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Chronic renal disease: the importance of nutrition

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Denise Elliott graduated from the University of Melbourne with a Bachelor in Veterinary Science with Honors in 1991. After completing an internship in Small Animal Medicine and Surgery at the University of Pennsylvania, Denise moved to the University of California-Davis where she completed a residency in Small Animal Medicine, a fellowship in Renal Medicine and Hemodialysis, and a residency in Small Animal Clinical Nutrition. Denise received board certification with the American College of Veterinary Internal Medicine in 1996 and with the American College of Veterinary Nutrition in 2001. The University of California-Davis awarded a PhD in Nutrition in 2001 for her work on Multifrequency Bioelectrical Impedance Analysis in Healthy Cats and Dogs. Denise is currently the Director of Scientific Communications for Royal Canin USA.

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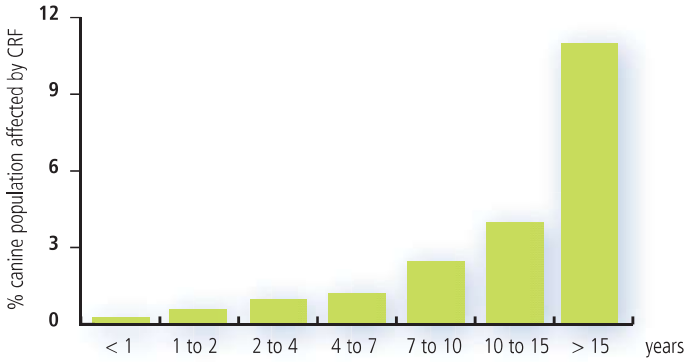
Hervé Lefebvre graduated from the National Veterinary School of Toulouse in 1988. After completing his doctoral thesis in 1994 he became a Diplomate of the European College of Veterinary Pharmacology and Toxicology in 2000. He is currently Professor of Physiology and he is in charge of the cytotoxicity department of the Pathophysiology and Toxicology Unit at the National Veterinary School of Toulouse. Since 1994, his main research interest has been pharmacokinetics in chronic renal disease, local tolerance to injectable medication and assessment of glomerular filtration and dosage regimen adjustment in dogs. Since 2000, he has been studying the biology of creatinine in dogs and the clinical interpretation of the plasma concentration of creatinine in different canine breeds for the early diagnosis of chronic renal failure in dogs. He has more than 60 publications and papers.

Chronic renal failure (CRF) ensues from the irreversible loss of the metabolic, endocrine and excretory capacities of the kidney. It is a common clinical problem occurring in 2-5% of dogs (Bronson, 1982; Lund et al, 1999). Chronic renal failure is considered a leading cause of death in older patients (Figure 1). The 1997 Morris Animal Foundation Animal Health Survey of 2,000 pet owners identified kidney disease as the third leading cause of death in dogs. The mean age of diagnosis in dogs is 6.5 years, with 45% of cases reported over 10 years of age (Polzin, 1989; Polzin et al 2000). The onset of renal failure tends to be insidious as renal function generally declines over a period of months to years. The uremic syndrome manifests when the residual renal mass is generally less than 25% of normal and compensatory changes fail to meet the metabolic and excretory needs of the body for homeostasis.

FIGURE 1 - THE PREVALENCE OF CHRONIC RENAL IN DOGS AS A FUNCTION OF AGE
(Adams, 1995)



Although chronic renal failure is a relatively common disorder in elderly dogs, it can occur at any age.

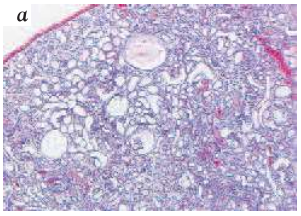
1 - Classification and etiology

Chronic renal failure is caused by replacement of functional nephrons by non-functional scar tissue and inflammatory infiltrates. The precise etiology is however multifactorial: it may be congenital or familial in origin or occur secondary to acquired disease processes that injure the renal glomeruli, tubules, interstitium or vasculature **(Table 1)**. Damage to the glomeruli, tubules, interstitium or vasculature results in entire nephron destruction with ultimate replacement by fibrous scar tissue **(Figure 2)**.

TABLE 1 - POTENTIAL CAUSES OF CHRONIC RENAL FAILURE

Immunological disorders	Polycystic Disease
- Systemic lupus erythromatosus	Idiopathic
- Glomerulonephritis	Familial
- Vasculitis	- Lhasa Apsos
Neoplastic disorders	- Shih Tzus
- Primary	- Norwegian Elkhounds
- Metastatic	- Sharpeis
Amyloidosis	- Dobermans
Nephrotoxic agents	- Samoyeds
Renal Ischemia	- Wheaten Terriers
Inflammatory disorders	- Cocker Spaniels
Infectious disorders	- Beagles
- Leptospirosis	- Keeshonds
- Pyelonephritis	- Bedlington Terriers
Renal Calculi	- Cairn Terriers
Urinary outflow obstructions	- Basenjis
Hereditary/Congenital	

The congenital and familial causes of chronic renal failure can be considered based on breed, family history and the date on which the renal disease commenced.



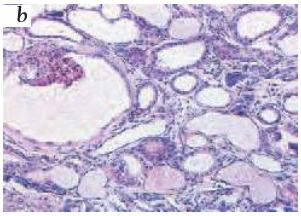


Figure 2 - Histopathological images of renal parenchyma in a Cocker Spaniel diagnosed with familial nephropathy
(a: x100 magnification) (b: x400 magnification); HE stain. The Bowman spaces are dilated and empty; some of them contain glomerular vascular components and protein deposits, some scattered tubules also contain protein material. Multifocal calcification of Bowman capsules, the tubule basement membrane and the glomeruli are observed.

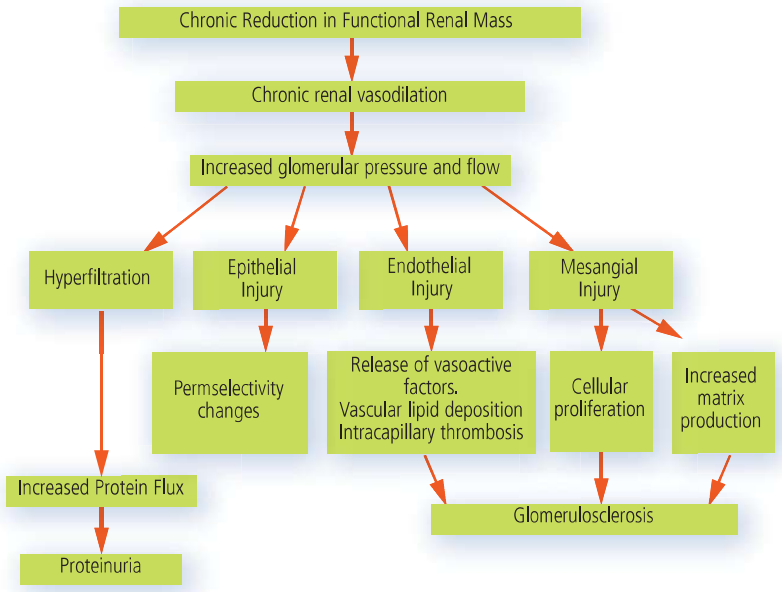
2 - Pathophysiology

Most of the nephrons of the diseased kidney fall into one of two categories. They are either non-functioning nephrons, as a result of destruction of any portion of their structures, or they are intact nephrons that function normally. Changes in renal function occur as a result of a reduction in the number of functioning nephrons. As the number of functioning nephrons diminishes, there are adaptations that occur in a regular sequence. When nephrons are damaged and essentially rendered non functional, the remaining "healthy" nephrons increase their size and their work load to compensate for nephron loss. This is referred to as the hyperfiltration theory **(Figure 3)**. Nephron hypertrophy and hyperfiltration is an adaptative mechanism to compensate for reduced nephron number.

Nevertheless the chronic increase in glomerular capillary pressure and/or glomerular plasma flow rate damages the endothelium, mesangium and epithelium. Mesangial matrix production, glomerular deposition of circulating lipid, and capillary thrombosis promote structural injury to the glomerulus. Tubulointerstitial damage, increased tubular ammoniagenesis, and soft tissue mineralization contribute to nephron injury and ultimately lead to nephron sclerosis. Continued nephron destruction initiates further compensation, promoting a self-perpetuating cycle of adaptation and injuries **(Figure 4)**.

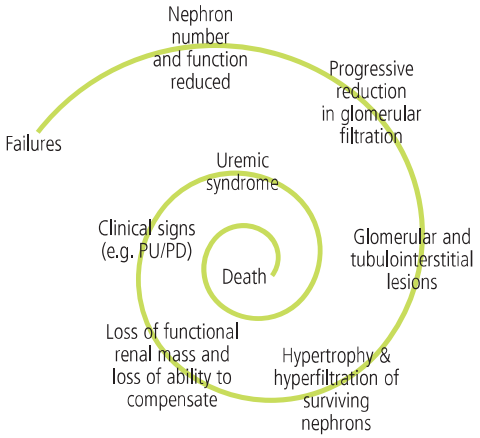
The progression of CRF has been described as occurring in four stages that are not sharply demarcated but rather, are phases in a continuing degenerative process with loss of more and more functioning nephrons **(Table 2)**.

FIGURE 3 - CENTRAL ROLE OF GLOMERULAR HYPERTENSION IN THE INITIATION AND PROGRESSION OF NEPHRON INJURY



Increase in single nephron glomerular filtration rate is mainly due to the vasoconstricting action of angiotensin II on the efferent arteriole, which consequently increases the filtration pressure. This leads to an increased glomerular capillary plasma flow and increased trans-capillary hydraulic pressure so that more plasma is filtered by each surviving nephron.

FIGURE 4 - ILLUSTRATION OF THE RELATIONSHIP BETWEEN RENAL INJURY, LOSS OF NEPHRONS, RENAL COMPENSATORY ADAPTATIONS, AND THE ULTIMATE PROGRESSION OF RENAL FAILURE



The compensatory changes maintain clinically stable disease until structural and functional damage exceeds a threshold beyond which progression of renal function and clinical signs of uremia occur. Chronic renal disease typically progresses to end-stage renal disease after a critical number of nephrons have been damaged.

Table 2 - International Renal Interest Society (IRIS) Classification of stages of renal disease and chronic renal failure in dogs

Stages	I	II	III	IV
Plasma Creatinine				
µmol/L	< 125	125 to 180	181 to 440	> 440
mg/dL	< 1.4	1.4 to 2.0	2.1 to 5.0	> 5.0

The four phases are:
(1) decreased renal reserve,
(2) renal insufficiency
(3) renal failure
(4) uremic syndrome.

Given the large reserve capacity of the kidney at least 60-70% of normal renal function must be lost before azotemia increases, although there may be some nephron hypertrophy during the first phase of decreased renal reserve. At this stage, the patient does not have any clinical symptoms although decreased urine concentrating ability may be noted. In renal insufficiency, up to 75% of the nephrons may be lost. There is mild azotemia, loss of urine concentrating ability and the patient becomes more susceptible to the effects of stresses such as large changes in fluid intake, protein and electrolytes. The patient may remain symptom-free if no overwhelming metabolic stress occurs.

In renal failure nephron loss may reach 90%. There is moderate to severe azotemia, anemia, decreased urine concentration ability and impaired ability to maintain electrolyte and acid base balance.

The pathogenesis of the uremic syndrome is complex and not fully understood. Many toxins are involved and no single compound is likely to explain the diversity of the uremic symptoms. Nitrogenous waste products of protein digestion and catabolism (e.g. urea, creatinine, ammonia, middle molecules, guanidine and its derivatives) accumulate when renal function is reduced and some of them contribute to many of the clinical consequences of uremic intoxication associate with chronic renal failure **(Table 3)**.

