Chapter 37

Chronic Kidney Disease

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"When things are investigated, then true knowledge is achieved."
Confucius

INTRODUCTION

Chronic kidney disease (CKD) is the most common disease affecting the kidneys of dogs and cats. It may be recognized by reduced kidney function or the presence of kidney damage. CKD is defined as kidney damage present for at least three months, with or without decreased glomerular filtration rate (GFR) or greater than 50% reduction in GFR persisting for at least three months (Polzin et al, 2005). Kidney damage is further defined as either 1) microscopic or macroscopic pathologic changes detected by histologic or direct visualization of the kidneys or 2) markers of damage detected by blood or urine tests or imaging studies. In the past, multiple terms were used to define the severity of renal functional abnormalities including renal insufficiency, renal failure and uremia. However, there has not been uniform agreement on the specific definition of renal insufficiency vs. renal failure. Therefore, it has been recently proposed by the International Renal Interest Society (IRIS) to replace these terms with a scheme to classify severity of CKD into four stages based on stable serum creatinine concentrations (**Table 37-1**). Two of the foundational assumptions inherent in this classification scheme are that the presence of CKD has been confirmed and that azotemia, if present, has been localized as renal in origin. This classification scheme emphasizes the continuum of severity of renal injury of dogs and cats with documented presence of kidney damage without evidence of azotemia in stage 1 CKD, to progressively more severe CKD with resultant increasing serum creatinine concentration for stages 2 to 4. Furthermore, by using the term "kidney disease" and staging the severity of disease, it is possible to facilitate understanding, communication and application of management guidelines for patients in each stage.

The goals of this chapter are to provide pathophysiologic concepts and practical nutritional management recommendations for dogs and cats with CKD. Nutritional management of patients with CKD includes measures to reduce signs of uremia and slow progression to later stages of disease. There is general agreement regarding nutritional management of CKD when overt signs exist; however, the role of nutritional intervention during earlier stages of CKD is less well defined. Thus, in a sense, the question is not whether to use nutritional management but when should it be initiated. Because detection of CKD in its early stages is difficult and there appears to be no harm in avoiding nutrient excess (e.g., phosphorus) during earlier stages, nutritional management should be considered by stage 2 CKD and is clearly indicated when serum creatinine exceeds 2 mg/dl (179 μmol/l) (Jacob et al, 2002; Ross et al, 2006). Similarly, significant and persistent renal proteinuria,

Table 37-1. International Renal Interest Society (IRIS) Staging System for Chronic Kidney Disease in Dogs and Cats.

Stage	Serum creatinine (dogs)	Serum creatinine (cats)	Substage based on proteinuria and hypertension	Comments
1	<1.4 mg/dl (<125 μmol/l)	<1.6 mg/dl (<140 μmol/l)	Proteinuria: NP/BP/P* Hypertension: N/L/M/H/nc/c/RND**	Non-azotemic CKD Clinical signs (other than PU/PD) usually absent
2	1.4-2.0 mg/dl (125-179 μmol/l)	1.6-2.8 mg/dl (140-249 μmol/l)	Proteinuria: NP/BP/P* Hypertension: N/L/M/H/nc/c/RND**	Mild renal azotemia (overlaps with reference range) Clinical signs (other than PU/PD) usually mild or absent
3	2.1-5.0 mg/dl (180-439 μmol/l)	2.9-5.0 mg/dl (250-439 μmol/l)	Proteinuria: NP/BP/P* Hypertension: N/L/M/H/nc/c/RND**	Moderate renal azotemia Extrarenal clinical signs usually begin in this stage
4	>5.0 mg/dl (>440 μmol/l)	>5.0 mg/dl (>440 μmol/l)	Proteinuria: NP/BP/P* Hypertension: N/L/M/H/nc/c/RND**	Severe renal azotemia Many extrarenal clinical signs usually present

Key: PU/PD = polyuria/polydipsia, UPC = urine protein-creatinine ratio, BP = blood pressure.
*NP = non-proteinuric (UPC <0.2), BP = borderline proteinuric (UPC = 0.2 to 0.4 in cats and 0.2 to 0.5 in dogs), P = proteinuric (UPC >0.4 in cats and >0.5 in dogs).
**N = minimal risk of complications (systolic BP <150 mm Hg), L = low risk of complications (systolic BP 150 to 159 mm Hg), M = moderate risk of complications (systolic BP 160 to 179 mm Hg), H = high risk of complications (systolic BP >180 mm Hg), nc = no evidence of hypertensive complications, c = hypertensive complications present, RND = risk not determined (blood pressure not measured).
Adapted from www.iris-kidney.com.

even in the absence of azotemia, reflects marked renal damage and signals the need for nutritional management regardless of the CKD stage.

