

# The Canine Kidney



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## KEY POINTS

- **Chronic renal failure is irreversible, but can be managed by medical therapy, of which dietary management is the key component.**
- **Dietary management can help to slow progression of disease; so early recognition is desirable and can be achieved through routine blood and urine analyses in older dogs.**
- **Dietary phosphorus restriction is of great importance since this helps reduce renal mineralization and renal secondary hyperparathyroidism, and helps to slow progression of disease.**
- **Phosphorus restriction should be implemented in all dogs with azotemia associated with primary renal failure, as well as in dogs with uremia.**
- **Protein restriction, in addition to phosphorus restriction, should be introduced following the onset of clinical signs and adjusted according to the severity of clinical and biochemical signs.**
- **Restriction of dietary protein is of clinical benefit in uremic patients since this will help to control polyuria/polydipsia, metabolic acidosis, and other uremic signs. It will also help limit phosphorus intake.**
- **Calcium supplementation may be required if the patient is hypocalcemic, but is contraindicated in the presence of hypercalcemia.**
- **Dietary sodium levels should be moderately restricted to help avoid the development of systemic hypertension, but introduction of a diet with controlled sodium content should be accomplished gradually to allow the failing kidneys to adapt.**
- **Water-soluble (B-complex) vitamins should be supplemented to compensate for polyuric losses and poor dietary intake.**
- **Energy should be supplied, to a large extent, from nonprotein sources to limit protein catabolism. Fat is useful since this increases both energy density and palatability of the diet.**

The kidneys are responsible for the excretion of nitrogenous and other metabolic waste products, and for the regulation of water, electrolyte, and acid-base balance. When renal function is reduced, dietary factors can influence the clinical course of the disease by improving clinical signs, and in some cases, by helping to delay progression of the disease.

## ANATOMY

The kidneys are paired organs that receive approximately 20% of the cardiac output via the renal arteries. Each kidney consists of an outer cortex and an inner medulla which projects into the renal pelvis. The ureter is a tubular structure that conveys urine from the renal pelvis to the bladder.

The nephron is the functional unit for urine production. At the proximal end of the nephron, the cup-shaped Bowman's capsule receives filtered blood from a dense network of capillaries, the glomerulus. The tubule that leads from the Bowman's capsule is divided into the proximal convoluted tubule, the loop of Henle (which extends into the renal medulla), and the distal convoluted tubule. Along with those of several other nephrons, the distal convoluted tubule opens into a common collecting duct and the ducts converge at the renal pelvis.

Blood is conveyed to the glomerulus by the afferent arteriole, branch of the renal artery, and leaves via the narrower efferent arteriole. The afferent arteriole divides into capillaries that surround the nephron tubules and eventually drain into the renal vein via the efferent arteriole.

## FUNCTION

The kidney is a complex organ with many functions. Through the production of urine, it excretes the waste products of protein metabolism and regulates fluid, electrolyte, and acid-base balance. The kidney also has a biosynthetic role, and is involved in the production of renin, erythropoietin, prostaglandins, and vitamin D<sub>3</sub>. In addition, the kidney is able to perform gluconeogenesis under conditions of starvation and is an important site for degradation of some peptide hormones.

Urine is produced by the ultra-filtration of blood from the glomerulus and subsequent modification of the filtrate in the renal tubule. Filtration is aided by the hydrostatic pressure in the capillaries, created by the difference in diameter of the afferent and efferent arterioles. In the normal kidney, large plasma proteins and blood cells are retained within the glomerular capillaries, but other plasma constituents pass into the capsular space and then into the tubule lumen. Most filtered substances are reabsorbed either passively or by active transport across the

tubular membrane back into the blood, while other substances are secreted into the tubular fluid. The modified filtrate passes from the tubule to the collecting duct where it emerges as urine.

## Excretory Function

The kidneys excrete the nitrogenous and other waste products of protein metabolism including:

- **Urea**
- **Creatinine**
- **Uric acid**
- **Phosphate**
- **Sulfate**

Other potentially toxic substances, such as drugs or poisons, are also excreted by the kidneys. Excretory products, which are poorly reabsorbed following glomerular filtration or are actively secreted into the tubular fluid, are concentrated in urine.

## Regulatory Function

The kidneys are responsible for the maintenance of water, electrolyte, and acid-base balance in the body:

- **Water homeostasis** by the kidney is mediated by the antidiuretic hormone (ADH), also known as vasopressin, which is secreted by the posterior pituitary gland in response to raised plasma osmotic pressure. The hormone acts to increase water reabsorption in renal tubules into the blood by increasing the permeability of the collecting duct.
- The kidneys are of primary importance in maintaining **sodium homeostasis**, but they are also involved in the regulation of other electrolytes, particularly potassium, phosphate, and calcium. Aldosterone, a mineralocorticoid hormone secreted by the adrenal gland, promotes sodium retention and potassium loss. Atrial natriuretic peptide is released from the atria in response to distension of the right atrium and promotes sodium and water excretion, and therefore opposes the effects of renin and aldosterone.
- The kidneys have a major role in controlling **acid-base equilibrium** of the plasma. Renal regulation of acid-base balance is achieved through a combination of selective hydrogen ion excretion, bicarbonate ion reabsorption or regeneration, and the presence of urinary buffers including phosphate and ammonia.