Table 3 - Examples of toxins implicated in the uremic syndrome

Oxalic acid	Dimethyl arginine
Parathyroid hormone	Amines
β-2 microglobulin	Phenols
Methylguanidine	Indoles
Guanidinosuccinic acid	Pseudouridine

3 - Clinical consequences of uremia

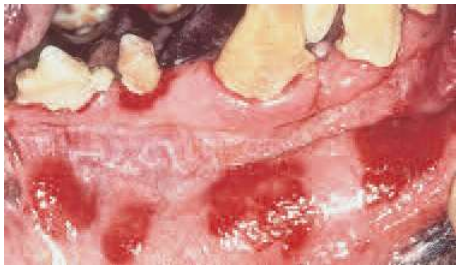
► Gastrointestinal consequences

Gastrointestinal intoxications including anorexia, nausea, vomiting, fetid breath, stomatitis, oral ulcerations **(Figure 5)**, tongue tip necrosis, gastritis, gastrointestinal ulcers, hematemesis, enterocolitis, diarrhea, intussusception and ileus are the most common and prominent clinical signs of uremia. These lesions and dysfunctions act singularly or in concert to induce gastrointestinal pathology.

Excess urea secreted in salivary and gastric juices is converted by urease producing bacteria to ammonia that directly damages the mucosa. Uremic toxins also injure the gastric mucus, mucosa, submucosa or vasculature, thereby reducing the protection afforded by the gastric mucosal barrier. Reduced renal clearance of gastrin leads to hypergastrinemia and stimulation of gastric acid production.

Increased diffusion of acid into the gastric wall induces inflammation, ulceration, and hemorrhage, in addition to perpetuating uremic toxin induced gastric injury. Vomiting occurs secondary to gastritis in addition to the direct effect of uremic toxins on the chemoreceptor trigger zone.

Figure 5 - *Oral lesions in uremic stomatitis/gingivitis.*



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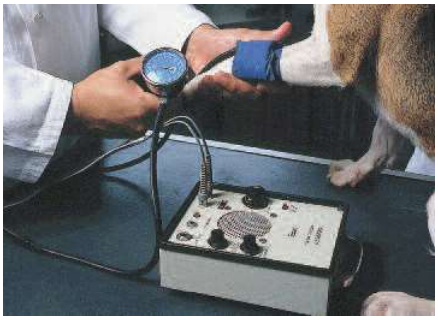


The Doppler technique and oscillometry are very common methods for detecting hypertension. Doppler is the recommended technique for cats. The oscillometric measurements in dogs can be unreliable due to differences in conformation, obesity or a thick coat (Stepien, 2001). *The animal's adaptation to the environment is critical to the interpretation of arterial pressure measurements, as stress can induce erroneous results. Six to ten measurements are recommended.*

► Neuromuscular consequences

The two major neurologic complications of uremia are uremic encephalopathy and neuropathy. Uremic encephalopathy is a term that reflects diffuse and non specific alterations of the cerebral cortex. The severity and progression of the neurological signs is generally correlated with the magnitude and progression of the azotemia. Typical signs include a progressive decline in alertness and awareness, dullness, lethargy, impaired mentation, altered behavior, confusion, stupor, tremors, ataxia, muscular cramps, fatigue, muscle weakness, seizures and coma. The neurological signs are due to the effects of uremic toxins, hyperparathyroidism, hypocalcemia, hypokalemia and hypertension.

► Cardiopulmonary consequences

Cardiopulmonary complications include hypertension, uremic cardiomyopathy, uremic pericarditis, pulmonary edema and uremic pneumonitis. Abnormalities in fluid, electrolyte and acid base balance may contribute to alterations in cardiac contractility and excitability. Azotemia and overhydration play a role in pericarditis, uremic cardiomyopathy and pulmonary edema. Hypertension arises secondary to a combination of activation of the renin-angiotensin aldosterone system, sodium retention, plasma volume expansion, activation of the sympathetic nervous system, decreased activity of vasodilatory substances, increased cardiac output, increased total peripheral vascular resistance and secondary hyperparathyroidism. Systemic hypertension predominately targets the kidneys (glomerulosclerosis), heart (left ventricular hypertrophy, myocardial ischemia), eyes (retinal detachment, hyphema, retinal hemorrhage) and brain (hypertensive encephalopathy, dementia, cerebrovascular hemorrhage). Uremic pneumonitis refers to the formation of a high protein pulmonary edema which is presumably a consequence of uremic toxins damaging alveoli and increasing capillary permeability.

► Ocular consequences

Common manifestations of advanced uremia include scleral and conjunctival injection and ocular pathology secondary to systemic hypertension. Opthalmoscopic findings include reduced pupillary light reflexes, papilledema, retinal arterial tortuosity, retinal hemorrhage, retinal detachment, hyphema, anterior uveitis and glaucoma. Ischemia and retinal degeneration result from sustained retinal arteriolar vasoconstriction which is an attempt to auto-regulate local blood flow in the face of sustained chronic hypertension.

► Metabolic and endocrine consequences

The kidney is responsible for the degradation of many peptide hormones and loss of this catabolic function can result in metabolic derangements caused by hormone excess. Deranged insulin metabolism may also contribute to hyperlipidemia. Other hormonal alterations include increased concentrations of gastrin, glucagon, growth hormone, prolactin and luteinizing hormone. Serum T4 concentrations are low and there is impairment in the conversion of T4 to T3 (euthyroid sick syndrome).

► Fluid, electrolyte and acid-base consequences

Metabolic acidosis is a frequent finding in renal disease and results primarily from the inability of the kidney to excrete hydrogen ions and regenerate bicarbonate. Chronic acidosis causes progressive bone demineralization, urinary calcium loss, hypokalemia and increases skeletal muscle protein catabolism which exacerbates azotemia.

Hyperphosphatemia is one of the most common regulatory derangements of CRF that arises secondary to reduced glomerular filtration of phosphorus. Hyperphosphatemia contributes to renal secondary hyperparathyroidism (see below), reduced calcitriol levels, soft tissue calcification, renal

osteodystrophy and hypocalcemia. Soft tissue mineralization develops as the calcium x phosphate product exceeds 60 (concentrations are expressed in mg/dL).The most commonly targeted organs include the gastric mucosa, bronchial walls, myocardium, endocardium, renal interstitium, glomeruli, lungs, and intercostal muscles. Renal mineralization will promote interstitial inflammation, fibrosis and progression of renal failure.

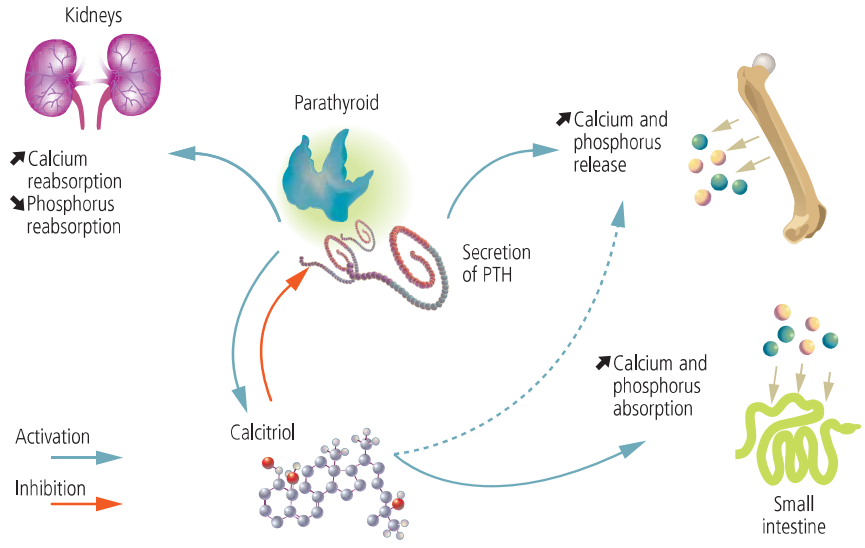
Hypokalemia is a common abnormality associated with chronic renal failure. The mechanism is unclear and includes excessive urinary potassium loss, inadequate dietary potassium intake, and acidifying diets. Hypokalemia causes generalized muscle weakness and pain which may present as cervical ventroflexion and a stiff, stilted gait. Hypokalemia also impairs protein synthesis, promotes weight loss, a poor hair coat and contributes to polyuria by decreasing the renal responsiveness to ADH. Chronic potassium depletion may indeed impair renal function by inducing a reversible, functional decline in GFR in addition to promoting renal injury by enhancing ammoniagenesis.

► Renal secondary hyperparathyroidism

Renal secondary hyperparathyroidism is a clinical syndrome that is characterized by increased secretion of parathyroid hormone (PTH). PTH secretion is stimulated by hypocalcemia and decreased plasma calcitriol concentrations. Hypocalcemia is a mass action (i.e. calcium x phosphate remains constant) consequence of renal retention of phosphate.

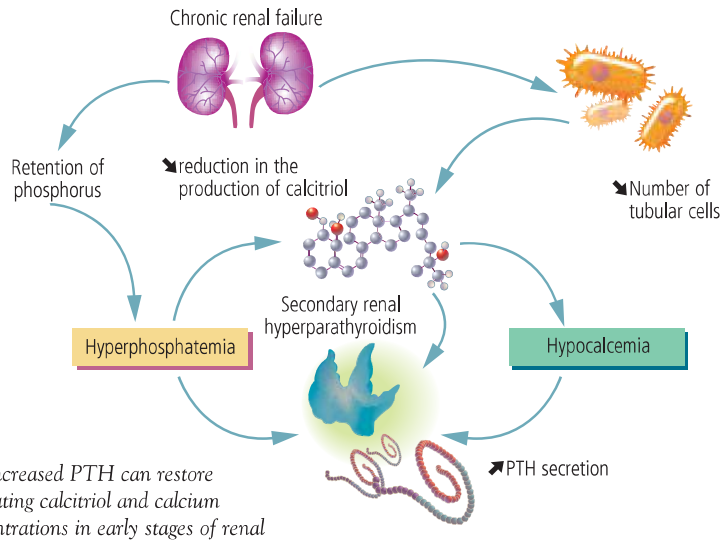
Calcitriol production is regulated at the level of the 1-α-hydroxylase enzyme in the kidney. Phosphate in excess and loss of functional renal mass result in a decrease in 1-α-hydroxylase activity and reduces the conversion of 25-dihydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 (calcitriol). Calcitriol deficiency reduces the intestinal absorption of calcium, reduces the release of calcium and phosphate from bone, reduces renal reabsorption of calcium and phosphate and increases the synthesis and release of PTH (**Figures 6A and 6B**).

FIGURE 6A - INFLUENCE OF PTH ON THE METABOLISM OF CALCIUM AND OF PHOSPHORUS



This diagram emphasizes the role of calcitriol deficiency (due predominantly to phosphorus inhibition of calcitriol synthesis and to the loss of renal functional mass) in initiating and perpetuating excess levels of parathyroid hormone (PTH).

FIGURE 6B - MECHANISM OF DEVELOPMENT OF RENAL SECONDARY HYPERTHYROIDISM IN CRF



The increased PTH can restore circulating calcitriol and calcium concentrations in early stages of renal failure when enough proximal tubular cells remain to synthesize calcitriol.

Initially the increased PTH concentration activates the remaining 1-alpha hydroxylase enzyme with a compensatory increased in calcitriol concentrations. However, with disease progression stimulation of 1-α-hydroxylase becomes ineffectual and calcitriol concentrations remain low. Complications of renal secondary hyperparathyroidism include osteodystrophy, soft tissue calcification, skeletal decalcification, cystic bone lesions, bone pain and growth retardation. Osteodystrophy most commonly occurs in immature patients and is recognized by demineralization of the bones. The teeth become movable and the jaw can be bent or twisted without fracturing (rubber jaw). Facial distortion may occur secondary to connective tissue proliferation. PTH has also been implicated as a uremic toxin and may contribute to the progression of renal failure.

► Hematologic consequences

The hydration state is evaluated by clinical examination, the measurement of hematocrit and total plasma proteins.

Normocytic normochromic non-regenerative anemia is the most common abnormality in uremia. The pathogenesis is multifactorial and includes inadequate production of erythropoietin by the diseased kidneys, reduced life span of red cells, nutritional deficiencies, uremic toxin induced inhibition of erythropoiesis and blood loss with consequent iron deficiency. Anemia will contribute to the clinical signs of lethargy and inappetance. Neutrophil function and cell mediated immunity is impaired in uremia, predisposing the uremic patient to infection. The specific causes of renal failure associated immunocompromise is not completely understood, although malnutrition, uremic toxins, PTH and vitamin D concentrations may be involved.

