fish oil (n-3 polyunsaturated fatty acids) reduced GFR compared with dogs supplemented with safflower oil (n-6 PUFA) or beef tallow. However the fish oil supplementation protected against renal mesangial matrix expansion, glomerulosclerosis and interstitial fibrosis. The protective effect may be mediated by the effect of fish oil to decrease intraglomerular capillary pressure and to blunt mediators of inflammation in the mesangium.

Thus, there is evidence that reduced intraglomerular capillary pressure and reduced GFR may be protective.

Dietary protein is known to affect GFR in dogs and cats with CKD where high protein diets increase GFR and low protein diets reduce it. While numerous studies in dogs with mild to moderate CKD failed to demonstrate

a protective effect of low protein diets on the progression of CKD, in a model of advanced CKD, histologic lesions were more severe in dogs fed a 42% protein diet compared to an 18% protein diet. A similar effect was noted in cats with induced CKD fed low and high protein diets.

The mechanism of glomerular injury associated with high protein diets may be mediated in part through increased intraglomerular hydrostatic pressure and subsequent increased filtration of plasma albumin. Increased albumin load on podocytes increased the presence of both mRNA and actual protein of transforming growth factor-beta1, a known inducer of sclerosis.

Tubulo-interstitial damage

This is mounting evidence that increased traffic of plasma proteins across the glomerular capillary wall does more than damage just the glomerulus and that tubular reabsorption of excessive filtered protein plays a major role in the progression of CKD.

In human patients with non-diabetic CKD, treatment with angiotensin converting enzyme inhibitors (ACEi) reduced proteinuria and the progression renal disease and in another study the protective effect of the ACEi was more marked in those patients that had heavier proteinuria. Further, in a Heymann nephritis model of CKD in rats, simultaneous treatment of ACEi, an angiotensin receptor antagonist and a statin drug that diminishes interstitial inflammation provided the best protection.

Current theories of the impact of filtered albumin and other proteins on the tubules in CKD focus on the observation that albumin upregulates tubular epithelial cell genes encoding for endothelin and a series of chemokines and cytokines that can lead to detrimental effects. Albumin is reabsorbed from the lumen of the proximal convoluted renal tubule into the apical membrane of epithelial cells by endocytosis into lysosomal vesicles. Central to subsequent processes is protein kinase C-dependent production of reactive oxygen species, nuclear factor-kappaB (NF-kappaB), and other protein kinases. NF-kappaB induces elaboration of fractalkine and other cytokines and chemokines that attract and increase adhesion for mononuclear cells, which play a role in inflammation and disease progression.

No studies have been performed to confirm these mechanisms in dogs and cats but in a proteinuria model in rats, treatment with ACEi and an endothelin-A and-B receptor antagonists, proteinuria, renal lesions and NF-kappaB production was suppressed.

There is speculation that chronic tissue hypoxia may also play a role in progression of CKD due to cellular energy depletion, loss of peritubular capillaries and interstitial fibrosis.

Hypokalemia is observed in cats with CKD but not in dogs. Affected animals have whole body potassium depletion and the classical signs are weakness, a stiff gait and ventroflexion of the neck. Serum creatine phosphokinase levels are usually elevated. The precise cause of hypokalemia in cats in not clear. However, recent evidence points to activation of the rennin-angiotensin-aldosterone system due to low sodium diets with subsequent avid tubular reabsorption of sodium and concurrent

obligatory secretion of potassium. There is evidence that hypokalemia may be a cause of progression in cats with CKD. Enhanced tubular production of ammonia in hypokalemia could lead to tubular damage.

Search Result #2: Proteinuria
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Proteinuria

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The normal glomerulus is a highly selective barrier for filtration based on size (and on charge in the case of larger molecules). While small dissolved particles are freely filtered, larger molecules are almost excluded (Table 1).

Table 1. Glomerular filtration of dissolved substances based on size

	M.W.	***S-E Radius***	***Filtrate/ Plasma***
Inulin	5300	1.4	1.0
Insulin	6000	1.6	0.9
Lysozyme	14,600	1.9	0.75
Myoglobin	16,900	1.9	0.75
PTH	9,000	2.1	0.65
Growth Hormone	20,000	2.1	0.6-0.7
Amylase	48,000	2.9	0.02
Albumin	69,000	3.6	0.02
Gamma Globulin	160,000	5.5	0.00
Ferritin	480,000	6.1	0.02

Under normal circumstances, only a small proportion of plasma albumin and almost no plasma globulins cross the glomerular filtration barrier to enter Bowman's space and the renal tubule. Of the filtered protein, almost all is reabsorbed in the proximal

convoluted tubule and only very small quantities are observed in the final urine. Proximal tubular reabsorption of albumin and other proteins is by inclusion into apical lysosomal vesicles which move into the cytoplasm wherein proteins undergo metabolic breakdown. Reabsorption of albumin in the proximal convoluted tubule is normally at or near the transport maximum so increased albuminuria may be observed either if there is an increase in the filtered load of protein (glomerular dysfunction) or with a decrease of tubular reabsorption of protein (tubular disease). Glomerular proteinuria can be minor to massive while tubular proteinuria is relatively minor.