CLINICAL IMPORTANCE

Prevalence of Chronic Kidney Disease

CKD is a common cause of morbidity and mortality in dogs and cats. In a survey of 1,600 pet dogs over five years of age examined at a European veterinary college for a variety of reasons, approximately 20% had abnormally increased markers of renal function. It is not known how many of these dogs had kidney disease (Leibetseder and Neufeld, 1991). In a cross-sectional study of 31,484 dogs and 15,226 cats evaluated in private practices across the United States in 1995, the prevalence of kidney disease was 2.2% in cats and 0.8% in dogs (Kirk et al, 2001). During 1990, the diagnosis of CKD in cats of all ages reported to the Veterinary Medical Data Base was 16 cases/1,000 cats examined. By 2000, diagnosis of CKD in cats of all ages was 96 cases/1,000 cats examined (Ross et al, 2006). Increased diagnosis of CKD in cats may be due to their living longer, more of them being screened for CKD and/or increased awareness of CKD by veterinarians. CKD appears to be a common cause of death in dogs and cats. In a retrospective study of dogs, 2% died from chronic nephritis, 2% from pyelonephritis and 1% from glomerulonephritis (Bronson, 1982). Thus, the overall mortality from kidney diseases was 5%. With the exception of cancer, kidney disease was the most common cause of death in this study. In a 1991 survey by the Morris Animal Foundation of readers of *Companion Animal News,* respondents indicated that of 325 cats that had died, 94 succumbed to kidney disease (MAF, 1991). By comparison, 39 of the 325 died of feline leukemia and 45 died due to other causes.

Relationship Between Age and Kidney Disease

CKD occurs in dogs and cats of all ages, but it is frequently a disease of older pets. In a retrospective study of 70 cats with CKD, diagnosed from 1973 to 1984, ages ranged from nine months to 22 years (mean, 9.2 ± 5.5 years). Nine cats (12.8%) were less than three years old, 24 (34.3%) were four to seven years old and 37 (52.9%) were more than seven years old (DiBartola et al, 1987). In a study of 175 cats diagnosed with CKD in Australia from 2000 to 2003, ages ranged from two to 21 years (mean, 13.2 ± 3.7 years). However, the majority (69%) were 12 to 18 years old (White et al, 2006). The mean age for cats diagnosed with CKD at the Animal Medical Center in New York from 2000 to 2002 was 12.8 ± 4.4 years (Boyd et al, 2008). Analysis of data from university teaching hospitals contributed to the Veterinary Medical Data Base from 1980 to 1990 indicated that 37% of cats with CKD were less than 10 years old, 31% of cats were between 10 and 15 years old and 32% of cats were older than 15 years (Lulich et al, 1992). In a 1995 survey of private practices, the mean ages of dogs and cats with kidney disease were 10.2 and 13.2 years, respectively (Kirk et al, 2001). Another study in dogs showed a similar relationship between aging and occurrence of CKD. Prevalence of CKD was reported to be nine cases/1,000 dogs of all ages examined, 12.5 cases/1,000 in dogs between seven and 10 years old, 24 cases/1,000 in dogs between 10 and 15 years old and 57 cases/1,000 in dogs over 15 years old (Polzin et al, 1995).

Causes of Kidney Disease

Familial Kidney Diseases

Juvenile kidney disease increases suspicion of a familial

Table 37-2. Kidney diseases suspected or confirmed to be inherited in dogs and cats.