► Hemostatic consequences

Uremia is characterized by abnormal hemostasis manifested as petechiae, ecchymoses, bruising, bleeding from gum margins or venipuncture sites, epistaxis and gastrointestinal bleeding. The major hemostatic abnormality is a qualitative defect in platelet function which is manifest by prolongation of the bleeding time (indirectly allows evaluation of vascular contractility, platelet numbers, platelet function, and factor VIII complex function).

4 - Clinical presentation

The onset and spectrum of clinical and pathological events occurring in patients with CRF will vary depending on the nature, severity, duration and rate of progression of the renal disease in addition to the presence or absence of coexisting disease. Historical findings include anorexia, depression, weakness, lethargy, weight loss, halitosis, nausea, vomiting, diarrhea, melena, polyuria and polydipsia. Pale mucous membranes, dehydration, hypothermia, stomatitis, oral ulceration, dull dry hair coat and poor body condition may be noted on physical examination. Abdominal palpation reveals small irregular kidneys. Congenital and familial causes of CRF should be suspected on the basis of breed, family history, and age of onset of the renal disease **(Table 1)**. Some patients will present with polydipsia/polyuria as the only historical sign, while other patients may be recognized by isothenuria noted on routine geriatric or pre-anesthetic laboratory screening.

5 - Diagnostic evaluation

A thorough initial evaluation including complete blood count (CBC), biochemical profile, urine analysis, urine culture and blood pressure measurement is indicated to plan the appropriate conservative management. Abdominal radiographs and or abdominal ultrasound will complement the initial laboratory data base.

Laboratory findings consistent with renal failure include azotemia (increase in BUN, creatinine), hyperphosphatemia, mild to severe metabolic acidosis, hypo or hyperkalemia, hypo or hypercalcemia, anemia, hyperlipidemia, bleeding tendencies, isothenuria, proteinuria and hypertension **(Table 4)**. These biological signs are not necessarily present in a single dog.

TABLE 4 - LABORATORY FINDINGS IN CRF

- Azotemia
- Abnormal urine specific gravity
- Hyperphosphatemia
- Non-regenerative anemia (normochromic, normocytic)
- Hypokalemia
- Hypocalcemia (sometimes hypercalcemia)
- Hyperamylasemia
- Hyperlipasemia

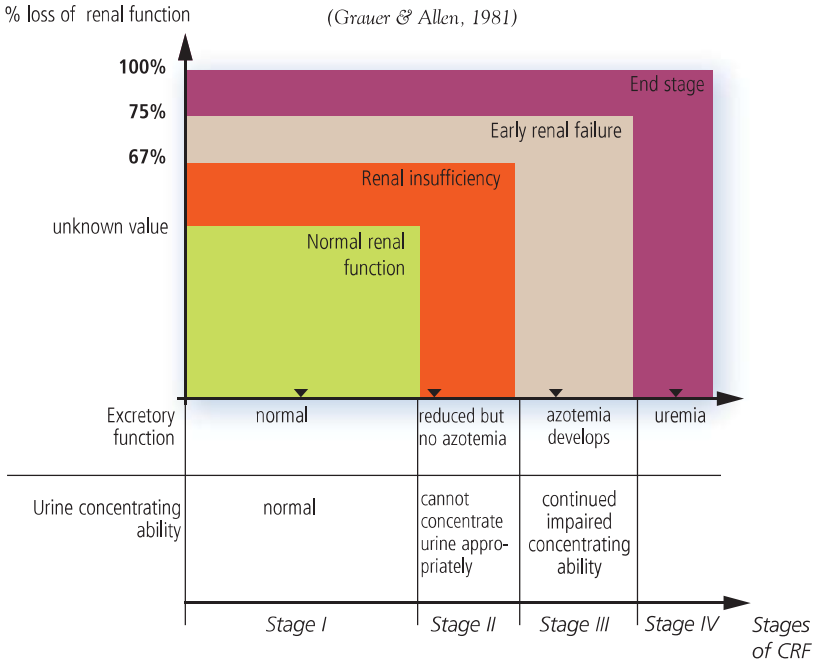
► Azotemia

The identification of azotemia requires delineation of pre-renal azotemia, pre-renal azotemia complicating chronic renal failure, acute renal failure, acute renal failure complicating chronic renal failure, post renal azotemia and post renal azotemia complicating chronic renal failure from uncomplicated chronic end-stage renal disease. Each of these disparate azotemic conditions may appear clinically quite similar, but rapid identification is required to formulate a therapeutic plan and guide prognosis **(Figure 7)**.

► Proteinuria

Dogs with CRF may or may not have proteinuria. Urine strip or stick tests used to screen for proteinuria detect mainly albumin (lower limit of detection ~50 mg/L) and not globulin. False positive results can occur if samples are very alkaline or contaminated by quaternary ammonium compounds.

FIGURE 7 - CONSEQUENCES OF RENAL DISEASE AND ITS PROGRESSION TO UREMIC SYNDROME
(Grauer & Allen, 1981)



The diagnosis of chronic renal failure is relatively straightforward. It is, however, more difficult to identify early renal disease prior to the development of clinical signs or laboratory abnormalities.

The semi quantitative results from dipstick tests must also be compared with the urinary concentration.

2+ proteinuria represents a more substantial protein loss if urine is dilute (USG 1.010) than if it is 4 times more concentrated (USG 1.040) **(Figure 8)**. The same principle lies behind use of urine protein to creatinine ratio (UPCR) to evaluate severity of proteinuria.

Sustained, severe proteinuria (typically 3 or 4+) strongly suggests glomerular damage, but only if hematuria and urinogenital inflammation are excluded by the absence of erythrocytes and leukocytes in urine sediment. If glomerular protein loss is suspected, proteinuria should be confirmed using the semiquantitative sulphosalicylic acid turbidometric test, which is simple enough to do in the practice laboratory, or urine protein should be quantified by a more precise method in an external laboratory. Not all proteinurias are pathological and pathological proteinurias can arise from non-renal lesions, so caution is advisable before attributing proteinuria to renal disease.

► Microalbuminuria

Microalbuminuria (i.e. urine albumin concentration < 1 mg/dL) has been suggested to be an early indicator of renal disease. However, recent studies have suggested that 56% of dogs that are microalbuminuric have systemic inflammatory, infectious or neoplastic disease. Therefore, the specificity of microalbuminuria for the diagnosis of early renal disease is not fully known.

FIGURE 8 - INTERPRETATION OF PROTEINURIA BASED ON URINARY DENSITY

Sample	1	2
USG	1.040	1.010
Proteinuria	++	++
Conclusion	uncertain	meaningful

If urine specific gravity is low, proteinuria is more significant.

► Glomerular filtration rate

The best indicator of renal function is the glomerular filtration rate (GFR). GFR is assessed by calculating the clearance of a solute by the kidney. Urinary inulin clearance is considered the gold standard reference method for measuring GFR. Unfortunately the technique of inulin clearance is labor intensive and best utilized in a research setting. The plasma exogenous creatinine clearance test (PECCT) involves a single injection of creatinine with timed plasma samples to detect plasma clearance of creatinine **(Figure 9)**. The test has been validated in the dog and provides a clinically useful tool to assess renal function *(Watson & al, 2002)*.

6 - Treatment

Tailored supportive medical therapy has been the mainstay of management for chronic renal failure for decades. The goals of medical management are to:
(1) reduce the renal work load
(2) alleviate the clinical signs and biological consequences of the uremic intoxications
(3) minimize disturbances in fluid, electrolyte, vitamin, mineral and acid base balance
(4) slow progression of the disease.

Therapy should not necessarily be expected to reverse or eliminate the renal lesions responsible for the CRF. However, when CRF progresses due to an evolving disease (pyelonephritis, chronic urinary obstruction, nephrolithiasis, renal lymphoma, some immune-mediated diseases), rapid identification and appropriate treatment of the disorder may halt or slow progression of the renal disease.

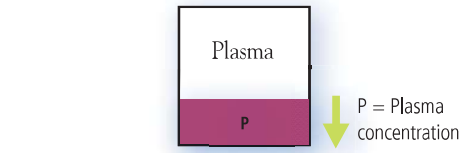
Chronic renal failure is progressive and dynamic, hence, serial clinical and laboratory assessment of the patient and modification of the therapy in response to changes in the patient's condition

is integral to successful therapy. Select therapeutic agents used in the management of chronic renal failure are listed in **Table 5**.

Many renal failure patients are exquisitely sensitive to the gastrointestinal side-effects of prescribed drugs. The clinician also needs to consider the potential adverse effects of "poly pharmacy" and drug interactions. Furthermore, many medications undergo renal excretion and the dosages will need to be modified to account for delayed clearance and the longer half life the drug. Ideally dosage adjustments should be made according to changes in drug clearance which may be estimated by measuring creatinine clearance. The drug dose is then adjusted according to the percent reduction in creatinine clearance (i.e. the ratio of the patients' creatinine clearance to normal creatinine clearance). For example if the normal dose is 10 mg/kg q 8 hrs and the creatinine clearance is 25% of normal, the dose should be altered to 2.5 mg/kg q 8 hrs or 10 mg/kg q 32 hours. For the owner's compliance, decreasing the dose is often better accepted than stretching the administration interval (although it might be necessary for specific drugs, i.e. concentration-dependent antibiotics). The dosage regimen should be adjusted for drugs mainly excreted (>80%) unchanged by the kidney, and for drugs which are not totally excreted by the kidney and have a low therapeutic index. e.g.:

- Gentamicin: renal excretion and low therapeutic index; prescription not recommended but sometimes necessary in case of multiresistant infections
- Carboplatin: antineoplastic agent with a very low therapeutic index and renal excretion.

FIGURE 9 - PRINCIPLE OF PLASMA CLEARANCE

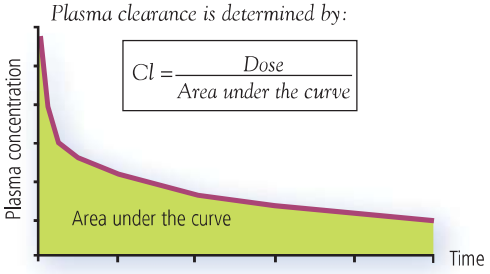


Clearance (Cl) reflects the amount of the substance (X) eliminated per time unit (t) related to the plasma concentration (P)

$$Cl = \frac{dX/dt}{P}$$

Plasma clearance is determined by:

$$Cl = \frac{Dose}{Area\ under\ the\ curve}$$



Although the relationship between serum creatinine concentration and creatinine clearance is not linear, creatinine clearance evolution can be estimated by the modifications of the serum creatinine concentration measured in standardized conditions for stages I and II of CRF.

► Anemia

Treatment of anemia encompasses administration of androgens, blood transfusions or erythropoietin replacement therapy with recombinant human erythropoietin. In addition, every attempt should be made to minimize blood loss by venipuncture, gastrointestinal ulcerations, gastrointestinal parasites and uremic bleeding. Androgen therapy is not particularly effective in increasing the hematocrit, although improvements in lean body mass and attitude have been reported *(Cowan et al, 1997)*. Blood transfusions will temporarily correct the anemia and are useful when rapid correction of the anemia is required prior to anesthesia or surgery. Repeated transfusions have been used to support the anemia of chronic renal failure but they are not recommended due to the increased risk of transfusion reaction.

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Recommendations regarding dietary therapy and other components of conservative medical management need to be individualized to patient needs based on clinical and laboratory findings.

