

The Feline Kidney



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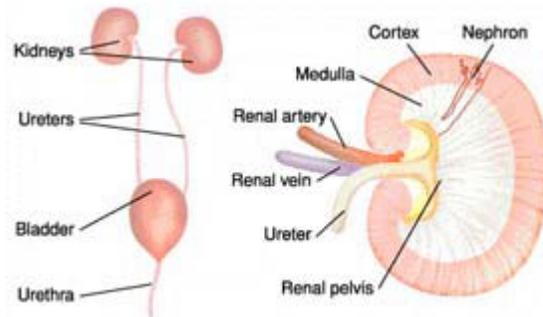
KEY POINTS

- **Chronic renal failure (CRF) is irreversible but can be managed by medical therapy, with dietary management being the key component thereof.**
- **Because dietary management may help to slow disease progression, early recognition through routine blood and urine analyses in older cats is desirable.**
- **Dietary phosphorus restriction is of greatest importance since it helps to reduce renal mineralization and renal secondary hyperparathyroidism and thus may help to slow progression of disease.**
- **Restriction of dietary protein is of clinical benefit in uremic patients because it will help to control polyuria/polydipsia, metabolic acidosis, and other uremic signs; it also helps to limit phosphorus intake.**
- **Excessive protein restriction in cats may increase the risk of protein malnutrition.**
- **Potassium supplementation is beneficial in most cats with CRF.**
- **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 avoid the development of systemic hypertension; however, introduction of a diet with restricted 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.**
- **Energy should be supplied from nonprotein sources to limit protein catabolism; fat is useful since this increases both energy density and palatability of the diet.**

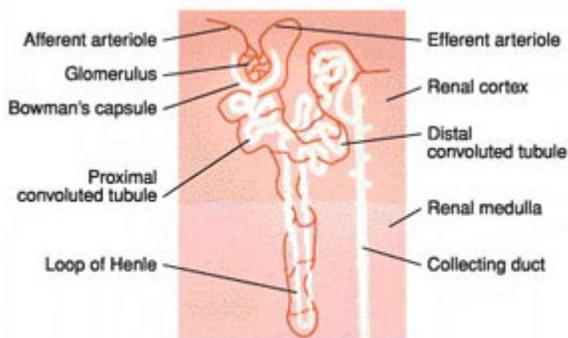
The kidneys are responsible for the excretion of nitrogenous and other metabolic waste products and for the regulation of water, electrolyte, and acid-base balance. When renal function is reduced, dietary factors can influence the clinical course of the disease by improving clinical signs and by helping 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 that projects into the renal pelvis. The ureter is a tubular structure that conveys urine from the renal pelvis to the bladder.



Diagrammatic representation of the kidney



Diagrammatic representation of a nephron

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. Subsequently, the vessel divides into capillaries that surround the nephron tubules and eventually drain into the renal vein.

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 the extracellular environment with respect to 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 D₃. 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 ultrafiltration of blood from the glomerulus and subsequent modification of the filtrate in the renal tubule. Filtration is aided by the hydrostatic pressure created as a result of 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 to become part of the urine. The modified filtrate finally emerges from a collecting duct as urine.

Excretory Function

The kidneys excrete 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 are concentrated in the urine if they are poorly reabsorbed following glomerular filtration or if they are actively secreted into the tubular fluid.

Regulatory Function

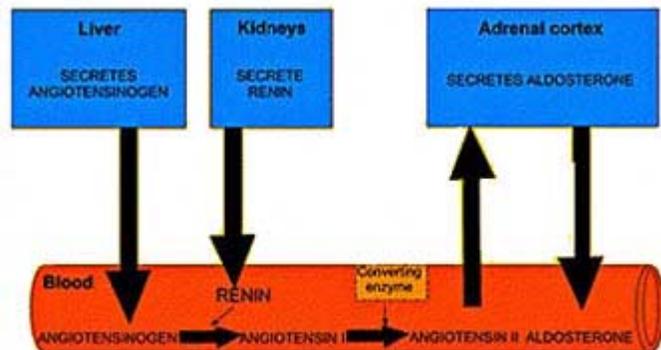
The kidneys are responsible for the maintenance of water, electrolyte, and acid-base balance in the body.