Kidney disease	Canine breeds	Feline breeds
Amyloidosis	Beagle, collie, foxhound, Chinese Shar-Pei, Walker hound	Abyssinian, Siamese, Oriental
Atrophic glomerulopathy	Rottweiler	–
Fanconi syndrome	Basenji, border terrier, miniature schnauzer, Norwegian elkhound, Shetland sheepdog	–
Glomerulonephropathy	Beagle, Bernese mountain dog, bull mastiff, Dalmatian, Doberman pinscher, soft-coated wheaten terrier	–
Glomerulosclerosis	Newfoundland	–
Hereditary nephritis	Bull terrier, English cocker spaniel, Samoyed	–
Medullary cystic disease	Miniature schnauzer	–
Polycystic kidney disease	Beagle, cairn terrier, collie, foxhound, miniature poodle	Domestic longhair cat, Himalayan, Persian
Primary renal glucosuria	Norwegian elkhound, Scottish terrier	–
Renal cystadenocarcinoma	German shepherd dog	–
Renal dysplasia	Alaskan malamute, beagle, boxer, bulldog, cavalier King Charles spaniel, chow chow, cocker spaniel, Dutch kookier, Great Dane, Great Pyrenees, golden retriever, Irish wolfhound, keeshond, Lhasa apso, Samoyed, Shih Tzu, soft-coated wheaten terrier, standard poodle, Yorkshire terrier	Persian
Renal telangiectasia	Pembroke Welsh corgi	–
Tubulointerstitial nephropathy	Norwegian elkhound	–
Unilateral renal agenesis	Beagle, Doberman pinscher	Domestic shorthair cat, Himalayan

nephropathy; however, juvenile kidney disease may be due to non-genetic causes. The specific term juvenile nephropathy has been used to describe disorganized nephrogenesis including kidney failure in young dogs. The term renal dysplasia describes abnormal differentiation of the kidneys. Specific histologic findings in renal dysplasia include fetal glomeruli, atypical tubular epithelia and persistent mesenchyme. Although renal dysplasia occurs most often as an inherited disorder, it can also be an isolated congenital abnormality that is not inherited. Juvenile nephropathy has been reported to occur in Alaskan malamutes, boxers and golden retrievers. Both males and females were affected. The lesions included moderate to severe interstitial fibrosis and mild to moderate lymphoplasmacytic interstitial inflammation. Mild to moderate tubular dilatation and atrophy were also present. Cystic glomerular atrophy and periglomerular fibrosis were prominent findings in most dogs (de Morais and DiBartola, 1995; de Morias et al, 1996; Chandler et al, 2007).

Familial disorders resulting in CKD have been documented or suspected to occur in a number of breeds (**Table 37-2**) (Lees, 1996). Familial nephropathies should be suspected when CKD is diagnosed in related pets with a higher frequency than would be expected by chance and there is no apparent underlying cause. Age of cats and dogs with familial nephropathies at presentation often is less than that of most pets presenting with CKD. In some familial nephropathies, the kidneys are seemingly normal at birth but because of an inborn metabolic defect, progressive structural and functional deterioration develops in the first few years of life. The term hereditary nephropathy is reserved for conditions in which an inherited basis has been documented by pedigree analysis or test breeding.

Hereditary nephropathy has been reported to occur in several breeds of dogs including Samoyeds, English cocker spaniels and bull terriers. Affected male Samoyed dogs with X-linked hereditary nephritis have splitting of glomerular basement membranes and develop overt CKD within the first year of life (Valli et al, 1991; Grodecki et al, 1997). The underlying inborn error is a defect in the formation of Type IV collagen. Carrier females with X-linked nephritis have isolated splitting of glomerular basement membranes although advanced CKD is not observed until later in life (Valli et al, 1991). In English cocker spaniels, a Type IV collagen defect is transmitted as an autosomal recessive trait (Davidson et al, 2007). Proteinuria is the initial finding and affected dogs typically die of terminal CKD between six and 24 months of age (Nash, 1989). Light microscopic renal lesions are mild and nonspecific but distinctive electron microscopic changes are observed in the glomerular basement membrane (Lees et al, 1998). The defect in bull terriers appears to be an autosomal dominant disorder (Hood and Savige, 1995). The rate of progression in bull terriers is quite variable with dogs dying of terminal CKD from a few months to 10 years of age. Hematuria is observed in many affected bull terriers.

Two distinct familial nephropathies have been reported to occur in soft-coated wheaten terriers (Littman et al, 2000; Ericksen and Grondalen, 1984). One nephropathy is a form of renal dysplasia. Kidneys from affected dogs are small, irregular and fibrous. Glomeruli are small and hypercellular and there are increased numbers of fetal glomeruli. The second form of nephropathy in soft-coated wheaten terriers is characterized by protein-losing enteropathy and concomitant nephropathy. Although a genetic basis for this syndrome has not been proven, dogs become symptomatic between two and five years of age. Membranoproliferative glomerulonephritis, glomerulosclerosis, or both, are present microscopically.