Effective erythropoiesis is readily obtained by the administration of recombinant human erythropoietin *(Cowgill et al, 1995; 1998)*. A dose dependent response in hematocrit can be seen within the first week of therapy, however 2 to 8 weeks of therapy is generally required to normalize the hematocrit. Erythropoietin therapy is initiated at 100 U/kg subcutaneously three times weekly with weekly monitoring of the hematocrit. Once the hematocrit is 35-40%, the dosing interval is decreased to twice weekly therapy. The lowest dose/frequency that maintains the hematocrit in the normal range should be identified by monitoring the hematocrit. Side effects of erythropoietin therapy include polycythemia, vomiting, seizures, pain at the injection site, fever and hypertension.

TABLE 5 - THERAPEUTIC AGENTS USED IN THE MANAGEMENT OF CHRONIC RENAL FAILURE*

Uremic Complication		Conventional Dose
Gastrointestinal	Chlorhexidine (solution 0.1-0.2%) Cimetidine† Ranitidine† Famotidine† Omeprazole Sucralfate† Misoprostol Metoclopramide† Chlorpromazine Acepromazine Cisapride	Oral rinse q6-8h 5-10 mg/kg PO, IM, IV q 6-8h 0.5-2.0 mg/kg PO, IV q8-12h 0.5-1.0 mg/kg PO, IM, IV q12-24h 0.5-1.0 mg/kg PO q24h 0.5-1 g PO q6-8h 1-5 mg/kg PO q6-12h 0.1-0.5 mg/kg PO, IM, SC q6-8h 0.2-0.5 mg/kg PO, IM, SC q6-8h 0.01-0.05 mg/kg PO IM, SC q8-12h 0.1-0.5 mg/kg PO q8-12h
Anemia	Erythropoietin Ferrous sulfate Stanozolol	100 U/kg SC 1-3 times per week 100-300 mg/day PO 1-4 mg PO q4h
Metabolic Acidosis	Sodium Bicarbonate Potassium Citrate	8-12 mg/kg PO q8-12h 40-60 mg/kg PO q8-12h
Hypokalemia	Potassium Gluconate Potassium Citrate	0.5 mEq/kg PO q12-24h 40-60 mg/kg PO q8-12h
Hyperphosphatemia	Aluminium hydroxide/carbonate/oxide Calcium acetate Calcium carbonate	30-90 mg/kg PO q12-24h 60-90 mg/kg PO q12-24h 90-150 mg/kg PO q12-24h
Renal Osteodystrophy	Calcitriol	1.5-6.0 ng/kg PO q24h
Hypertension	Amlodipine Benazepril Enalapril Imidapril Ramipril Propranolol It is recommended that treatment with antihypertensive agents be commenced with the lowest dose and increased gradually	0.05-0.3 mg/kg PO q12-24 h 0.25-0.50 mg/kg PO q 24 h 0.5 mg/kg PO q12-24 h 0.25 mg/kg PO q24 h 0.125-0.250 mg/kg PO q24 h 0.1-1 mg/kg PO q8-12 h
Proteinuria	Angiotensin conversion enzyme inhibitors (Benazepril, Enalapril, Imidapril and Ramipril)	Regimen: see Hypertension

** Most of these drugs have not been approved for use in the dog.*
† Agent undergoes renal excretion and the dosage must be adjusted accordingly to prevent toxicity.

Some dogs will develop erythropoietin antibodies that effectively neutralize endogenous and exogenous erythropoietin. These patients are identified by either refractory anemia or the development of anemia weeks to months following institution of therapy. Diagnosis requires elimination of other causes of anemia and bone marrow assessment of myeloid to erythroid ratios (M:E ratio > 10). Treatment requires cessation of recombinant erythropoietin therapy. After therapy is stopped, the antibody concentrations will decline and the pretreatment levels of endogenous erythropoietin and hematocrit will be obtained. Blood transfusions may be required until the hematocrit stabilizes. The future availability of canine recombinant erythropoietin will eliminate the development of antibodies to human recombinant erythropoietin *(Randolph et al, 2004)*.

A risk-benefit assessment is necessary prior to institution of human recombinant erythropoietin. Erythropoietin therapy is generally recommended when the packed cell volume is less than 25%. At this stage, the benefits of improved clinical status with increases in appetite, body weight, energy level and sociability appear to out weigh the risks of antibody formation. Iron deficiency secondary to gastrointestinal blood loss generally accompanies CRF. Iron status can be assessed by serum iron, transferrin, ferritin, or total iron binding capacity (TIBC). Oral supplementation with iron sulfate (100 to 300 mg/day) is recommended, particularly in patients starting erythropoietin replacement therapy. Intramuscular iron dextrans can be used, however, the risk of iron overload is increased. Side effects of iron therapy include gastrointestinal disturbances (diarrhea).

Two to eight weeks are generally needed to normalize the hematocrit during erythropoietin replacement therapy.

► Acidosis

Alkalinizing agents (potassium citrate, sodium bicarbonate, calcium carbonate) should be initiated when the TCO_2 or bicarbonate concentration is less than 18 mmol/L. Alkalinization therapy will improve the clinical signs of anorexia, lethargy, nausea, vomiting, muscle weakness and weight loss in addition to preventing the catabolic effects of metabolic acidosis on protein metabolism.

Sodium bicarbonate is the most commonly utilized alkalinizing agent but it will contribute to the sodium load of the patient and may need to be avoided in patients with hypertension or cardiac insufficiency. Calcium carbonate should be used with caution in hyperphosphatemic patients as the increased dietary calcium may precipitate soft tissue mineralization. Potassium citrate provides the additional advantage of supplying potassium and may be attractive for patients with both hypokalemia and metabolic acidosis. The dose of alkalinizing agent needs to be individualized for each patient and requires routine monitoring of acid base status.

► Fluid balance

Compensatory polydipsia balances excessive fluid loss associated with polyuria, however, some patients will fail to consume sufficient water to prevent volume depletion. In these cases, cautious fluid supplementation should be used to prevent dehydration and attendant vascular depletion. Maintenance fluids (eg plasmalyte 56, plasmalyte M, Normosol M) can be administered subcutaneously. Chronic administration of lactated ringers solution or sodium chloride will cause hypernatremia due to failure to provide sufficient free water. Conversely, 5% dextrose in water is hypotonic and should not be administered subcutaneously.

► Hypokalemia

Potassium supplementation is indicated when the serum potassium concentration is less than 4 mmol/L and may be achieved by oral potassium gluconate or potassium citrate supplementation. Muscle weakness typically resolves within five days of institution of therapy. Side effects include gastrointestinal irritation, ulceration, nausea and vomiting. Potassium dosage should be adjusted by monitoring the serum potassium concentration and response to supplementation.

► Antihypertensive therapy

Antihypertensive therapy is indicated upon the repeatable demonstration of systemic hypertension. The clinical diagnosis of hypertension should never be made on the basis of a single blood pressure measurement.

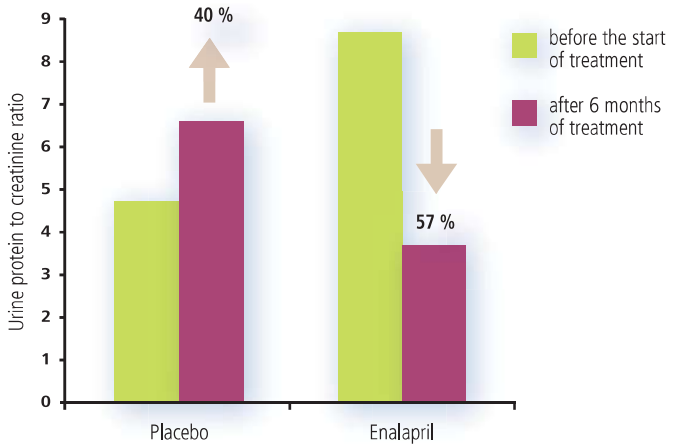
IRIS *(http://www.iris-kidney.com/)* considers that an animal with CRF is hypertensive when its systolic blood pressure exceeds 180 mm Hg. If the systolic blood pressure is between 150 and 179 mm Hg, and if there is some extrarenal evidence of hypertension (eg. retinopathy, left ventricular hypertrophy), the animal is also considered hypertensive. Otherwise, the case is borderline and re-evaluation of blood pressure is recommended within 2 months.

The goal of antihypertensive therapy is to lower the blood pressure to the normal range. The initial selection of antihypertensive agent will be guided by the presence or absence of clinical signs of hypertension, i.e. signs of retinal detachment and hemorrhage dictate a more aggressive therapeutic approach to lower systemic blood pressure and restore vision in a timely fashion. Repeated blood pressure determinations will be required to modify and guide a step wide selection of antihypertensive drugs.

Antihypertensive drugs include diuretics, adrenergic antagonists (propanolol), ACE-inhibitors, calcium channel blockers (amlodipine), and vasodilators. Selection of the appropriate therapeutic agent should be made on the basis of appropriate hypertensive control, expense, and side-effects. The most commonly recommanded treatment relies on the association between ACE-inhibitors and amlodipine. With ACE-inhibitors alone, blood pressure can be decreased by 30 mm Hg.

The blood pressure should be rechecked within 2 weeks following institution of therapy. If there has been no response consider:
(1) increasing the dose of the current drug
(2) change to a different class of drug
(3) adding an additional drug to the therapeutic regime.

FIGURE 10 - MEAN VALUE OF URINE PROTEIN TO CREATININE RATIO IN DOGS TREATED WITH PLACEBO OR ENALAPRIL
(Grauer et al, 2000)



Proteinuria increased in dogs receiving the placebo, whereas it decreased in dogs receiving enalapril.

Long term monitoring of blood pressure is required as frequent dosage adjustments may be required and some patients will become refractory to the initial therapy necessitating therapeutic modification.

ACE inhibitors have been used in normotensive dogs with glomerular disease. Enalapril has been shown to significantly reduce proteinuria and improve the clinical signs in dogs with naturally occurring glomerulonephritis **(Figure 10)** *(Grauer & al, 2000)*. Proteinuria is not only a biological sign of renal injury, but also an aggravation factor of CRF. Reducing proteinuria is hence a therapeutic goal. Only the ACE inhibitors have a demonstrable antiproteinuria effect in dogs. Ace inhibitors can also slow down the progression of CRF *(Lefebre & Toutain, 2004)*.

► Hyperphosphatemia

Minimizing hyperphosphatemia will limit renal secondary hyperparathyroidism, renal osteodystrophy, soft tissue calcification and the progression of renal failure. The restriction of dietary intake and oral administration of intestinal phosphorus binding agents **(Table 6)** normalizes serum phosphate concentrations. Intestinal phosphate binding agents combine with phosphate contained in dietary and digestive secretions to form insoluble complexes that are excreted in the feces. They should be mixed with the food prior to feeding to ensure maximal phosphate binding effectiveness.

TABLE 6 - SUMMARY OF PHOSPHATE BINDING AGENTS CLASSIFICATION

Products containing aluminum: - aluminum hydroxide - aluminum carbonate - aluminum oxide	Prolonged use of products containing aluminum can predispose to aluminum toxicity (although not reported in dogs)
Products based on calcium: - acetate - carbonate - citrate*	Products based on calcium may favor hypercalcemia and are contra-indicated in dogs with serum concentrations in excess of the reference range
Sevelamer	Polymer used in humans as an intestinal phosphate binding agent. It is not absorbed and does not predispose to hypercalcemia. Nevertheless, there are no data on its use in dogs

* *Calcium citrate increases aluminum absorption in the intestine and must not be used in conjunction with phosphate binding agents containing aluminum.*

► Calcitriol replacement therapy

Calcitriol replacement therapy can limit renal secondary hyperparathyroidism. However supplementation is required for life *(Nagode et al, 1996)*. Therapy mandates serial measurement of serum calcium and phosphorus levels to avoid hypercalcemia and soft tissue mineralization. The risk of hypercalcemia is heightened by the concurrent administration of calcium based intestinal phosphate binding agents. Calcitriol should not be given with meals because it enhances intestinal calcium and phosphate absorption. In addition, the serum phosphorus concentration must be within the normal range prior to initiating therapy to minimize the risk of soft tissue calcification. The serum PTH concentration should return to normal or almost normal within 1 to 2 weeks of initiating therapy.

A recent study *(Gerber et al, 2003)* indicated that calcitriol concentration was within reference range for most dogs with renal failure. These results suggest that calcitriol replacement would not be required in such patients.