- **Water homeostasis** by the kidney is mediated by 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 by increasing the permeability of the collecting duct.
- The kidneys are of primary importance in maintaining **sodium homeostasis** but are also involved in the regulation of other electrolytes, particularly potassium, phosphate, and calcium. Aldosterone, a mineral corticoid hormone secreted by the adrenal gland, promotes sodium retention and potassium loss. Atrial natriuretic peptide is released from cells in 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, and vitamin D₃ (calcitriol) and of prostaglandins and antihypertensive lipids.

- **Renin** is secreted by the kidney in response to lowered intraarteriole pressure. It transforms angiotensinogen to angiotensin I, which is then converted to its active form, angiotensin II, by an “angiotensin-converting enzyme,” primarily in the lungs. 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 oppose the effects of renin.
- **Erythropoietin** is necessary for red blood cell formation in bone marrow.
- The **conversion of vitamin D₃** to its active form α -1,25-dihydroxycholecalciferol (calcitriol) is carried out in the kidneys and mediated by the enzyme 1- α -hydroxylase in response to a fall in plasma calcium concentration. Activation is facilitated by parathyroid hormone (PTH). Active vitamin D₃ promotes calcium absorption in the gut.

CLINICAL DISORDERS

Renal failure is defined as the inability of the kidneys to adequately perform their normal functions resulting in the development of azotemia and disturbances of fluid, electrolyte, and acid-base balance. Because the kidney has a large functional reserve capacity, signs of disease do not occur until 65-75% 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 2 weeks' duration.

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

factors, as well as primary renal disease. Azotemia may be present in animals without overt signs of clinical disease.

Glomerular filtration rate is the rate of fluid movement through the glomerular capillary walls into Bowman's space.

Uremia is the polysystemic toxic syndrome that 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 GFR and the rapid development of azotemia and uremia. Intrarenal causes of ARF include:

- **Acute tubular necrosis** (nephrosis) resulting from injury due to nephrotoxins or ischemia
- **Acute nephritis**, usually associated with septicemia or chronic infections, such as pyometritis, cutaneous abscess, or pyothorax
- **Idiopathic** (i.e., no cause can be determined)
- **Acute trauma**

Acute renal failure of renal origin must be differentiated from azotemia of prerenal or postrenal 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.

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 ARF may be vague and 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 (>15 ml urine/kg bodyweight/day)

If untreated, renal failure progresses and may result in severe systemic disease, manifesting as:

- **Shock**
- **Disseminated intravascular coagulation** (DIC)
- **Respiratory distress**
- **Neurologic disturbances**
- **Coma and death**

Laboratory Findings

Hematology

- Regenerative anemia associated with blood loss
- Thrombocytopenia
- Stress or inflammatory leukogram
- Basophilic stippling of red blood cells in lead toxicity
- Raised packed cell volume (PCV) if dehydrated

Biochemistry

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

Urinalysis and Urine Culture

- Specific gravity:
 - <1.035 - 1.040 in primary renal failure
 - >1.045 in prerenal azotemia
- Osmolality:
 - <350 mOsm/L (dilute) in primary renal failure
 - >500 mOsm/L (concentrated) in prerenal azotemia
- Urinary sediments (protein, blood, crystals, tubular casts, and/or cells, depending on etiology)
- Positive urine culture with pyelonephritis

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

	Acute renal failure	Chronic renal failure
History	Previously healthy	PUPD, inappetence, weight loss
Body score	Normal	May be thin to cachectic
Kidney size	Normal to enlarged	Variable; normal, small and irregular, or enlarged
Anaemia	Possible from blood loss or haemolysis	Common, due to lack of erythropoietin
Potassium	+ Hyperkalaemic	+ Hyperkalaemic
Phosphorus	Hyperphosphataemic	Hyperphosphataemic (same)
Urine sediment	Active: Casts, debris	Inactive usually
Urine production	Anuric, oliguric or polyuric	Polyuric
Prognosis	Potentially reversible	Irreversible, but manageable

Clues to the Differentiation of Acute Verses chronic renal failure

Diagnosis

Diagnosis of ARF is based on the acute onset of azotemia (of renal origin), an inability to concentrate urine, and uremic signs, which may be accompanied by oliguria. The history may reveal exposure to causal factors including trauma, nephrotoxins, and ischemic injury. It is important to differentiate ARF from CRF.

Management

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

- Early recognition of disease
- Identification and treatment of specific 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:

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

Fluid therapy is of primary importance, and rehydration with Hartmann's solution 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 a lower sodium content (e.g., 0.45% NaCl and 2.5% dextrose) should be given, and fluid input should equal output. If the animal remains oliguric, appropriate diuretic therapy may be introduced.