## Biosynthetic Function

The kidneys are involved in the biosynthesis of renin, erythropoietin, vitamin D<sub>3</sub> (calcitriol), prostaglandins, and antihypertensive lipids.

- **Renin** is secreted by the kidneys in response to lowered intra-arteriole pressure. Renin transforms angiotensinogen to angiotensin I, which is then converted to its active form, angiotensin II, by an “angiotensin converting enzyme.” Angiotensin II causes vasoconstriction, retention of sodium and water, and increased thirst, which combine to raise blood pressure both in the glomerulus (to maintain glomerular filtration) and in the systemic circulation.
- The kidney also produces substances (lipids and prostaglandins) that are **antihypertensive** in their action, and so oppose the effects of renin.
- **Erythropoietin** is necessary for red blood cell formation in bone marrow.
- The **conversion of vitamin D<sub>3</sub>** to its active form alpha 1,25- dihydroxycholecalciferol (calcitriol) is carried out in the kidneys, mediated by the enzyme 1- $\alpha$ -hydroxylase, in response to a fall in plasma calcium concentration. Activation is facilitated by the parathyroid hormone (PTH). Active vitamin D<sub>3</sub> promotes calcium absorption in the gut.

## CLINICAL DISORDERS

Renal failure describes the inability of the kidneys to adequately perform their normal functions resulting in the development of azotemia, the loss of urine concentrating ability, and disturbances of fluid, electrolyte, and acid-base balance. Because the kidney has a large functional reserve capacity, signs of disease do not usually occur until 65% to 75% of nephrons have been destroyed. Renal disease may, therefore, be present for some time before renal failure is detected.

Renal failure may be described as **acute** or **chronic**. Renal failure is regarded as chronic if it is of more than two weeks duration.

**Azotemia**, which develops as a consequence of excretory failure, is increased concentrations of urea, creatinine, or other nonprotein nitrogenous compounds in blood, and is associated with a reduction in the **glomerular filtration rate (GFR)**. It may, however, be the result of pre- or

post-renal factors, as well as primary renal disease. Also, azotemia may be present in animals without overt signs of clinical disease.

**Uremia** is the polysystemic toxic syndrome, which develops with the progression of renal failure and is characterized by the presence of clinical signs in association with azotemia. Presenting clinical signs are likely to include:

- **Polyuria** and **polydipsia**
- **Anorexia** and **weight loss**
- **Lethargy**
- **Pallor** and/or **ulceration** of mucous membranes
- **Vomiting** and, perhaps, **diarrhea**
- **Neurologic signs** in some cases

## Acute Renal Failure

Acute renal failure (ARF) describes a sudden reduction in renal function associated with a sudden decrease in the glomerular filtration rate (GFR), and the rapid development of azotemia and uremia. Intra-renal causes of ARF include:

- **Acute tubular necrosis** (nephrosis) resulting from injury due to nephrotoxins or ischemia.
- **Acute nephritis**, which may be associated with infections such as *Leptospira canicola* or other bacterial or viral agents
- **Acute trauma**

ARF of renal origin must be differentiated from azotemia of pre-renal or post-renal origin.

**Prerenal azotemia** is a consequence of reduced renal perfusion and may result from shock, dehydration, heart failure, hypoadrenocorticism, thrombosis of the renal artery, or massive blood loss. In prerenal azotemia, there is an increased urine specific gravity (>1.035) if there is no concurrent renal disease or other disorder affecting urine-concentrating ability. Prolonged ischemia will result in acute tubular necrosis and ARF.

**Postrenal azotemia** results when urine outflow is obstructed; the most usual cause is urolithiasis. Obstruction may also occur as a result of neoplasms, anatomic abnormalities, herniation, or damage to part of the lower urinary tract. If unrelieved, the obstruction can lead to the rapid development of ARF or, if the lesion is unilateral, to hydronephrosis. Rupture of the urinary tract may also result in postrenal azotemia but is not always associated with renal failure. Hyperkalemia can be a serious complication of urinary obstruction.

## Diagnosis

Early signs of ARF can be vague and nonspecific, including lethargy, anorexia, vomiting, and diarrhea. Diagnosis of ARF is confirmed by a detailed history, physical examination, and results from urinalysis, laboratory investigation, and imaging. The history may reveal exposure to causal factors including trauma, nephrotoxins, and ischemic injury, although often the etiology cannot be elucidated. Diagnosis is often based on the acute onset of azotemia (of renal origin) and uremic signs often accompanied by oliguria. It is also important to differentiate ARF from CRF.

Nephrotoxins include:

- **Ethylene glycol** (in antifreeze)
- **Antibiotics:** aminoglycosides, tetracycline, cyclosporin
- **Chemotherapeutics:** amphotericin B, *cis*-platinum, doxorubicin
- **Anesthetics:** methoxyflurane
- **Heavy metals:** lead, thallium, zinc, arsenic, mercury
- **Hypercalcemia:** malignancies, hyperparathyroid, vitamin D toxicity
- **Other causes:** carbon tetrachloride, chloroform, iodinated contrast media

## Clinical Signs

Initial signs of acute renal failure may be vague and can include:

- **Lethargy** and **depression**
- **Anorexia**
- **Nausea** and **vomiting**
- **Dehydration**
- **Kidney pain** in some cases
- **Oliguria** (< 7 ml urine/ kg bodyweight/day)
- Occasionally, **anuria** (< 2 ml urine/kg bodyweight/day) or **polyuria**

If untreated, renal failure may progress and result in severe systemic disease.