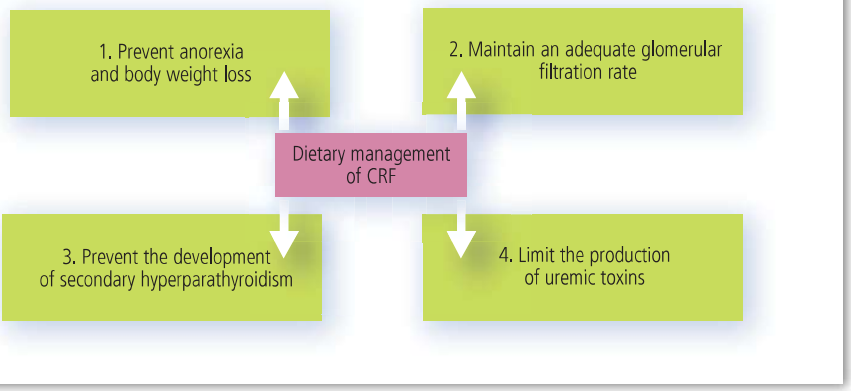
► Gastrointestinal disorders

Antiemetics such as metoclopramide or phenothiazine derivatives can be used to suppress central vomiting centers. Histamine receptor blocking drugs (cimetidine, ranitidine, famotidine) or proton pump blockers (omeprazole) in combination with gastrointestinal protectorant agents such as sucralfate or misoprostol may be used to prevent gastrointestinal ulceration.

7 - Nutritional management

Dietary therapy has remained the cornerstone of management of chronic renal failure for decades. The goals of dietary modification are to (1) meet the patient's nutrient and energy requirements, (2) alleviate clinical signs and consequences of the uremic intoxication, (3) minimize disturbances in fluid, electrolyte, vitamin, mineral and acid base balance, and (4) slow progression of the renal failure **(Figure 11)**.

FIGURE 11 - DIETARY MANAGEMENT OF CRF: 4 MAIN GOALS



► Energy

Sufficient energy needs to be provided to prevent endogenous protein catabolism which will result in malnutrition and exacerbation of azotemia. Although the energy requirements of dogs with chronic renal failure are unknown, they are presumed to be similar to healthy dogs. Dogs should be fed 132 kcal x body weight $(kg)^{0.75}$ per day. Determination of caloric requirements may vary by as much as 25%. Hence energy intake should be individualized to the patient needs based on serial determinations of body weight and body condition score. Carbohydrate and fat provide the non-protein sources of energy in the diet. Diets designed for the management of chronic renal failure are typically formulated with a high fat content because fat provides approximately twice the energy per gram of carbohydrate. Therefore fat increases the energy density of the diet which allows the patient to obtain its nutritional requirements from a smaller volume of food. A smaller volume of food minimizes gastric distention, which reduces the likelihood of nausea and vomiting.

► Protein

Azotemia and uremia are due to the accumulation of protein metabolites derived from excessive dietary protein and degradation of endogenous protein. High protein intake exacerbates the azotemia and morbidity of chronic renal failure *(Polzin et al, 1983)*, while protein malnutrition is strongly correlated with morbidity and mortality.

The rationale for formulating a diet that contains a reduced quantity of high quality protein is based on the premise that controlled reduction of non essential amino-acids results in decreased production of nitrogenous wastes with consequent amelioration or elimination of clinical signs, even though renal function remain essentially unchanged. Indeed, studies have shown that modifying dietary protein intake can reduce blood urea nitrogen and provide clinical benefits to dogs with chronic renal failure *(Polzin et al, 1983; Finco et al, 1985; Polzin & Osborne, 1988; Polzin et al, 1983; Leibetseder & Neufeld, 1991; Jacob et al, 2002)*. Modified protein diets also moderate the magnitude of polyuria and polydipsia because less solute is delivered to the kidneys in the form of nitrogenous waste products. The magnitude of anemia may also be reduced, as nitrogenous waste

products are incriminated in hemolysis, shortened red blood cell survival and blood loss by gastrointestinal ulcerations and impaired platelet function.

Protein restriction has been demonstrated to slow the rate of progression of renal disease in rats and people. It is less certain if protein restriction alters progression of renal failure in dogs *(Finco et al, 1985; 1992a; 1992b; 1994; 1999; Robertson et al, 1986; Polzin et al, 1988)*. Most studies have been performed using the remnant kidney model, which does not necessarily reflect naturally occurring disease. In addition, some of the studies have been confounded by alterations in energy and/or phosphate intake in addition to protein restriction. Brown et al reported that protein restriction did not alleviate glomerular hypertension, hypertrophy, hyperfiltration or progression in dogs with induced renal failure *(Brown & al, 1990; 1991a)*. Although protein moderation has been clearly demonstrated to improve the clinical status of the uremic patient, it is less clear what effect protein moderation has on progression of renal disease.

The goal of dietary protein restriction is to reduce the plasma urea as much as possible whilst avoiding protein malnutrition. Although urea is not a major uremic toxin it is regarded as an index for all nitrogenous wastes, hence therapies designed to reduce urea concentration are presumed to reduce other uremic toxins and usually correlate with clinical improvement (*Leibetseder & Neufeld, 1991; Hansen et al, 1992; Jacob et al, 2002)*. Urea concentration may be influenced by dietary protein intake, dehydration, catabolism, gastrointestinal bleeding, sepsis, and drug administration (glucocorticoids, tetracyclines). Most pets have minimal clinical signs when the urea is less than 28 mmol/L or 1.7 g/L (BUN < 80 mg/dL) **(Table 7)**.

TABLE 7 - CONVERSION TABLE BETWEEN BUN AND PLASMA UREA

BUN* (mg/dL)	10	20	30	40	50	60	80	100	120	140
Plasma urea (mmol/L)	3.6	7.1	10.7	14.2	17.8	21.4	28.5	35.6	42.7	65.1
Plasma urea (g/L)	0.2	0.4	0.6	0.8	1.0	1.2	1.7	2.1	2.5	3.9

**BUN is largely used in the US, while urea is generally used in Europe.*
BUN x 0.356 = plasma urea (mmol/L) and 1 mmol urea = 60 mg urea.

The minimal dietary protein requirements for dogs with chronic renal failure are not known, but are presumed to be similar to the minimal protein requirements of normal dogs, i.e. 1.33 g/kg/day (2.62 g/kg $BW^{0.75}$ or 20 g/1000 kcal ME according to NRC 2006). However, this degree of restriction is necessary only in animals with profound renal failure, and more liberal prescriptions can be fed to dogs with greater renal function. Every patient symptomatic for chronic renal failure should benefit from a protein restricted diet. Most renal dry diets contain between 12 and 18% proteins, i.e. 30-45 g/1000 kcal).

The dietary protein should be adjusted to minimize excesses in azotemia while simultaneously avoiding excessive restriction of dietary protein because of the risk of protein malnutrition. If evidence of protein malnutrition occurs (hypoalbuminemia, anemia, weight loss or loss of body tissue mass), dietary protein should be gradually increased until these abnormalities are corrected. High quality protein sources must be used in the formulation of restricted protein diets to minimize the risks of essential amino acid deficiency.

Owner dietary compliance can be checked by calculating the BUN:Creatinine ratio (BUN and creatinine are expressed in mg/dl). On a normal diet it will be around 25 whereas on a restricted protein diet it will be around 10. A BUN:Creatinine ratio greater than 30 is usually associated with gastrointestinal bleeding, dehydration or sepsis.

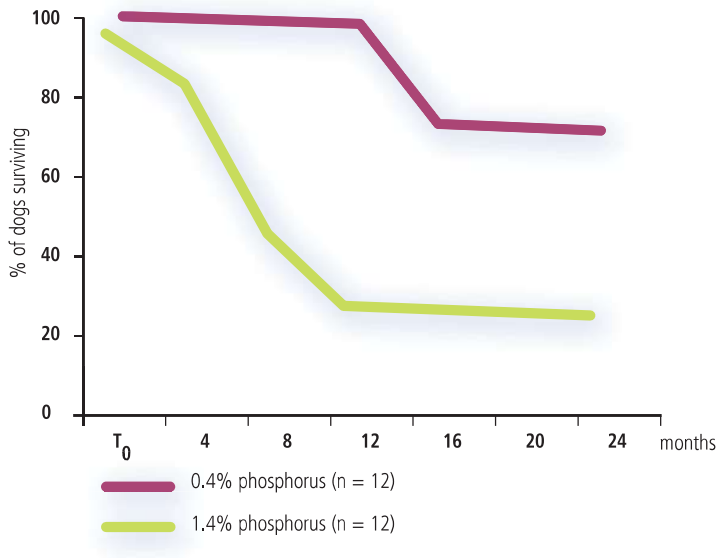
► Vitamins, minerals and electrolytes

> Phosphorus

Phosphate retention and hyperphosphatemia occur early in the course of renal disease and play a primary role in the genesis and progression of renal secondary hyperparathyroidism, renal osteodystrophy, relative or absolute deficiency of 1,25-dihydroxyvitamin D, and soft tissue calcification. By minimizing hyperphosphatemia, secondary hyperparathyroidism and its sequellae can be prevented. In addition, dietary phosphorus restriction has been shown to slow the progression of renal failure in dogs *(Brown et al, 1991b)*.

FIGURE 12 - INFLUENCE OF DIETARY PHOSPHORUS RESTRICTION ON LIFE EXPECTANCY OF DOGS WITH CHRONIC RENAL FAILURE

(Finco et al, 1992a)



After 2 years, 75% of the dogs receiving the low phosphorus diet were still alive, but only 33% in the group receiving the high-phosphorus diet were alive.

In one study of dogs with surgically induced reduced renal function, dogs fed a low phosphorus diet (0.44% DM) had a 75% survival versus a 33% survival in dogs fed a high phosphorus diet (1.44% DM) *(Finco et al, 1991b)*. Renal function also deteriorated more rapidly in the high phosphorus group **(Figure 12)**.

The mechanism of how phosphate restriction slows progression of renal disease is not fully understood. It may be related to decreased phosphate retention, decreased soft tissue mineralization or prevention of secondary hyperparathyroidism.

The goal of therapy is to normalize serum phosphate concentration. This may be achieved by limiting dietary phosphate intake. If normophosphatemia can not been accomplished within 2-4 weeks of implementing dietary phosphate restriction, intestinal phosphate binders should be added to the treatment plan. These agents should be administered with the diet.

> Calcium

Dietary calcium is less important than phosphate in chronic renal failure and hypo, normo, or hypercalcemia may be observed. It has been recommended that the total calcium x phosphorus (expressed in mg/dL) product should not exceed 60. This may promote further soft tissue calcification and lead to progression of renal damage. For example, if the calcium concentration is 12 mg/dL and the phosphate concentration is 8 mg/dL, then the calcium x phosphate product is 12x8 = 96, which exceeds 60. Hence calcium supplementation needs to be individualized and adjusted according to response in terms of measured total blood calcium.

> Sodium

Hypertension is common in dogs with CRF *(Jacob et al, 2003)*. Furthermore, hypertension has been implicated as a factor that contributes to the progression of renal failure. Dogs with naturally occurring chronic renal disease and a systolic blood pressure greater than 180 mmHg were more likely to develop a uremic crisis and to die compared with dogs that have a normal systolic blood pressure *(Jacob et al, 2003)*. Furthermore, the risk of developing a uremic crisis and of dying increased significantly as systolic blood pressure increased.

Sodium restriction has been recommended to alleviate hypertension associated with failure of the kidneys to excrete sodium. However, altering sodium intake from 0.5 to 3.25 g Na/1000 kcal did not influence development of hypertension or affect glomerular filtration rate in dogs with surgically induced renal reduction *(Greco et al, 1994a; 1994b)*. Therefore the ideal dietary sodium concentrations for dogs with chronic renal failure are not yet clearly defined. Current recommendations are normal to mildly restricted sodium diets. The capacity to adjust sodium excretion rapidly in response to changes in intake becomes severely impaired as renal failure progresses. If sodium intake is rapidly reduced, dehydration and volume contraction may occur with the potential of precipitating a renal crisis. Hence, a gradual change from the pet's previous diet to the salt restricted diet is recommended.