Additional therapeutic measures that may be required include:

- **Avoidance** of nephrotoxic drugs
- **Gastric protectants** and **antiemetics** to alleviate GI disturbances
- **Potassium supplementation** in stabilized, polyuric patient with hypokalemia
- **Nutritional support**
- **Insulin** (with glucose) to correct severe hyperkalemia
- **Calcium gluconate** to counteract the immediate effect of hyperkalemia on myocardium
- **Sodium bicarbonate** to correct metabolic acidosis (if pH <7.1) and/or hyperkalemia
- Institution of **antihypertensive therapy**
- **Antibiotic therapy** if a urinary tract infection is present

If there is no response to aggressive therapy within 24 to 36 hours, peritoneal dialysis should be considered.

Dietary Management

Maintenance of energy intake is important in uremic patients to prevent the catabolism of tissue proteins to meet energy requirements.

Subsequently, nutritional support must be provided. The principles of dietary therapy are the same as those outlined for the management of CRF. 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 it does not require general anesthesia.

Chronic Renal Failure

Chronic renal failure is a relatively common syndrome in older cats and represents the end stage of a number of renal diseases. It is a condition in which existing renal damage is irreversible and often 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 apparent until at least 65-75% of renal tissue is destroyed; thus unless blood and urine parameters are routinely monitored, early cases often go undetected.

Laboratory Findings

Hematology

- Normocytic normochromic nonregenerative, or poorly regenerative, anemia
- Reduced platelet count

Biochemistry

- Raised BUN
- Raised plasma creatinine
- Hyperphosphatemia
- Hypokalemia or, in some (usually advanced) cases, hyperkalemia
- Decreased total CO₂ (metabolic acidosis)
- Hypercholesterolemia

Urinalysis

- Specific gravity: <1.035 - 1.040 (often <1.018)
- Sediment (protein, blood, crystals, and/or casts on etiology)

Etiology

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

- Glomerulonephritis
- Pyelonephritis
- Chronic interstitial nephritis
- Renal amyloidosis
- Neoplasia, especially lymphosarcoma
- Hydronephrosis
- Renal urolithiasis
- Congenital renal disease
- Feline infectious peritonitis

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 (e.g., feline leukemia virus, feline infectious peritonitis), 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 CRF.

This primary glomerular disease results 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 asymptomatic cases.

Nephrotic syndrome is a consequence of advanced glomerular disease characterized by marked proteinuria and hypoalbuminemia and then generalized edema. In severe cases, it may be complicated by the presence of CRF.

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. 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, as much as possible, allowing for the correction of hypoalbuminemia.

Pyelonephritis

Pyelonephritis is an inflammatory condition of the renal parenchyma caused by bacterial infection; in the majority of cases, the involvement is bilateral. Most are associated with an ascending urinary tract infection due to vesicoureteral reflux, but hematogenous infection can occur if there is preexisting tissue damage or urinary obstruction that interferes with elimination of bacteria. Inflammation and suppuration of the kidney are followed by tissue destruction and fibrosis, which may eventually lead 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, as is 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 if bacteriuria is present, and patients with uremic signs should be managed accordingly.

Renal Amyloidosis

Renal amyloidosis is caused by the deposition of a hyaline protein, amyloid, in renal tubules (as opposed to the glomeruli in dogs) and usually occurs in association with other chronic systemic inflammatory disease. A familial predisposition has been reported in the Abyssinian breed.

Renal Neoplasia

Primary renal neoplasia is rare in the cat but renal carcinomas do occasionally occur, giving rise to weight loss, anorexia, pyrexia, and hematuria. Lymphosarcoma is the commonest tumor affecting the feline kidney and is often associated with feline leukemia virus infection. CRF 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 dilation of the renal pelvis leading to 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 pyonephrosis, which presents clinically and is treated as for pyelonephritis.

Bilateral, complete obstruction results in the rapid development of ARF before extensive hydronephrotic changes are evident. CRF will develop only if both kidneys are affected (if, for example, the obstruction is partial and bilateral) or if function is otherwise impaired in the contralateral kidney.

Renal Urolithiasis

Renal urolithiasis is rare in cats since most feline 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.

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.

Congenital Renal Disease

Congenital renal disease can give rise to CRF in young cats (usually less than 24 months of age). Specific disorders include:

- **Agenesis of the renal cortex**
- **Renal fusion**
- **Polycystic kidneys** (more common in long-haired cats)
- **Hydronephrosis**

The dry form of *feline infectious peritonitis* may occasionally result in the formation of perivascular granulomas in the kidneys and the development of CRF. Affected kidneys are usually enlarged.