Measurement and Assessment of Proteinuria

Methods commonly used to measure protein levels in urine include:

1. Microalbuminuria (MA) test. The test is specific for albumin, corrects for urine specific gravity and is accurate for levels between 1-30 mg/dl.
2. Urine dipstick test: The test detects albumin levels as low as 30 mg/dl. Excessively alkaline and highly concentrated urine can cause false positive results. Results should be interpreted with simultaneous consideration of the urine specific gravity.
3. Urinary sulfosalicylic acid turbidometric test: Confirms dipstick findings and eliminates the false positive reactions that such tests often produce.
4. Urine protein/creatinine ratio (UPC): This test is performed on a single spot urine sample and values are proportional to 24-hour urine excretion of protein. The Biuret method is inappropriate for estimation of urine protein because concentrations are so low. The Coumassie Blue test and Trichloro-acetic acids tests are accurate.

Hematuria and urinary tract infection elevate urinary protein levels. Such conditions should be corrected before attempting to interpret proteinuria as a reflection of glomerular disease.

Prior to the introduction of the MA test, expected normal values for protein in urine were: Dipstick: Zero to trace (corresponding to < 30 mg/dl); UPC: < 1 (corresponding to < 30 mg/kg/day). Now with the MA test capable of identifying patients with urinary albumin levels between 1-30 mg/dl, new values for normal need to be defined. At this point it is not yet clear to what extent "normal" animals may be microalbuminuric. The presence of MA may be significant or of no consequence with respect to development and progression of renal disease. One survey indicated the presence of MA in an increased proportion of older dogs.

Once the presence of proteinuria has been confirmed consideration should be given to determination of the source, magnitude and persistence (Table 2). Heavy proteinuria usually indicates serious disease.

Table 2. Clinical classification of proteinuria

- Prerenal: Plasma protein abnormality, e.g., Bence-Jones proteinuria
- Renal:
    - Functional: Transient, e.g., extreme exercise
    - Pathological:
        - Glomerular: Increased capillary wall permeability
        - Tubular: Decreased tubular reabsorption of protein

- Interstitial: Exudate from peritubular capillary

- Postrenal:
  - Urinary: Exudate from lower urinary tract, e.g., UTI
  - Extraurinary: Genital exudations

Causes and mediators of glomerular injury

Glomerular proteinuria is caused by decreased selectivity of the glomerular filtration barrier so that large proteins are filtered from the plasma into the renal tubular. This may be due to generalized vasculopathies, specific accumulation of antigen-antibody complexes in various locations in the glomerulus, or amyloidosis (Table 3). Tubular proteinuria has been identified in human medicine and may occur in veterinary medicine but as yet this phenomenon has yet to be well defined in small animal clinical patients.

Although proteinuria is a common phenomenon, in most instances the glomerulus is affected secondary to disease processes occurring elsewhere in the body. The filtration function of the glomerulus renders it uniquely susceptible to injury and many "non-renal" diseases induce proteinuria (Table 3). Often, the primary disease process is self-limiting, the degree of proteinuria is mild and transient, and there are few or limited consequences for long-term renal function.

Chronic inflammatory conditions with mild antigen excess promote development of circulating antigen-antibody complexes that deposit in the glomerular basement membrane (GBM). Alternatively, free antigens can deposit in the GBM and antibodies can bind to form the antigen-antibody complex *in situ*. Antigen-antibody complexes activate complement, which induces infiltration of neutrophils and macrophages and initiates a complex array of inflammatory mediators and growth factors that disrupt normal glomerular structure and function.