When an ACE-inhibitor is prescribed in a dog receiving a low sodium diet, it is recommended to check the arterial pressure and the renal function during the first few days of treatment.

> Potassium

Potassium deficiency has been identified in some dogs with chronic renal failure. Potassium status should be monitored and intake adjusted accordingly with oral potassium gluconate on an individual basis.

> Vitamins

Water-soluble vitamins are excreted in urine and deficiency may develop due to polyuria associated with chronic renal failure. These losses may be a contributing cause of anorexia and replacement of the losses may be beneficial in correcting or preventing anorexia. Commercially available renal failure diets contain additional amounts of water-soluble vitamins and further supplementation is not required.

Renal excretion of vitamin A is reduced in people with chronic renal failure. A recent study reported that dogs with naturally occurring renal disease had higher plasma concentrations of retinol compared to healthy dogs *(Raila et al, 2003)*. Therefore, it appears prudent to avoid supplements containing vitamin A.

► Acid base balance

The kidneys are central to the maintenance of acid base balance. As renal function declines, the capacity to excrete hydrogen ions and reabsorb bicarbonate ions is reduced and metabolic acidosis ensues. Metabolic acidosis increases renal ammoniagenesis which induces tubular inflammation and lesions due to complement activation, contributing to the progression of renal failure.

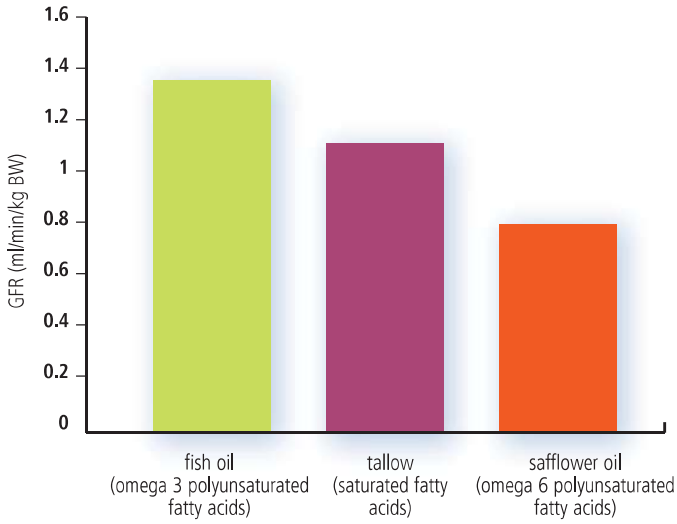
In addition, metabolic acidosis increases catabolism and degradation of skeletal muscle protein, disrupts intracellular metabolism, promotes dissolution of bone mineral exacerbating azotemia, loss of lean body mass and renal osteodystrophy. Dietary protein restriction results in the consumption of reduce quantities of protein-derived acid precursors, however, supplementation with additional alkalinizing agents such as sodium bicarbonate, calcium carbonate or potassium citrate may be required.

► Omega 3 & 6 fatty acids

Long chain ω-3 fatty acids (EPA-DHA) compete with arachidonic acid and alter eicosanoid, thromboxane and leukotriene production *(Bauer et al, 1999)*. Remnant kidney studies in dogs have reported that long chain ω-3 fatty acid supplementation (menhaden fish oil) reduces inflammation, lowers systemic arterial pressure, alters plasma lipid concentrations and preserves renal function **(Figure 13)** *(Brown et al, 1996; 1998a; 1998b; 2000)*. The efficacy of shorter chain ω-3 fatty acids such as those found in linseed oil, are not yet known.

FIGURE 13 - INFLUENCE OF FEEDING DIFFERENT DIETARY FATTY ACIDS OVER 20 MONTHS ON GLOMERULAR FILTRATION RATE IN 3 GROUPS OF DOGS SUFFERING FROM CRF

(Brown et al, 1996)



Compared to a diet consisting of mostly omega 6 fatty acids, a diet with a high fish oil content appears to improve GFR in the long term whilst minimizing the development of glomerulosclerosis

Omega 6 fatty acids (safflower oil) appear to be detrimental in dogs with naturally occurring renal disease by acutely increasing glomerular filtration rate *(Bauer et al 1997)*.

Some commercially available diets have an adjusted ω-6: ω-3 ratio however, rather than focusing on ratios, the absolute concentrations of specific omega-3 fatty acids would be more appropriate. Such studies have not yet been reported.

► Fiber

Fermentable fiber is a recent addition to the nutritional management of CRF. It is hypothesized that the fermentable fiber provides a source of carbohydrate for gastrointestinal bacteria which consequently utilize blood urea as a source of nitrogen for growth. The increase in bacterial cell mass increases fecal nitrogen excretion and has been suggested to decrease the blood urea nitrogen concentration and reduce the need for protein restriction. However, the major concern with this concept is that unlike BUN, the classical uremic toxins (middle-molecules) are too large in molecular size to readily cross membrane barriers. As a consequence, it is highly unlikely that these toxins are reduced by bacterial utilization of ammonia. Furthermore, studies to document these changes have not yet been reported. As a consequence, widespread application of fermentable fiber as a nitrogen trap cannot be recommended at this time.

However, even moderate renal disease alters duodenojejunal motility and decreases colonic transit time in dogs *(Lefebvre et al, 2001)*. Therefore, dietary fiber may be beneficial for improving gastrointestinal health and motility.

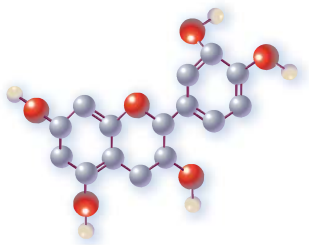
► Antioxidants

Endogenous oxidative damage to proteins, lipids and DNA is thought to play an important role in the progression of renal disease in humans (*Locatelli et al, 2003; Cochrane et al, 2003*).

Nutrients such as **vitamin E, vitamin C, taurine, carotenoids and flavanols** are effective antioxidants that trap free radical species. Humans with chronic renal disease have been shown to have lower concentrations of vitamin E and vitamin C, and high concentrations of markers of lipid peroxidation (*Jackson et al, 1995*). These studies suggest that humans with chronic renal disease have oxidative stress. Studies in rats have suggested that supplementation with vitamin E may modulate tubulointerstitial injury and glomerulosclerosis, suggesting that vitamin E may slow progression of renal damage (*Hahn et al, 1998; 1999*). One study in children with focal segmental glomerulosclerosis reported that vitamin E supplementation decreased proteinuria (*Tahzib et al, 1999*). There have not been any studies evaluating oxidative stress or antioxidant status in dogs with renal disease.

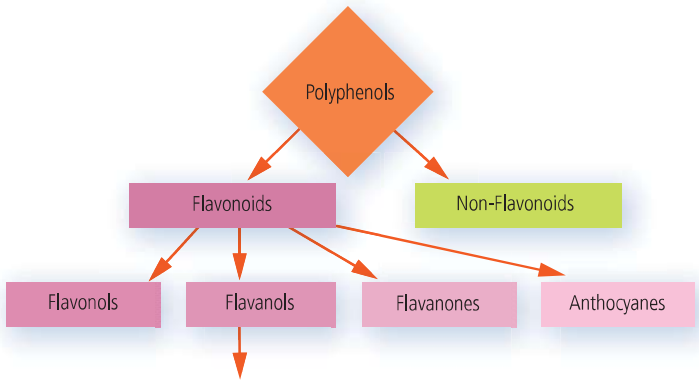
Flavanols, a subclass of flavonoids, are polyphenolic antioxidants which are found in a variety of plants. **(Figure 14)**. Epigallocatechin gallate is recognized as one of the most active flavanols in protection against oxidation **(Figure 15)**. Within plants, flavanols are powerful antioxidants that protect the integrity of the cell membrane and genetic material. Flavanols also chelate metal ions such as iron and copper, which may contribute to their antioxidant activity by preventing redox-active transition metals from catalyzing free radical formation. In addition, flavonols also appear to modulate antioxidant enzyme systems.

FIGURE 14 - CATECHIN MOLECULE



The base structure of flavanols consists of two aromatic rings connected with three carbons to form a six-member heterocyclic ring.

FIGURE 15 - FLAVANOLS WITHIN THE FAMILY OF POLYPHENOLS



Monomers: catechin, epicatechin, epigallocatechin galate
Oligomers: procyanidins
Polymers: tannins

Plants that have high flavanol concentrations include cocoa, grapes, and green tea.

Flavanols have been reported to be beneficial in renal disease. Flavanols stimulate the production of nitric oxide which relaxes the vascular system. Daily administration of flavanols to rats was associated with a significant reduction in both systolic and diastolic blood pressure *(Jouad et al, 2001)*. Flavanols appear to decrease glomerular capillary pressure in rats with chronic renal failure by:
1) stimulating the production of nitric oxide
2) relaxing the smooth muscle fibers
3) inhibiting angiotensin converting enzyme.

8 - Feeding strategy

Dietary therapy is only effective in ameliorating the clinical signs of uremia if it is administered appropriately. Patients with chronic renal failure often have reduced appetites. In addition, an altered sense of taste and smell has been reported in people. These factors can be aggravated by the handicap of reduced dietary intake due to reduced palatability of the modified protein diets for dogs with chronic renal failure.

However, it is not the palatability of the diets per se, but the effect of uremia on the sense of taste and smell and the development of food aversion that contribute to inappetance. In this regard, it is not advisable to institute dietary changes when patients are hospitalized, as there is a high risk that the patient will develop food aversion. Rather, the renal support diet should be instituted in the home environment when the pet is stable.

Reduced food intake leads to malnutrition and wasting, which contribute to many aspects of uremia including impaired immune function, delayed wound healing, decreased strength and vigor, and increased morbidity and mortality. Indeed, malnutrition has been implicated as a factor influencing outcome in humans with renal failure. Therefore, prevention of malnutrition by ensuring adequate nutrient intake is crucial in the management of renal failure.

Enteral feeding tubes should be instituted for nutritional support upon documentation of a 10-15% loss of BW in conjunction with a declining body condition score and a history of poor dietary intake. Enteral feeding tubes are also advantageous as they circumvent the need for subcutaneous fluid therapy and ease the administration of oral medications.

(For more details concerning enteral tube feeding, **see chapter 14**: critical care nutrition)

► Clinical studies of the influence of the diet on naturally occurring chronic renal failure

The effects of feeding diets with a low phosphorus and moderately restricted protein content have been investigated in dogs with mild to moderate chronic renal failure *(Leibetseder & Neufeld, 1991)*. Thirty-two dogs with early chronic renal failure were fed a low phosphorus medium protein commercial diet for 28 weeks, and an additional 28 dogs were fed a home-made diet formulated to mimic the commercial diet. Fourteen dogs were euthanized throughout the course of the study due to progression of renal failure. Within four weeks of feeding either the commercial or the home made diet, the concentrations of blood urea nitrogen and phosphorus had almost normalized. Both diets were found to be palatable, body weights and serum albumin concentrations remained stable, and the physical condition of the dogs was considered improved. The results of this study suggest that dogs with mild to moderate chronic renal failure benefit from early management with a phosphate and protein restricted diet.

The effect of a modified protein, low phosphate diet on the outcome of dogs with stable, naturally occurring CRF has recently been reported *(Jacob et al, 2002)*. Dogs with mild to moderate CRF that were fed a renal diet had a 70% reduction in the relative risk of developing a uremic crisis,

remained free of uremic signs almost 2.5 times longer and had a median survival that was three times longer than dogs with CRF that were fed a maintenance diet. Renal function declined more slowly in the dogs that were fed the renal diet. The primary cause of death in dogs fed the maintenance diet was renal-related.