Signs may include:

- **Shock**
- **Disseminated intravascular coagulation (DIC)**
- **Respiratory distress**

- **Neurologic disturbances**
- **Coma and death**

Some animals may present with acute onset of renal failure, but with a history of signs suggestive of chronic disease, including weight loss and polyuria/polydipsia. It is important to distinguish between patients with ARF, and those with acute decompensation of chronic renal failure, since the prognosis is better for patients with ARF with early and appropriate treatment.

### *Laboratory Findings*

#### ***Hematology***

- Regenerative anemia associated with blood loss
- Thrombocytopenia
- Stress or inflammatory leukogram
- Raised packed cell volume (PCV) if dehydrated

#### ***Biochemistry***

- Raised blood urea nitrogen (BUN), which may be influenced by dietary protein intake, dehydration, or gastrointestinal hemorrhage
- Raised plasma creatinine
- Hyperkalemia
- Hyperphosphatemia
- Hypercalcemia in some cases; low or normal serum calcium in others

#### ***Urinalysis and Urine Culture***

- Specific urine gravity:
  - 1.008 - 1.012 (isotheruria) in primary renal failure
  - 1.030 in pre-renal azotemia
- Osmolality:
  - < 350 mOsm/l (dilute) in primary renal failure
  - > 500 mOsm/l (concentrated) in pre-renal azotemia
- Urinary sediments: protein, blood, crystals, tubular casts, cells, depending on etiology
- Positive urine culture with pyelonephritis

### ***Management***

Acute renal failure is potentially reversible, but successful management involves:

- Early recognition of disease
- Identification and treatment of specific underlying causes

- Anticipation of potential renal damage associated with known risk factors
- Prompt implementation of therapy to support renal function and prevent progression of organ failure

Initially, treatment is aimed at the correction of life-threatening abnormalities including:

- **Dehydration**
- **Hyperkalemia**
- **Metabolic acidosis**

Fluid therapy is of primary importance and rehydration (with Hartmanns' or 0.9% NaCl) may be sufficient to correct mild hyperkalemia and metabolic acidosis.

Once rehydrated, diuresis is promoted to eliminate uremic waste and to optimize renal blood flow and GFR. Fluids with lower sodium content (e.g., 0.45% NaCl and 2.5% dextrose) should be given and fluid input should equal output. If the dog remains oliguric, appropriate diuretic therapy may be introduced.

Additional therapeutic measures that may be required include:

- **Avoidance** of nephrotoxic drugs
- **Gastric protectants** and **anti-emetics** to alleviate gastrointestinal disturbances
- **Potassium supplementation** in stabilized, polyuric patient with hypokalemia
- **Nutritional support**
- **Antibiotic therapy** if infection is present
- Institution of **antihypertensive therapy**
- **Insulin** (with glucose) to correct severe hyperkalemia
- **Sodium bicarbonate** to correct metabolic acidosis and/or hyperkalemia
- **Calcium gluconate** to counteract the immediate effects of hyperkalemia on myocardium

### **Dietary Management**

Maintenance of energy intake is important in uremic patients to help decrease the catabolism of endogenous proteins and to meet energy requirements. The principles of dietary therapy are the same as those outlined for the management of chronic renal failure. The anorexic patient may be encouraged to eat by a variety of methods, but if voluntary intake is insufficient, some form of enteral tube feeding may be required. Nasoesophageal or nasogastric intubation is preferred since these do not require general anesthesia.

## Chronic Renal Failure

Chronic renal failure (CRF) is a relatively common syndrome in older dogs and represents the end stage of a number of renal diseases. Chronic renal failure is usually progressive, but dietary measures can improve the clinical signs of uremia associated with CRF and may help to slow progression of the condition. Clinical signs of CRF are not usually apparent until at least 65% to 75% of renal tissue is destroyed; so early cases often go undetected.

### *Etiology*

A number of renal diseases may result in CRF, but in advanced cases, it is often not possible to differentiate between them. Specific causes of CRF include:

- **Glomerulonephritis**
- **Renal amyloidosis**
- **Pyelonephritis**
- **Chronic nephritis**
- **Primary renal neoplasia**
- **Hydronephrosis**
- **Renal urolithiasis**
- **Juvenile nephropathies**

### **Glomerulonephritis**

Glomerulonephritis is usually caused by the deposition of immune complexes within the glomeruli and subsequent inflammatory reaction. It can occur in association with any disease in which antigen-antibody complexes are formed, including infection, neoplasia, parasitism, and autoimmune disease. In the early stages, corticosteroid therapy may help to stabilize the patient in the short term, but most cases eventually progress to chronic renal failure.

**Nephrotic syndrome** is a consequence of advanced glomerular disease and is characterized by marked proteinuria, hypoalbuminemia, and generalized edema. In severe cases, it may be complicated by the presence of chronic renal failure. Management of nephrotic syndrome involves a combination of dietary therapy, correction of hypovolemia using intravenous plasma expanders, and diuretic therapy to remove retained edema fluid. Restricted protein and sodium diets are recommended. In cases that are complicated by the presence of CRF with azotemia, the dietary protein level should be balanced, such that the clinical signs of uremia are controlled while allowing for the correction of hypoalbuminemia.