Pathophysiology

Chronic renal disease results in a progressive loss of functional tissue. However, compensatory mechanisms help to maintain normal kidney function until approximately 65-75% of nephrons have been destroyed. A decline in 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 potassium homeostasis**
- **Impaired sodium homeostasis**
- **Failure to maintain acid-base balance**
- **Impaired erythropoietin synthesis**
- **Systemic hypertension**

In most cats, a progressive decline in renal function occurs, with patients ultimately dying of uremic complications.

Disturbances of Fluid Balance

Renal tubular damage in CRF impairs the animal's ability to concentrate urine, partly due to an insensitivity to ADH, which 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 loss. This produces the characteristic polyuria and compensatory polydipsia of CRF.

In cats, however, this phenomenon is less pronounced than in dogs. Cats have a higher intrinsic urine-concentrating ability that appears to be maintained for longer in CRF. In addition, cats tend to urinate out of sight of their owners and thus polyuria may initially go unobserved. Restriction of water intake in the polyuric animal can lead to dehydration and a worsening of azotemia and may precipitate the onset of ARF. Urinary losses of water-soluble vitamins (*David's text*) are also increased in polyuric CRF.

Impaired Excretion of Nitrogenous Waste

Reduced glomerular filtration results in the accumulation of metabolic waste products in plasma, particularly those 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 (particularly urea) in blood may contribute to a number of observed uremic signs, including:

- **Polydipsia** and **polyuria**
- **GI signs**
- **Neurologic signs**

Gastrointestinal signs, including oral and GI ulceration, vomiting, and occasionally diarrhea, are multifactorial in origin. Uremic toxins may promote:

- **Hypergastrinemia**, leading to increased gastric acid secretion
- **Stimulation of the chemoreceptor trigger zone in the brain**, causing nausea and vomiting

Neurologic signs are quite important, particularly in the contribution they may make to anorexia, depression, nausea, and vomiting. PTH may be an important neurologic toxin in this respect. Occasionally, 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.

Hyperfiltration

With the progressive destruction of functional nephrons in renal disease, surviving nephrons undergo a compensatory response characterized by:

- **Glomerular hypertrophy**
- **Glomerular hypertension**
- **Glomerular hyperfiltration**

Initially, these adaptive changes are beneficial. By enhancing whole kidney GFR, they help to maintain renal function, provided that the kidneys are not subjected to undue physiologic stress. At this stage, the animal is said to be in *compensated renal failure*.

However, these sustained adaptive changes may also be detrimental since they are thought to induce glomerular sclerosis in the surviving nephrons and may therefore exacerbate renal injury.

The effect would be to further reduce GFR and thereby initiate a self-perpetuating cycle of events that may contribute to the progression of CRF.

As a result of the compensatory mechanisms, CRF is not clinically apparent until approximately 65-75% of nephrons have been destroyed. At this stage, factors that act to decrease GFR exceed the capacity of the damaged kidney to compensate and whole kidney GFR is reduced.

Glomerular hypertrophy is an increase in size of the glomerulus.

Glomerular hypertension describes an increase in glomerular capillary pressure that may arise independently of systemic hypertension.

Glomerular hyperfiltration is an increase in single nephron GFR.

Impaired Mineral Homeostasis

Impaired Phosphorus Homeostasis

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

Renal mineralization appears to be common in cats with CRF and may be an important factor in 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, PTH promotes uptake of calcium into cells, which, if excessive, can cause 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 occurs in tubule lumens, which contributes 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.

Impaired Potassium Homeostasis

Hypokalemia has been shown to be the most common electrolyte abnormality in cats with CRF. Increased urinary potassium losses may represent a primary renal abnormality peculiar to cats with CRF and can lead to potassium depletion if compounded by decreased dietary potassium intake. Acid-base balance will also affect distribution of potassium between intra- and extracellular compartments of the body. Diets that promote acidic urine, particularly if they are marginal in potassium content, may induce hypokalemia in cats and should be avoided in animals with CRF.

Hypokalemia may be an important cause of muscle weakness in cats with CRF, but it is also thought to adversely affect renal function and thus contribute to the progression of renal damage.

A number of cats in CRF are hyperkalemic, and this may be a reflection of the severity of renal insufficiency. This emphasizes the need for monitoring of potassium status in cats with CRF and adjusting intake on an individual basis.