► Monitoring

Regular monitoring to ensure that dietary and medical management remains optimal for the needs of the patient is crucial for the well being and long term successful treatment of the chronic renal failure patient. Owner compliance may also be improved by frequent patient evaluation. Patients should be reevaluated within 2 weeks of initiating therapy and then 3 to 4 times per year. Recheck examinations should always be made 2 weeks following medication or dietary change. Erythropoietin and antihypertensive therapy will initially require weekly evaluation until the appropriate maintenance dosage is achieved.

A complete history, physical examination, body weight, body condition score and laboratory evaluation including CBC, biochemical panel, urine analysis, urine culture and blood pressure evaluation is indicated. Urine culture should become a routine part of follow up studies as chronic renal failure patients are predisposed to urinary tract infection, which are often clinically "silent".

Practical measures to improve intake include the use of highly odorous foods, warming the foods prior to feeding and stimulating eating by positive reinforcement with petting and stroking behavior.

When oral ulcerations are present, application of local xylocaine gel about 10 minutes before the meal may decrease the pain associated with food intake.

Appetite stimulants such as the benzodiazepam derivatives or serotonin antagonists may be judiciously administered, however, in these cases, more aggressive therapy such as esophagostomy or gastrotomy tube feeding is often more effective *(Elliott et al, 2000)*.

A complete list of all medications and doses that the client is currently administering to the pet should be obtained to verify compliance. In addition, some owners will self-adjust medications or simply may be confused by previous instructions.

A complete dietary history including the type of diet (dry versus wet), the amount eaten each day (eaten is more important than amount offered), the method of feeding, and all treats, snacks and supplements should also be obtained. This information is invaluable for monitoring the response to dietary therapy.

► Expected outcome and prognosis

CRF is a progressive disease that ultimately results in death. The goal of medical and nutritional management is to ensure the highest quality of life for the patient, for the longest period of time. Success depends on owner acceptance and compliance and a coordinated medical approach.

Despite appropriate tailoring of the therapy to the patient's condition, chronic renal failure is typically dynamic and progressive and eventually leads to end-stage renal failure. The severity of the clinical signs and uremic complications and the probability of improving renal function (by removing pre-renal contributions, controlling infection etc) will aid in determination of the prognosis.

The severity of the renal function and long term prognosis is best determined by the serum creatinine concentration. Prognosis and outcome will be heavily influenced by the response to conservative medical therapy and the rate of progression of the renal dysfunction.

Dietary and conventional medical therapy generally become poorly accepted or ineffective at stage IV of CRF as defined by IRIS (when plasma creatinine exceeds 5 mg/dL or 400 µmol/L). At this point owners are frustrated with the poor quality of life of their pet and euthanasia is often the ultimate outcome. Renal transplantation or chronic intermittent hemodialysis (two or three times per week) are then the only viable options.

Conclusion

Chronic renal failure is the clinical syndrome resulting from irreversible loss of the metabolic, endocrine and excretory capacities of the kidney. CRF is the third leading cause of death in dogs. Nutrition has been the cornerstone of management for decades. The goals of dietary modification are to meet the patient's nutrient and energy requirements, alleviate clinical signs and consequences of uremia, minimize disturbances in fluid, electrolyte, vitamin, mineral, and acid base balance and to slow progression of renal failure. Regular monitoring to ensure that dietary and medical management remains optimal for the needs of the patient is crucial for the well being and long term successful treatment of the chronic renal failure patient.

Definitions

Azotemia: Increased concentrations of blood urea nitrogen and/or creatinine and other nitrogenous waste products in the blood

Renal Azotemia: Denotes azotemia caused by renal parenchymal lesion

Renal Disease: Implies renal lesions are present, however, does not qualify the etiology, severity or distribution

Renal Failure: State of decreased renal function that allows persistent abnormalities (azotemia, inability to concentrate urine) to exist

Renal Insufficiency: Begins when renal reserve is lost. Animals appear outwardly normal, but have a reduced capacity to compensate for stresses such as infection or dehydration

Renal reserve: The percentage of nephrons not necessary to maintain normal renal function. The renal reserve is generally greater than 50%

Uremic syndrome: Constellation of clinical signs including anemia, gastroenteritis, acidosis which occur at the ultimate stage of renal failure

Frequently asked questions: Chronic Renal Failure

Q	A
Can I add broths and meat juices to the diet to improve palatability?	No, we do not recommend adding any supplements to the diet. Adding supplements to the diet may unbalance the key dietary features that we are trying to control with the diet.
Is dry or canned food better for my pet with renal disease?	For most pets with kidney disease, it will not matter whether they eat canned or dry food, as long as they are both formulated to assist the management of renal disease. For some pets that do not drink adequate amounts of water to maintain hydration, canned food may be beneficial to aid the ingestion of water.
When should you start to feed the renal diet?	Renal diets should be implemented as soon as the diagnosis of kidney disease is made. However, renal diets should not be fed to pets that are sick and hospitalized. Rather they should be implemented in the pets normal home environment. Hospitalization is a very stressful event for pets. Changing the food at that time may foster food aversion.
How often should my pet be rechecked?	The frequency that a pet is rechecked will depend on what concurrent medications that the pet is currently receiving. For pets with early disease, they should be rechecked every 3-4 months. If pets are on hypertensive agents, or erythopoietin therapy, they may need rechecking every two weeks until the ideal dose of the medication is identified to stabilize the pet.
What do I do if the pet is not eating enough food and loosing weight?	If the pet is not eating adequate amounts of food to maintain body weight, then assisted feeding by the placement of esophagostomy or gastrostomy tubes should be considered. Therefore, on the days that the pet will not eat the appropriate amount of food, the food can be blended and administered to the pet.

References

Adams LG - Phosphorus, protein and kidney disease. Proceedings of the Petfood Forum 1995; S. 13-26.

Bauer JE, Markwell PJ, Rawlings JM et al. - Effects of dietary fat and polyunsaturated fatty acids in dogs with naturally developing chronic renal failure. J Am Vet Med Assoc 1999; 215: 1588-1591.

Bauer J, Crocker R, Markwell PJ - Dietary n-6 fatty acid supplementation improves ultrafiltration in spontaneous canine chronic renal disease. J Vet Intern Med 1997; 126: 126.

Bronson RT - Variation in age at death of dogs of different sexes and breeds. Am J Vet Res 1982; 43: 2057-2059.

Brown SA, Finco DR, Crowell WA et al. - Single-nephron adaptations to partial renal ablation in the dog. Am J Physiol 1990; 258: F495-503.

Brown SA, Finco DR, Crowell WA et al. - Dietary protein intake and the glomerular adaptations to partial nephrectomy in dogs. J Nutr 1991a; 121: S125-127.

Brown SA, Crowell WA, Barsanti JA et al. - Beneficial effects of dietary mineral restriction in dogs with marked reduction of functional renal mass. J Am Soc Nephrol 1991b; 1: 1169-1179.

Brown SA, Brown CA, Crowell WA et al. - Does modifying dietary lipids influence the progression of renal failure? Vet Clin North Am Small Anim Pract 1996; 26: 1277-1285.

Brown SA, Finco DR, Brown CA - Is there a role for dietary polyunsaturated fatty acid supplementation in canine renal disease? J Nutr 1998a; 128: 2765S-2767S.

Brown SA, Brown CA, Crowell WA et al.- Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. J Lab Clin Med 1998b; 131: 447-455.

Brown SA, Brown CA, Crowell WA et al. - Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. J Lab Clin Med 2000; 135: 275-286.

Cochrane AL, Ricardo SD - Oxidant stress and regulation of chemokines in the development of renal interstitial fibrosis. Contrib Nephrol 2003; 139: 102-119.

Cowan LA, McLaughlin R, Toll PW et al. - Effect of stanozolol on body composition, nitrogen balance, and food consumption in castrated dogs with chronic renal failure. J Am Vet Med Assoc 1997; 211: 719-722.

Cowgill L - Medical management of the anemia of chronic renal failure. In: Osborne C, Finco D, eds. Canine and Feline Nephrology and Urology. Williams & Wilkins, Baltimore; 1995: 539-554.

Cowgill LD, James KM, Levy JK et al. - Use of recombinant human erythropoietin for management of anemia in dogs and cats with renal failure. J Am Vet Med Assoc 1998; 212: 521-528.

Elliott DA, Riel DL, Rogers QR - Complications and outcomes associated with use of gastrostomy tubes for nutritional management of dogs with renal failure: 56 cases (1994-1999). J Am Vet Med Assoc 2000; 217: 1337-1342.

Finco DR, Crowell WA, Barsanti JA - Effects of three diets on dogs with induced chronic renal failure. Am J Vet Res 1985; 46: 646-653.

Finco DR, Brown SA, Crowell WA et al. - Effects of dietary phosphorus and protein in dogs with chronic renal failure. Am J Vet Res 1992a; 53: 2264-2271.

Finco DR, Brown SA, Crowell WA et al. - Effects of phosphorus/calcium-restricted and phosphorus/calcium-replete 32% protein diets in dogs with chronic renal failure. Am J Vet Res 1992b; 53: 157-163.

Finco DR, Brown SA, Crowell WA et al. - Effects of aging and dietary protein intake on uninephrectomized geriatric dogs. Am J Vet Res 1994; 55: 1282-1290.

Finco DR, Brown SA, Brown CA et al. - Progression of chronic renal disease in the dog. J Vet Intern Med 1999; 13: 516-528.

Gerber B, Hassig M, Reusch CE - Serum concentrations of 1,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol in clinically normal dogs and dogs with acute and chronic renal failure. Am J Vet Res 2003; 64: 1161-6.

Grauer GF, Allen TA - Chronic renal failure in the dog. Compend Contin Educ Pract Vet 1981; 3: 1009-1017.

Grauer GF, Greco DS, Getzy DM et al. - Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Intern Med 2000; 14: 526-533.

Greco DS, Lees GE, Dzendzel GS et al. - Effect of dietary sodium intake on glomerular filtration rate in partially nephrectomized dogs. Am J Vet Res 1994a; 55: 152-159.

Greco DS, Lees GE, Dzendzel G et al. -Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. Am J Vet Res 1994b; 55: 160-165.

Hahn S, Kuemmerle NB, Chan W et al. - Glomerulosclerosis in the remnant kidney rat is modulated by dietary alpha-tocopherol. J Am Soc Nephrol 1998; 9: 2089-2095.

Hahn S, Krieg RJ Jr, Hisano S et al. - Vitamin E suppresses oxidative stress and glomerulosclerosis in rat remnant kidney. Pediatr Nephrol 1999; 13: 195-198.

Hansen B, DiBartola SP, Chew DJ et al. - Clinical and metabolic findings in dogs with chronic renal failure fed two diets. Am J Vet Res 1992; 53: 326-334.

Jackson P, Loughrey CM, Lightbody JH et al. - Effect of hemodialysis on total antioxidant capacity and serum antioxidants in patients with chronic renal failure. Clin Chem 1995; 41: 1135-1138.

Jacob F, Polzin DJ, Osborne CA et al. - Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs. J Am Vet Med Assoc 2002; 220: 1163-1170.

Jacob F, Polzin DJ, Osborne CA et al. - Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure. J Am Vet Med Assoc 2003; 222: 322-329.

Jouad H, Lacaille-Dubois MA, Lyoussi B et al. - Effects of the flavonoids extracted from Spergularia purpurea Pers. on arterial blood pressure and renal function in normal and hypertensive rats. J Ethnopharmacol 2001; 76: 159-163.

Leibetseder JL, Neufeld KW - Effects of medium protein diets in dogs with chronic renal failure. J Nutr 1991; 121: S145-149.

Lefebvre HP, Ferre JP, Watson AD et al. - Small bowel motility and colonic transit are altered in dogs with moderate renal failure. Am J Physiol Regul Integr Comp Physiol 2001; 281: R230-238.

Lefebvre HP, Toutain PL - Angiotensin-converting enzyme inhibitors in the therapy of renal diseases. J Vet Pharmacol Ther 2004; 27(5): 265-81.

Locatelli F, Canaud B, Eckardt KU et al. - Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant 2003; 18: 1272-1280.

Lund EM, Armstrong PJ, Kirk CA et al. - Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999; 214: 1336-1341.