## **Renal Amyloidosis**

Renal amyloidosis is caused by the deposition of amyloid, a hyaline protein, in renal glomeruli and usually occurs in association with other chronic systemic inflammatory disease. The prognosis is poor and most patients die within a few months of the onset of clinical signs. Clinically, amyloidosis can only be differentiated from glomerulonephritis by biopsy and histopathologic examination. Both of these primary glomerular diseases result in proteinuria, which may progress to the development of nephrotic syndrome and/or CRF. Restricted protein diets suitable for the management of CRF are recommended for cases showing asymptomatic proteinuria.

## **Pyelonephritis**

Pyelonephritis is an inflammatory condition of the renal parenchyma most often caused by bacterial infection. In the majority of cases, the involvement is bilateral. Most are associated with an ascending urinary tract infection due to vesico-ureteral reflux. However, hematogenous infection can occur if there is pre-existing tissue damage or urinary obstruction which interferes with elimination of bacteria. Inflammation and suppuration of the kidney is then followed by tissue destruction and fibrosis leading, eventually, to CRF. Acute cases present with signs of urinary tract infection, plus fever, vomiting, and lumbar pain. Appropriate antibacterial therapy is essential at this stage, together with treatment of any underlying cause. Chronic cases occur if the infection is not completely eliminated and/or the reflux persists and may be either asymptomatic or show episodic exacerbation with acute signs. Antibacterial therapy is indicated in cases of bacteriuria, and those with uremic signs should be managed accordingly.

## **Primary Renal Neoplasia**

Primary renal neoplasia is rare in the dog, but renal cell carcinomas and nephroblastomas (in young dogs) do occasionally occur, giving rise to weight loss, anorexia, pyrexia, and hematuria. Benign hemangiomas can produce significant hematuria. Secondary metastases from tumors at other sites, especially lymphosarcoma, are more common. Chronic renal failure develops if both kidneys are affected or if the contralateral kidney is nonfunctional.

## **Hydronephrosis**

Hydronephrosis may occur in a kidney following complete or partial obstruction to urine outflow from that kidney. Back pressure causes dilatation of the renal pelvis with progressive ischemic atrophy and necrosis of renal parenchyma. This can result in a grossly enlarged, fluid-filled kidney with a much-reduced mass of functional tissue. Hydronephrosis may be complicated by infection, resulting in clinically manifested pyonephrosis, and is treated as for pyelonephritis. Bilateral, complete obstruction results in the rapid development of acute renal failure (ARF) before extensive hydronephrotic changes are evident. CRF will only develop if both kidneys are

affected (if, for example, the obstruction is partial and bilateral) or if function is otherwise impaired in the contralateral kidney. Treatment involves the early relief of any obstruction, where possible, or removal of the affected kidney if the remaining kidney is functioning normally. Appropriate therapeutic measures should be introduced if signs of CRF are evident.

### **Renal Urolithiasis**

Renal urolithiasis is rare in dogs since most canine uroliths form in the bladder. When present, however, they may obstruct urine outflow leading to ARF or hydronephrosis, predispose to pyelonephritis, and cause local damage to renal parenchyma. It is possible to dissolve nonobstructing uroliths of some types, particularly struvite, by medical and/or dietary means. Surgical intervention is indicated when dissolution *in situ* is not possible, or if more urgent removal of the urolith is required.

### **Juvenile Nephropathies**

Juvenile nephropathies can give rise to chronic renal failure in young dogs, usually less than 24 months of age. There is an inherited predisposition in certain breeds for some juvenile renal disorders. Specific disorders include:

- Renal aplasia or hypoplasia (in Doberman Pinschers and Beagles)
- Ectopic kidneys
- Polycystic kidneys (in Cairn Terriers and Beagles)
- Renal cortical hypoplasia (in Cocker Spaniels)
- Renal dysplasia (in Shih Tzus, Lhasa Apsos, Soft Coated Wheaten Terriers)
- Glomerular sclerosis (in Doberman Pinschers)
- Glomerular fibrosis (in Samoyeds and Norwegian Elkhounds)
- Cystic glomerular atrophy (in Standard Poodles and Doberman Pinschers)
- Telangiectasia (in Pembroke Corgis)

Renal tubular defects may occur in some breeds, giving rise to impaired reabsorption of various substances, such as:

- Hyperuricosuria (in Dalmatians)
- Cystinuria (in English Bulldogs and Dachshunds)
- Primary renal glycosuria (in Norwegian Elkhounds, Basenjis, Scottish Terriers)
- Fanconi's syndrome (in Norwegian Elkhounds, Basenjis, Shetland Sheepdogs, and Schnauzers)

## ***Pathophysiology***

Chronic renal disease results in a progressive loss of functional tissue, but compensatory mechanisms, such as hyperfiltration help to maintain normal kidney function until approximately 65% to 75% of nephrons have been destroyed. The inevitable decline in glomerular filtration rate (GFR) results in renal failure in which all of the functions of the renal parenchyma are impaired. The observed clinical and laboratory signs of CRF may be related to:

- **Disturbances of fluid balance**
- **Impaired excretion of nitrogenous metabolic waste products**
- **Impaired phosphorus homeostasis**
- **Impaired homeostasis of sodium and potassium**
- **Failure to maintain acid-base balance**
- **Impaired erythropoietin synthesis**
- **Lipid abnormalities**

A progressive decline in renal function often occurs, with patients ultimately dying of uremic complications.