Table 3. Diseases associated with proteinuria

DOG	***CAT***
Infectious	**Infectious**
Bacterial endocarditis	Feline leukemia virus
Brucellosis	Feline infectious peritonitis
Dirofilariasis	Mycoplasma polyarthritis
Ehrlichiosis	
Leishmaniasis	
Pyometra	
Borreliosis	

Chronic bacterial infection	
Rocky Mountain spotted fever	
Septicemia	
Neoplastic Inflammatory	**Neoplastic Inflammatory**
Pancreatitis	Pancreatitis
Systemic lupus erythematosus	Systemic lupus erythematosus
Polyarthritis	Other immune-mediated dis.
Prostatitis	Chronic skin disease
Inflammatory bowel disease	
Immune mediated hemolytic anemia	
Other immune-mediated dis.	
Sulfonamide hypersensitivity	
Other	**Other**
Idiopathic	Idiopathic
Hyperadrenocorticism	Amyloidosis
Amyloidosis	Chronic kidney disease
Chronic kidney disease	
Inherited nephropathies	
IgA nephropathy	
Soft coated Wheaton terrier nephropathy	

In a small proportion of animals with glomerulonephritis and in most dogs with glomerular amyloidosis, glomerular injury and urinary protein loss is so massive that it leads to hypoalbuminemia, edema and ascites. The combination of heavy proteinuria, hypoproteinemia and peripheral edema is known as the nephrotic syndrome. Severe, unrelenting GN reduces GFR with eventual development of

chronic kidney disease (CKD). Dogs with severe proteinuria develop hypercholesterolemia, hyperfibrinogenemia, hypertension, and hypercoagulopathy due to renal loss of antithrombin III.

Role of proteinuria in the progression of chronic kidney disease

There is evidence that proteinuria may be involved in the progression of CKD. In human patients with diabetes mellitus and in patients with hypertension, development of microalbuminuria is a sentinel predicting the onset of CKD. Similar phenomena have been observed in dogs with IgA nephropathy and in soft-coated Wheaton terriers with familial renal disease where appearance of MA portends overt renal disease. In separate studies, azotemic dogs and cats with higher levels of proteinuria on first presentation had reduced survival.

In addition, in humans, the appearance of MA has been associated with increased risk of myocardial infarction in patients with other major risk factors. One study in non-azotemic cats indicated decreased survival from all causes when the UPC exceeded 0.43.

Emerging evidence implicates breakdown products of reabsorbed tubular protein in the progression of renal damage in CKD. Renal tubules respond to proteinuria by increasing reabsorption of filtered protein. Filtered antibodies may attach directly to the tubular epithelial cells inducing injury. Filtered proteins and lipids that undergo tubular reabsorption are metabolized to toxic substances that induce interstitial inflammation and fibrosis.

Diagnosis

Microalbuminuria may be observed in dogs under a wide variety of conditions including vasculopathies, immune responses to non-renal disease, hemodynamic effects (corticosteroid administration), and renal disease. The presence of microalbuminuria may be an early diagnostic marker for serious occult renal and non-renal disease or may be a transient incidental finding associated with an already identified condition. If MA is detected in 2-3 consecutive tests in an otherwise normal appearing dog, non-renal conditions known to induce microalbuminuria should be ruled out before concluding that intrinsic renal disease may be the cause of altered glomerular permselectivity.

The hallmark of diagnosis in GN is quantitation of 24-hour protein excretion. Daily protein excretion can be measured in a 24-hour urine collection or estimated from the urine protein to creatinine ratio of a single sample of urine according to the following equation: 24 hr Urine Protein (mg/kg/day) = $U_{Pr/Cr}$. x 30.

In practice, urine protein concentration (mg/dl) is divided by urine creatinine concentration (mg/dl). In normal animals $U_{Pr/Cr} < 1$ is normal, between 1 and 3 is questionable and greater than 3 is consistent with GN. Dogs with nephrotic syndrome usually spill more than 200 mg/kg/day of protein in the urine so have a $U_{Pr/Cr}.> 6$.

Once glomerulonephropathy is recognized, a diligent search for the underlying cause should be undertaken. An antinuclear antibody test for systemic lupus erythematosus, tests for dirofilariasis, and thoracic and abdominal radiographs for pyometra, abscesses, and neoplastic processes should be performed.

The nature of glomerular injury can be characterized by examination of biopsy specimens under light microscopy. Staining with H & E and silver stains can provide an indication of cellular morphology of the lesion, thickening of the GBM, and the extent of glomerulosclerosis. Examination of Congo Red stained tissues under polarized light allows confirmation of amyloidosis. Immunofluorescence using antibodies directed against complement and immunoglobulins can establish whether glomerular injury is due to immune-complex deposition. Electron microscopy provides further definition of the location of antigen-antibody deposits.

Table 4. Management of heavy proteinuria

- Immunosuppressive agents
  - Azathioprine
  - Corticosteroids
  - Cyclophosphamide
- Inhibitors of the inflammatory processes
  - Specific thromboxane inhibitor
- Dietary adjustment
  - Reduced protein
  - High N3:N6 polyunsaturated fatty acid ratio
- Vasoactive agents
  - Angiotensin converting enzyme inhibitors
  - Antihypertensive agents
- Anticoagulants
  - Aspirin
- Diuretics