Nagode LA, Chew DJ, Podell M - Benefits of calcitriol therapy and serum phosphorus control in dogs and cats with chronic renal failure. Both are essential to prevent or suppress toxic hyperparathyroidism. Vet Clin North Am Small Anim Pract 1996; 26: 1293-1330.

Polzin DJ, Osborne CA, Stevens JB et al. - Influence of modified protein diets on the nutritional status of dogs with induced chronic renal failure. Am J Vet Res 1983; 44: 1694-1702.

Polzin DJ, Osborne CA - The importance of egg protein in reduced protein diets designed for dogs with renal failure. J Vet Intern Med 1988; 2: 15-21.

Polzin DJ, Leininger JR, Osborne CA et al. - Development of renal lesions in dogs after 11/12 reduction of renal mass. Influences of dietary protein intake. Laboratory Investigation 1988; 58: 172-183.

Polzin DJ - Diseases of the kidneys and ureters. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine, 3rd ed. WB Saunders, Philadelphia; 1989: 1963-2046.

Polzin DJ, Osborne CA, Jacobs F et al. - Chronic Renal Failure. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine-Diseases of the Dog and Cat, 5th ed. WB Saunders, Philadelphia; 2000: 1634-1661.

Raila J, Forterre S, Kohn B et al. - Effects of chronic renal disease on the transport of vitamin A in plasma and urine of dogs. Am J Vet Res 2003; 64: 874-879.

Randolph JF, Scarlett J, Stokol T et al. - Clinical efficacy and safety of recombinant canine erythropoietin in dogs with anemia of chronic renal failure and dogs with recombinant human erythropoietin-induced red cell aplasia. J Vet Intern Med 2004; 18: 81-91.

Robertson JL, Goldschmidt M, Kronfeld DS et al. - Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. Kidney Int 1986; 29: 511-519.

Stepien RL - Diagnosis of canine hypertension. Proceedings of the 19th Annual Veterinary Medical Forum, American College of Veterinary Internal Medicine; Denver, 2001: 871.

Tahzib M, Frank R, Gauthier B et al. -Vitamin E treatment of focal segmental glomerulosclerosis: results of an open-label study. Pediatr Nephrol 1999; 13: 649-652.

Watson AD, Lefebvre HP, Concordet D et al. - Plasma exogenous creatinine clearance test in dogs: comparison with other methods and proposed limited sampling strategy. J Vet Intern Med 2002; 16: 22-33.

EXAMPLES HOME-PREPARED THE DIETETIC TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Beef, minced meat, 20% fat . . . . . 250 g
Potato, cooked, with skin . . . . . 700 g
Rapeseed oil . . . . . 50 g

Add a low-phosphorus mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	g/1000 kcal
Protein	19	37
Fat	34	66
Available carbohydrate	36	70
Fiber	4	8

INDICATIVE RATIONING			
Energy value (metabolizable energy): 1550 kcal/1000 g of diet prepared 5110 kcal/1000 g DM			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	140	45	1460
4	240	50	1580
6	320	55	1690
10	470	60	1810
15	640	65	1920
20	790	70	2030
25	940	75	2140
30	1080	80	2240
35	1210	85	2350
40	1330	90	2450

Key Points

- **Reducing the phosphorus content** to mitigate the less good phosphorus excretion by the kidney during CRD and prevent the risk of hyperparathyroidism, which aggravates renal failure.
- **Increasing the energy concentration** to help limit the meal volume while covering energy requirements. The goal is to compensate the fall in appetite.
- **Moderating the protein content** to compensate the fall in the glomerular filtration rate

** The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
*** The fractioning of the daily amount over two or three meals is recommended to favor good digestion.*

DIETS ADAPTED TO CHRONIC RENAL DISEASE

Example 2

COMPOSITION
(1000 g diet)

Pork, shoulder with skin ..... 125 g
Whole egg ..... 125 g
Rice, cooked ..... 730 g
Rapeseed oil ..... 20 g

Add a low-phosphorus mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy): 1520 kcal/1000 g of diet prepared 5050 kcal/1000 g DM			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	140	45	1490
4	240	50	1610
6	330	55	1730
10	480	60	1840
15	650	65	1960
20	810	70	2070
25	960	75	2180
30	1100	80	2290
35	1230	85	2390
40	1360	90	2500

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	g/1000 kcal
Protein	18	36
Fat	18	37
Available carbohydrate	62	127
Fiber	1	2

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

© Lanceau

An adapted diet helps triple the median survival time of dogs with chronic renal disease.

Key Points
to remember:

The role of nutrition in the management and prevention of chronic renal disease

Chronic renal disease (CRD) in dogs is often associated with a waxing and waning appetite. Therefore the **palatability of the food** is a key criterion in the management of CRD.

When the kidney loses its functional capacity, phosphorus is no longer adequately excreted and the concentration increases in plasma. Ultimately, hyperphosphatemia causes hyperparathyroidism that aggravates CRD. One of the goals of treatment is to normalize the blood phosphate concentration. It has been clearly shown that the **dietary restriction of phosphorus** slows the progression of renal disease in dogs.

Supplementation with alkalizing agents such as sodium bicarbonate, calcium carbonate or potassium citrate can prove necessary to combat metabolic acidosis.

Contrary to a common misconception, the protein **content of the food** does not have any impact on the progression of renal disease. It is therefore useless to systematically reduce the protein in the diet of an aging dog. Conversely, in dogs with CRD the goal of protein reduction is to reduce the magnitude of uremia. To prevent protein malnutrition, moderate restriction of the order of 35-40 g protein/1000 kcal is preferable. Too severe protein reduction could actually have negative effects, by forcing the dog to catabolize its body proteins to meet its needs.

Energy intake must be sufficient to prevent endogenous protein catabolism that leads to malnutrition and aggravated azotemia.

An **increased intake of omega 3 fatty acids (EPA and DHA)** helps limit the reduction in glomerular filtration rate.

Hypokalemia is commonly observed in dogs with renal disease, except in the terminal stage, when hyperkalemia may be observed. **Reestablishing a normal serum potassium concentration** is essential to the dog's quality of life.

It has long been recommended to reduce the **sodium content** in the diets of patients with CRD. However, recent work (see chapter seven) would appear to show that too low of a sodium content (0.4-0.5 mg/1000 kcal) could have a deleterious effect on renal function. Low sodium intake could contribute to glomerular hypertension by increasing the secretion of aldosterone and activating the renin-angiotensin system. These results are yet to be confirmed but they caution against too severe sodium restriction in the diet of patients with CRD.

Aging dogs generally suffer from renal disease hence it is necessary to **enrich the food with antioxidants** to help combat free radical production.

Focus on:

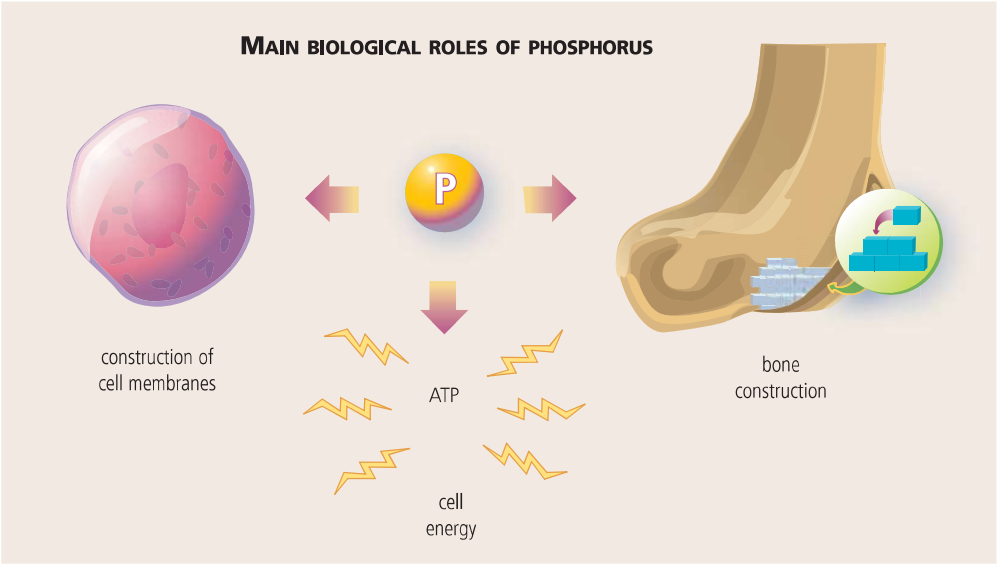
PHOSPHORUS

Etymologically speaking, the word phosphorus means 'light-bringing.' It was discovered in 1669 by a German alchemist, Hennig Brandt. By evaporating urine and calcifying the residue, he obtained phosphorus in gas form that shone in the dark.

In the form of phosphates, phosphorus enters into the composition of bone. Eighty-six percent of the phosphorus in the organism is stored in the structure of the skeleton.

Phosphorus is also incorporated into large molecules such as DNA, RNA and membrane phospholipids. In addition, it is an active constituent of the adenosine triphosphate molecule (ATP), which stores the energy living organisms need to function properly.

The reasons why phosphorus leads to progression of CRD have yet to be determined with certainty. Following the reduction of the renal function, phosphorus accumulates in the blood. The organism responds physiologically by increasing the secretion of parathyroid hormone (PTH). This response initially helps maintain the phosphorus within normal thresholds, but also leads to the release of phosphate and calcium from bone reserves.

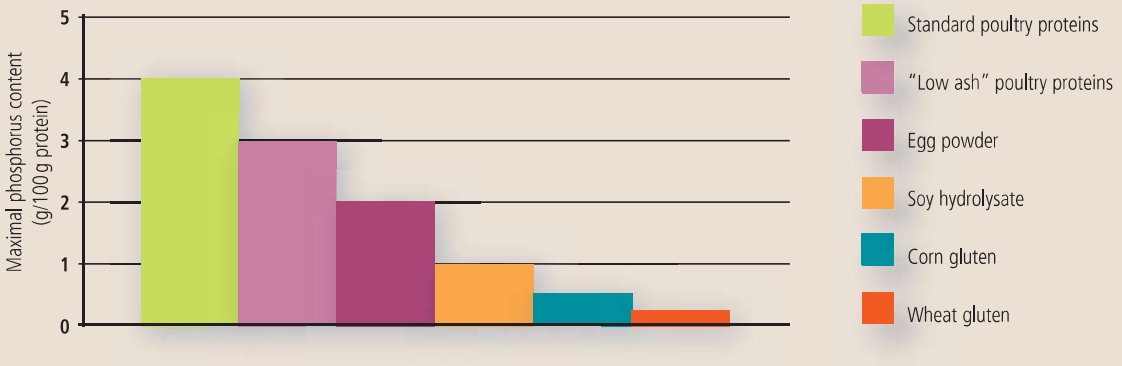


In time, even this compensatory response is not enough to reestablish homeostasis. Phosphorus and calcium accumulate, leading to the mineralization of soft tissue. In the kidney, this phenomenon accelerates the loss of functional nephrons. In addition, PTH may act as an uremic toxin, which also aggravates the clinical symptoms and progression of CRD.

In CRD patients, the goal is therefore to limit the phosphorus content of the food to 0.40-0.80 g/1000 kcal. At the same time, the increase in the calcium content also helps reduce the digestive absorption of phosphorus. If such a level does not help normalize the serum phosphate concentration, the use of phosphate binding agents (aluminum hydroxide, calcium carbonate etc) should be considered.

While it is vital to limit the phosphorus content in the food, the difficulty lies in the necessity of finding raw ingredients that are low in phosphorus. Animal protein sources traditionally used in dog food are fairly high in phosphorus. For example, there is 1.6-2.5% phosphorus on a DMB in dehydrated poultry proteins. This level is dependent on the overall content of remaining mineral matter after sieving. Vegetable protein sources that are lower in phosphate concentration (wheat or corn gluten, soy protein isolate hydrolysate) are an interesting alternative.

PHOSPHORUS CONTENT OF SEVERAL PROTEIN SOURCES USED IN DOG FOOD



Wheat or corn gluten helps supply high quality proteins while simultaneously reducing the ingestion of phosphorus.