### **Disturbances of Fluid Balance**

Renal tubular damage in chronic renal failure (CRF) impairs the animal's ability to concentrate urine, partly due to insensitivity to antidiuretic hormone (ADH) that may occur with azotemia. Furthermore, the increased solute load (minerals and nitrogenous waste products) delivered to each surviving nephron, together with defective tubular reabsorption of sodium, results in an osmotic diuresis and increased water losses.

This produces the characteristic polyuria and compensatory polydipsia of CRF. In dogs, it is an early presenting sign that may be evident before the onset of azotemia, but occurs less commonly in cats. Restriction of water intake in the polyuric animal can lead to dehydration and a worsening of azotemia, and may precipitate the onset of acute renal failure.

### **Impaired Excretion of Nitrogenous Metabolic Waste Products**

Reduced glomerular filtration results in the accumulation of metabolic waste products in the plasma, particularly those waste products related to the breakdown of proteins. Urea and creatinine are the main nitrogenous waste products that accumulate, resulting in azotemia. Although the importance of urea and creatinine as major uremic toxins is currently controversial, elevated concentrations in blood, particularly of urea, may contribute to a number of observed uremic signs including:

- **Polydipsia** and **polyuria**
- **Gastrointestinal signs**
- **Neurologic signs**

### *Gastrointestinal Signs*

Gastrointestinal signs include oral and gastrointestinal ulceration, vomiting, and occasionally, diarrhea. The pathogenesis of these problems is likely multifactorial and includes:

- Decreased mucosal blood flow
- Hypergastrinemia, leading to increased gastric acid secretion
- Stimulation of the chemoreceptor trigger zone in the brain, causing nausea and vomiting
- Gastroduodenal reflux
- Acidosis
- Calcium phosphate deposition in the gastric mucosa and submucosa due to high serum phosphorus and mobilization of calcium

### *Neurologic Signs*

Neurologic signs can be quite important, particularly in the contribution they may make to anorexia, depression, nausea, and vomiting. Parathyroid hormone (PTH) may be an important neurologic toxin in this respect. Seizures (“uremic fits”) may occur in the terminal stages of uremia and although the precise mechanism for this is unclear, hypocalcemia or calcium deposition in brain tissues have been implicated.

### **Impaired Phosphorus Homeostasis**

Hyperphosphatemia due to impaired renal phosphate excretion will occur when the glomerular filtration rate drops to about 20% of normal. Raised serum phosphorus can result in renal mineralization, **secondary hyperparathyroidism**, and potentially contribute to the progression of renal damage.

Renal mineralization appears to be common in dogs with CRF and may be an important factor in the progression of the disease. Soft tissue mineralization occurs, even in the healthy animal, when the concentrations of calcium and phosphorus in plasma exceed the solubility product of calcium-phosphate salts.

In addition, parathyroid hormone (PTH) promotes uptake of calcium into cells. Excessive calcium uptake into cells causes cell death. Renal tubular cells are particularly susceptible to these toxic effects because they have high numbers of PTH receptors. Subsequently, as serum phosphorus concentration rises, precipitation of calcium-phosphate may occur in tubule lumens, contributing to further renal damage. Hyperparathyroidism may thus promote a vicious cycle of

cell death leading to decreased renal ability to contribute to phosphate homeostasis, increased PTH levels, and the loss of more renal tissue.

**Renal secondary hyperparathyroidism** occurs as a result of a sustained increase in secretion of parathyroid hormone (PTH). Hyperphosphatemia contributes to the synthesis and release of PTH, which is promoted by:

- **Decreased calcitriol levels**
- **Hypocalcemia**
- **Direct influence of phosphorus** on the parathyroid gland

### *Decreased Calcitriol Levels*

In CRF, production of calcitriol (alpha 1,25 cholecalciferol) is reduced because:

- Elevated serum phosphorus inhibits the activity of the enzyme 1- $\alpha$ -hydroxylase in the kidney
- Synthesis of the enzyme is decreased owing to a reduction in functional renal mass

### *Hypocalcemia*

Serum calcium levels are normally tightly regulated by the combined actions of calcitriol and PTH. Hypocalcemia can, however, occur in some dogs with CRF as a result of:

- Decreased intestinal absorption due to low calcitriol levels
- Decreased dietary intake due to anorexia
- Deposition of calcium-phosphate complex in tissues, which reduces serum ionised calcium.  
This is unlikely to occur unless serum phosphorus levels are very high, as in advanced CRF

Elevated serum calcium may be present in some advanced cases of CRF, because the negative feedback mechanism by which hypercalcemia suppresses PTH secretion, is impaired at low calcitriol concentrations. In the healthy animal, PTH decreases elevated serum phosphorus by depressing tubular reabsorption of phosphate. In CRF, however, this homeostatic mechanism is unable to completely control serum phosphorus concentration, and sustained PTH release becomes an undesirable effect. Parathyroid hormone is thought to be an important uremic toxin, which may contribute to:

- **Anemia**
- **Neurotoxicity**
- **Dyslipoproteinemias**
- **Insulin resistance**
- **Renal osteodystrophy**

- **Promotion of soft tissue calcification**
- **Progression of renal damage**

### ***Renal Osteodystrophy***

Renal osteodystrophy is characterized by an increased osteoclastic resorption of bone in an attempt to maintain circulating calcium levels, and its replacement with fibrous tissue. Its effects are most marked in the bones of the skull, giving rise to soft “rubber” jaws, loosening of teeth, and in the young animal, facial hyperostosis. Mobilization of calcium and phosphate from bone in renal osteodystrophy may promote soft tissue calcification by raising serum concentrations of ionized calcium and inorganic phosphate.