Impaired Sodium Homeostasis

Sodium homeostasis is maintained primarily by the kidneys. In the diseased state, as 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 changes in sodium intake becomes progressively limited as the disease advances.

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**

Renal Secondary Hyperparathyroidism

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

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

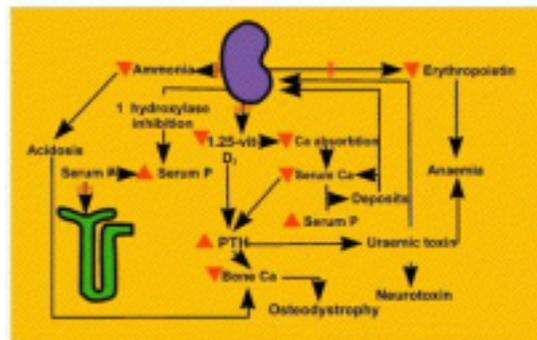


Diagram of Development of Renal Secondary Hyperparathyroidism.

In the healthy animal, PTH helps to normalize elevated serum phosphorus by depressing tubular reabsorption of phosphate. In CRF, however, this homeostatic mechanism is unable to control serum phosphorus concentration and sustained PTH release becomes an undesirable effect. PTH is thought to be an important uremic toxin, which may contribute to:

- **Anemia**
- **Neurotoxicity**
- **Dyslipoproteinemia**
- **Insulin resistance**
- **Renal osteodystrophy**
- **Promotion of soft tissue calcification**
- **Progression of renal damage**

Decreased Calcitriol Levels

In CRF, production of calcitriol (α -1,25 covalciferol) is reduced because:

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

Hypocalcemia

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

- **Decreased intestinal absorption** due to low calcitriol levels
- **Decreased dietary intake** following anorexia
- **Deposition of calcium-phosphate complex** in tissues, which reduces serum ionized 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.

Renal Osteodystrophy

Renal osteodystrophy is characterized by an increased osteoclastic resorption of bone due to increased PTH (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.

Failure to Maintain Acid-Base Balance

Renal failure results in a decreased 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, potentially leading to acid retention and metabolic acidosis.

Metabolic acidosis is common in cats with CRF and 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, increase 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 CRF.

Impaired Erythropoietin Synthesis

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

- **Lethargy**
- **Weakness**

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**
- **GI ulceration and bleeding**

Progression of Chronic Renal Failure

In most cats, 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 that promote further renal injury and a continued decline in function. They include:

- **Failure to regulate phosphorus**
- **Glomerular hypertension**

- **Systemic hypertension**
- **Metabolic acidosis**
- **Hypokalemia**
- **Renal inflammation**

A number of these factors can be influenced by dietary management.

Uremic Toxins

Uremic toxins are those substances that are responsible for the production of clinical signs associated with uremia.

The major uremic toxins are now thought to include:

- **Parathyroid hormone**
- **Urea**
- **Aliphatic amines**
- **Polyamines**

Urea is thought to be of minor importance as a uremic toxin, but is important as a marker of uremia. Creatinine is considered nontoxic.

Clinical Signs

Presenting clinical signs are likely to include:

- Anorexia and weight loss
- Lethargy and weakness
- 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.
- Polyuria and polydipsia (less common than in the dog)

Some cases may also exhibit:

- Neurologic signs
- Osteodystrophy
- Ocular lesions associated with systemic hypertension

Diagnosis

Diagnosis of CRF is based on the chronic (>2 weeks) presence of azotemia (of renal origin) and uremic signs. It is important to differentiate ARF from CRF, but findings that are suggestive of chronic disease include the presence of normocytic normochromic anemia and evidence of small kidney size and renal osteodystrophy.

MANAGEMENT

Dietary manipulation is a cornerstone in the conservative medical management of CRF and represents an important 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 possible. Additional supportive measures may include, where appropriate:

- Maintenance of normal hydration through the provision of unlimited access to drinking water or via intravenous fluid replacement in cases of persistent vomiting
- Avoidance of nephrotoxic drugs
- Avoidance of stress
- Phosphorus binders
- Demulcent mouth washes and H₂ antagonists, such as ranitidine, to alleviate GI disturbances
- Administration of sodium bicarbonate to correct metabolic acidosis
- Supplementation with calcitriol and calcium
- Erythropoietin
- Institution of antihypertensive therapy
- Anabolic agents
- Anticonvulsant therapy
- Antibiotic therapy if infection is present

While it is not possible to effect a cure in CRF patients, appropriate medical management can result in good quality of life for the patient for months to years. Early diagnosis and treatment of CRF may improve long-term survival, but owner recognition of potential problems may be delayed because early clinical signs may be relatively subtle in cats. Detection of early cases may be facilitated through routine blood and urine analyses in the older animal.