### **Impaired Homeostasis of Sodium and Potassium**

Sodium homeostasis is maintained primarily by the kidneys. In the diseased state, as glomerular filtration rate (GFR) falls, each surviving nephron increases its fractional excretion of sodium to cope with the increased load. In general, this response is adequate to maintain sodium balance until the condition is very advanced. However, the ability of the kidney to adapt to increases in sodium intake becomes progressively limited.

Retention of sodium is likely to contribute to the development of systemic hypertension, the consequences of which include:

- **Left ventricular hypertrophy**
- **Neurologic abnormalities**
- **Ocular lesions**
- **Progression of renal damage**

In the dog, plasma levels of potassium are usually well regulated in CRF, and unlike the cat, hypokalemia is a rare complication in this species. It may, however, occur:

- Following reduced potassium intake
- With over-administration of potassium-losing diuretics.

Hyperkalemia may be seen in the terminal stages of CRF.

### **Failure to Maintain Acid-Base Balance**

Renal failure results in a limited capacity for renal excretion of hydrogen ions, primarily as a result of reduced renal mass. The loss of functional tissue results in impaired tubular reabsorption of bicarbonate leading, potentially, to acid retention and metabolic acidosis.

Metabolic acidosis is less common in dogs than in cats with CRF, due to the dog's ability to conserve bicarbonate more effectively until the advanced stages of disease.

Metabolic acidosis may be an important factor in progression of renal failure. With sustained acidosis, generation of ammonia (as a urinary buffer) in intact nephrons is increased. High tissue concentrations of ammonia have toxic and inflammatory effects and may contribute to progressive renal injury. Metabolic acidosis may also be associated with lethargy, inappetence, vomiting, and capillary fragility.

Metabolism of proteins, particularly animal proteins with a high content of sulfur amino acids, increases the acid load for renal excretion. Dietary protein restriction may, therefore, help to alleviate metabolic acidosis. In addition, diets that promote acidic urine, such as those used for the management of struvite urolithiasis, should be avoided in animals with chronic renal failure.

### **Impaired Erythropoietin Synthesis**

Normochromic, normocytic anemia is common in dogs with CRF and its degree of severity is an important indicator of the chronicity of renal failure. Although it is often overlooked in practice, anemia may contribute significantly to clinical signs of CRF, including:

- **Lethargy**
- **Weakness**
- **Inappetence**
- **Weight loss**

It is a multifactorial problem but the principal cause is reduced production of erythropoietin.

Other contributory factors, mediated by accumulated **uremic toxins**, include:

- **Further suppression of bone marrow**
- **Reduced red blood cell survival**
- **Platelet defects**
- **Gastrointestinal ulceration and bleeding**

### ***Uremic Toxins***

Uremic toxins are endogenous substances usually eliminated through or catabolized by the kidney, and are present in increased amounts when kidney function is decreased. They are responsible for producing the clinical signs associated with uremia. Urea and creatinine are not

thought to be as toxic as some other compounds, but as they increase in the course of renal failure and are easily measured, they serve as markers for uremic toxicity.

Uremic toxins include:

- Parathyroid hormone
- Gastrin
- Polyamines
- Middle molecules
- Aliphatic amines
- Polyamines
- Guanidino compounds

Other metabolic imbalances that contribute to the signs of uremia include:

- Hypokalemia
- Metabolic acidosis

### **Lipid Abnormalities**

Abnormalities in lipid metabolism that may occur in dogs with renal failure include:

- Increased low-density lipoproteins
- Decreased high-density lipoproteins
- Shift in cholesterol from high-density to low-density lipoproteins

In addition to creating a more atherogenic environment, these abnormalities may be responsible for the development of glomerular sclerosis and may contribute to the **progression of renal damage**.

### ***Progression of Chronic Renal Failure***

In most dogs, CRF is a progressive condition, although a small number will remain stable or even improve over time. Ongoing primary renal disease may be responsible for progression in some cases but secondary factors, operating independently of the primary disease, have also been implicated. These factors may initiate a self-perpetuating cycle of events, which promote further renal injury and a continued decline in function. They include:

- Failure to regulate phosphorus
- Glomerular hypertension
- Systemic hypertension

- Metabolic acidosis
- Renal inflammation
- Lipid abnormalities

It is, however, possible to influence a number of these factors by dietary management in order to slow progression of disease.

## ***Diagnosis***

Diagnosis of CRF is based on the chronic (more than 2 weeks) presence of azotemia of renal origin. Routinely used diagnostic tests include urinalysis, urine culture, urine protein:creatinine ratio, serum biochemistry, and complete blood count. It is also important to differentiate ARF from CRF, and findings that are suggestive of chronic disease include the presence of normocytic, normochromic anemia, small kidney size, and evidence of renal osteodystrophy.

## ***Clinical Signs***

Presenting clinical signs of chronic renal failure are likely to include:

- Polyuria and polydipsia
- Anorexia and weight loss
- Lethargy
- Pallor and/or ulceration of mucous membranes
- Vomiting and, perhaps, diarrhea
- Small, end-stage kidneys or enlarged kidneys due to hydronephrosis, pyelonephritis or renal neoplasia

Some cases may also exhibit:

- Neurologic signs
- Osteodystrophy (“rubber jaw,” facial hyperostosis)
- Ocular lesions associated with systemic hypertension

## ***Laboratory Findings***

### ***Hematology***

- Nonregenerative or mildly regenerative, normochromic, normocytic anemia
- Reduced platelet count

### ***Biochemistry***

- Raised blood urea nitrogen (BUN)

- Raised plasma creatinine
- Hyperphosphatemia
- Low, normal, or high serum calcium levels
- Raised alkaline phosphatase (AP) activity with renal secondary hyperparathyroidism and bone mineralization
- Hypercholesterolemia and hypoalbuminemia in nephrotic syndrome

### *Urinalysis*

- Specific gravity:
  - <1.030 if <65% of nephrons functional
  - 1.008 - 1.012 (isosthenuria) if < 75% of nephrons are functional
- Sediment (protein, blood, crystals, casts, WBCs, RBCs, depending on etiology)

## **Management**

Dietary manipulation is the cornerstone in the conservative medical management of CRF, but this represents only one aspect of the therapeutic strategy. Where an underlying primary disease has been identified, or if pre- or post-renal components are involved, specific therapy to correct these may be required. Where appropriate, additional supportive measures may include:

- Maintenance of normal hydration through the provision of unlimited access to drinking water, or via intravenous fluid replacement in cases of persistent vomiting or dehydration
- Avoidance of stress
- Oral administration of sodium bicarbonate to correct metabolic acidosis
- Administration of anabolic agents
- Use of intestinal phosphorus binders
- Supplementation with calcitriol and calcium
- Demulcent mouth washes and H<sub>2</sub> antagonists, such as ranitidine, to alleviate gastrointestinal disturbances
- Erythropoietin administration
- Avoidance of nephrotoxic drugs
- Institution of antihypertensive therapy
- Antibiotic therapy

Whereas it is not possible to affect a cure in CRF patients, appropriate medical management can result in good quality of life for the patient for months to years. In this respect, early diagnosis of CRF is desirable, as dietary modification has been shown to influence the progression of renal damage in the dog. Early detection may be facilitated through routine blood and urine analyses in the older animal, (e.g., in conjunction with “Older Pet Clinics”). These types of clinics

encourage owners of apparently healthy older dogs to test for azotemia as a sign of early renal failure, thus enabling early dietary management aimed at slowing progression of disease.

### **Dietary Management**

It is possible to influence the progression and effects of CRF by dietary manipulation. The goals may be summarized as follows:

- To meet the patient's nutrient and energy requirements
- To ameliorate clinical signs of uremia by reducing protein catabolites
- To minimize electrolyte, vitamin, and mineral disturbances
- To slow progression of renal failure

Since many of the clinical signs related to CRF are associated with the accumulation of toxic protein catabolites and failure to excrete phosphorus, the emphasis in dietary therapy is on modification of the phosphorus and protein contents of the diet. However, other dietary components to be considered include calcium, sodium, potassium, and water-soluble vitamins, together with the fat and dietary energy content.

### ***Phosphorus***

Dietary phosphorus restriction is a crucial part of management of CRF and has been shown to slow progression of renal failure in dogs and enhance survival rates (Brown *et al.*, 1991, Finco *et al.*, 1992). The mechanism for this effect remains unexplained, but it is likely that effects are related to a reduction in phosphorus retention that helps to limit:

- Secondary hyperparathyroidism
- Renal mineralization

Phosphorus restriction should, therefore, be initiated early in the course of CRF and should be considered for all dogs with azotemia resulting from primary renal failure. In azotemic dogs, phosphorus restriction should be the main dietary focus and is considerably more important than protein restriction.

The dietary therapy based on feeding low phosphorus diets aims to control serum phosphorus concentration and secondary hyperparathyroidism. Depending on the patient's phosphorus status, further control of hyperphosphatemia may be required and can be obtained with the use of oral phosphorus binding agents. These should be used only after patient acclimation to the diet, should always be administered with food, and are not useful in anorectic animals.

If phosphorus-binding agents do not achieve the goal of normalizing PTH concentrations, consideration should be given to supplementation with calcitriol. A once-daily oral regimen at an average dose of 2.5 ng/kg has been recommended for dogs. If calcitriol therapy is initiated, it is essential that serum calcium and phosphorus concentrations be monitored regularly.

### *Calcium*

Calcium per se does not affect progression of renal failure, although a decrease in serum ionized calcium levels may contribute to increased PTH release.

Recommendations in man, suggest that the calcium-phosphorus product [Ca x P] in the blood should not exceed 55 mg/dl, as this may promote soft tissue calcification and lead to further progression of renal disease. This may equally apply to dogs, and calcium should therefore only be supplemented in individuals who are not hypercalcemic.