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 animal's nutrient and energy requirements
- To ameliorate clinical signs of uremia by reducing protein catabolites

- To minimize electrolyte, vitamin, and mineral disturbances
- To try to slow progression of renal failure
- To decrease hyperphosphatemia and minimize secondary hyperparathyroidism

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 potassium, calcium, sodium, and water-soluble vitamins, together with the dietary energy content and fat.

Phosphorus

Dietary phosphorus should be restricted. Dietary phosphorus restriction is an important part of management of CRF and may slow progression of renal failure, even though the mechanisms are not fully understood. It is likely that the beneficial effects are related to a reduction in phosphorus retention that helps to limit:

- **Renal mineralization**
- **Secondary hyperparathyroidism**

Phosphorus restriction should therefore be initiated early in the course of CRF and should be considered for any cat with azotemia shown to result from primary renal failure.

Dietary therapy aims to normalize serum phosphorus concentration and control secondary hyperparathyroidism. Further control of hyperphosphatemia may be obtained with the use of oral phosphorus-binding agents, which should always be administered with food.

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 cats. If calcitriol therapy is initiated, it is essential that serum calcium and phosphorus concentrations are monitored regularly.

Protein

Restriction of dietary protein is beneficial in uremic patients. Restriction of dietary protein is of clinical benefit in uremic patients since this:

- Minimizes the accumulation of protein catabolites
- Helps to 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

Nevertheless, excessive protein restriction is to be avoided since this can result in protein malnutrition and the catabolism of endogenous proteins. Uremia is a catabolic state that may adversely affect several aspects of protein metabolism. In addition, renal failure may lead to increased urinary losses of protein or specific amino acids. The protein requirements of cats in CRF have not been established but it is likely that they may be different, possibly higher, than those of the healthy animal. It is therefore important that high-quality protein sources are used in the formulation of restricted-protein diets to minimize the risks of essential amino acid deficiency.

Because of their unique metabolism of protein, cats are at greater potential risk of protein malnutrition than dogs when protein intake is restricted. Furthermore, extremely low-protein diets tend to be unpalatable to cats, which may reduce intake and further increase the risk of protein malnutrition. Diets for all cats with CRF should therefore be palatable and contain sufficient protein to meet the cat's nutritional requirements, which should not be less than 18-20% of metabolizable energy in the diet.

It is not clear whether dietary protein restriction has any impact on the progression of renal failure in cats. Current recommendations are that *all* cats with azotemia of renal origin and moderate hyperphosphatemia (that persist following rehydration) should be fed diets that are restricted in phosphorus and moderately restricted in protein, even when they are not showing signs of uremia.

Energy

Sufficient energy should be available from nonprotein sources to meet the patient's requirements. Feeding an energy-dense diet, in which the energy content is derived from nonprotein sources, minimizes tissue catabolism and helps to reduce nitrogenous waste production. Appetite is often poor in affected animals, so 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. Fat is particularly useful in this respect, since it increases energy density and aids palatability of the diet. For this reason, canned diets designed to support cats with CRF tend to be high in fat.

Water-Soluble vitamins

Dietary vitamin levels should be adequate to compensate for possible losses. Requirements for water soluble (B-complex) vitamins are increased in cats with CRF because of :

- Reduced intake (inappetence)
- Increased urinary losses in polyuric cases

Other Nutrients

Potassium

Dietary potassium levels should be enhanced for most cats with CRF, but regular monitoring of potassium status is essential. Hypokalemia is a significant problem in cats with CRF, and supplementation in these cases is beneficial. However, hyperkalemia may be a complication in a small number of cases, requiring an adjustment of dietary intake.

Calcium

Dietary calcium levels should be adjusted to suit the individual patient. Serum calcium levels may be low, normal, or high in cats with CRF. Calcium supplementation may be required in hypocalcemic individuals but contraindicated in the presence of hypercalcemia.

Sodium

Dietary sodium levels should be moderately restricted. Sodium balance may be disrupted in advanced CRF, and systemic hypertension can occur in affected cats. It is currently recommended that dietary sodium levels are either normal or *moderately* restricted, since excessive sodium restriction may also be detrimental. Because 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.