Serum calcium levels may be low, normal, or high in dogs with CRF. Therefore dietary calcium levels should be adjusted to suit the individual patient; whereas calcium supplementation may be required in hypocalcemic individuals and is contraindicated in the presence of hypercalcemia.

### *Sodium*

Sodium balance may be disrupted in advanced CRF and systemic hypertension can occur in affected dogs.

There is some controversy regarding the prevalence of hypertension in dogs with chronic renal disease; some reports suggest a prevalence of 58% to 93%, whereas others suggest a much lower figure (Cowgill and Kallet 1983, Michell and Bodey 1994). Hypertension in renal patients is important for two reasons:

- It can result in a number of pathophysiologic consequences including left ventricular atrophy, neurologic abnormalities, and ocular lesions.
- It may contribute to progression of renal disease.

The reduction of blood pressure in hypertension is thus a desirable goal of therapy. It is recommended that dietary sodium levels are either normal or *moderately* restricted, since excessive sodium restriction may also be detrimental. Severe sodium restriction could promote volume depletion in dogs with CRF that are unable to adapt to such a low sodium intake. Since CRF impairs the capacity for rapid adjustment to changes in sodium intake, any modification in dietary sodium content should be accomplished gradually over several days.

## *Water-Soluble Vitamins*

Polyuria is a very common clinical sign in dogs with CRF. Water-soluble vitamins are excreted in urine and are not stored within the body, thus there is a risk of polyuric patients developing a deficiency for these vitamins. Dietary vitamin levels should be adequate to compensate for possible losses.

Additionally, dogs with CRF may show a reduction in appetite and may not eat enough to meet their energy and nutrient requirements. Increased levels of B vitamins are therefore recommended in diets designed to support dogs with chronic renal disease.

## *Protein*

Contrary to historic belief, dietary protein restriction does not slow progression of renal disease. Restriction of dietary protein is, however, beneficial in uremic patients, as it:

- Minimizes the accumulation of protein catabolites
- Helps limit the intake of dietary phosphorus
- Reduces the protein-related solute load on the failing kidneys, thereby lessening the severity of polydipsia/polyuria
- Decreases the acid load which may help to control metabolic acidosis

The protein requirements of dogs with CRF have not been established, but it is likely that they may be as high, possibly higher, than those of healthy animals. Many azotemic dogs do not show any, or mild, clinical signs and may therefore lead a normal life, most likely requiring normal levels of dietary protein intake.

Even though dietary protein restriction is beneficial to uremic dogs, excessive restriction is to be avoided, since it can result in protein malnutrition. Furthermore, uremia is a catabolic state, which may adversely affect several aspects of protein metabolism. In addition, renal failure may lead to increased urinary losses of protein or specific amino acids. It is therefore important that high quality protein sources are used in the formulation of restricted protein diets, in order to minimize the risks of essential amino acid deficiency.

For dogs with CRF, a staged approach to management is recommended. All cases will benefit from phosphorus restriction. Additionally, early cases are generally best maintained on protein intake that adequately meets adult maintenance requirements. More advanced cases, which are showing clinical signs of uremia, should be fed diets which are restricted in both phosphorus and protein. Where possible, the degree of protein restriction should be individualized according to the dog's clinical and biochemical status.

## *Energy*

It is important to minimize the metabolism of protein, both from dietary and endogenous sources, in dogs with CRF, since protein break down will add to the amount of nitrogenous waste production, which need to be excreted through the impaired kidneys. Feeding an energy-dense diet, in which the energy content is derived to a large extent from nonprotein sources, can help to decrease tissue catabolism and reduce nitrogenous waste products.

Both carbohydrates and fat are alternative nutrients supplying calories, but of the two, fat offers certain advantages. Fat is very energy dense and offers approximately twice the energy per gram. Additionally, fat is very palatable to dogs.

As appetite is often poor in affected animals, the energy density of the diet should be high to enable the animal to obtain its nutritional requirements from a relatively small volume of food. Adequate levels of dietary fat are therefore particularly useful, increasing the energy density and ensuring good palatability.

## **SUMMARY**

Dietary management is a key element in the conservative medical treatment of chronic renal failure. Appropriate dietary modifications can alleviate clinical signs of uremia and may help to slow progression of the disease. In particular, phosphorus restriction helps to limit renal mineralization and secondary hyperparathyroidism, and has been shown to slow progression of renal damage. This is therefore an important measure to address early in the course of the disease, both in azotemic and uremic patients.

Restriction of dietary protein is of clinical benefit to uremic patients since this minimizes the accumulation of protein catabolites, limits the intake of dietary phosphorus, reduces the protein-related solute load, and reduces the dietary acid load. Nevertheless, excessive protein restriction is to be avoided since this can result in breakdown of endogenous protein sources and ultimately in protein malnutrition.

A staged approach to the dietary management of chronic renal failure is recommended for dogs, in which phosphorus is restricted in the early stages of azotemia. Protein should be fed at an individualized level based on the patient's clinical and biochemical status, restricted only to a level which will help to avoid the development of uremia. Feeding an energy-dense diet, in which the energy content is derived to a large extent from nonprotein sources, helps to decrease tissue catabolism and reduce nitrogenous waste production. Other nutrients to be considered include calcium, sodium, potassium, and water-soluble vitamins.

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