Renal amyloidosis has been recognized in related dogs of two

Table 37-3. Elements of the physical examination that should be emphasized in patients with suspected chronic kidney disease.

Body weight and body condition score
Cardiovascular system: Abnormal heart sounds? Increased tortuosity of superficial veins? Systemic blood pressure (direct or indirect measurement) abnormalities? Pulse rate and character?
Cervical region: Thyroid masses (cats)?
Fundus: Retinal detachment? Hemorrhage? Increased tortuosity of arteries? Retinal edema? Lipemia retinalis?
Genitourinary tract (urethra, prostate gland, penis, prepuce, vulva): Shape? Position? Pain? Discharge?
Hydration status
Kidneys: Both palpable? Size? Shape? Position? Surface contours? Pain? Bilaterally symmetrical?
Musculoskeletal: Muscle masses? Evidence of osteodystrophy?
Oral examination: Mucosal ulcers? Pallor? Necrosis or discoloration of tongue?
Temperature, pulse, heart and respiratory rates
Urinary bladder: Size? Position? Shape? Pain? Thickness of wall? Intraluminal masses? Grating sensation?

Table 37-4. Diagnostic tests for evaluating patients with suspected chronic kidney disease.

Bacterial urine culture
Complete blood cell count
Diagnostic imaging (abdominal radiography and/or ultrasonography)
Excretory urography, if indicated for obstructive uropathy
Renal biopsy, if indicated for evaluation of persistent proteinuria or suspected renal neoplasia
Serum biochemistry profile
Systemic blood pressure measurement
Urinalysis, including microscopic examination of urine sediment
Urine protein-creatinine ratio

breeds (beagles, Chinese Shar-Peis) and related Abyssinian cats (Chew et al, 1982; Boyce et al, 1984; Bowles and Mosier, 1992; DiBartola et al, 1986, 1990). Histologic findings in renal tissue from beagles include moderate to severe glomerular amyloidosis with inconsistent mild medullary interstitial amyloidosis (Bowles and Mosier, 1992). Medullary amyloid was identified in all Chinese Shar-Pei dogs and nine dogs (64%) had glomerular involvement (DiBartola et al, 1990). In 15 Abyssinian cats involved in one study, amyloid was deposited in the medullary interstitium of all cats and 11 cats had glomerular involvement (DiBartola et al, 1986).

Acquired Kidney Diseases

CKD may result from a variety of systemic conditions that cause kidney damage or there may be no apparent underlying cause. Infectious, inflammatory and immune-mediated diseases (e.g., leptospirosis, rickettsial diseases, pyelonephritis, amyloidosis) may cause inflammation of the renal interstitium or glomeruli. Glomerulonephritis secondary to systemic infectious, inflammatory or neoplastic diseases may be a common cause of CKD, especially in dogs. Renal neoplasia, particularly lymphoma in cats, may be a cause of CKD. Drugs that may cause nephrotoxicosis include antimicrobials (aminoglycosides), antifungals (amphotericin B), analgesics (aspirin, ibuprofen and phenylbutazone), immunosuppressive agents (penicillamine) and chemotherapeutic drugs (cisplatin, methotrexate and daunorubicin) (Grauer, 1996). Geriatric patients may be at greater risk for drug-induced nephrotoxicity because of a decline in kidney function associated with aging, use of multiple drugs with nephrotoxic potential and altered metabolism and excretion that occurs in older patients.

PATIENT ASSESSMENT

History

Historical findings in patients with CKD may include polyuria/polydipsia (less frequent in cats than dogs), lethargy, inappetence, vomiting, weight loss, nocturia, constipation, diarrhea, acute blindness (associated with hypertension) and seizures or coma (terminal uremia). Cats also may have ptyalism and muscle weakness with cervical ventriflexion due to hypokalemic myopathy. In a retrospective study of cats with CKD, polyuria and polydipsia were observed in 40%, vomiting in 52%, inappropriate urination in less than 10% and diarrhea in 3% (Lulich et al, 1992). Nonspecific signs such as inappetence and weight loss also are common in dogs and cats with CKD. Rarely, signs of thromboembolic disease (e.g., severe respiratory distress, posterior paresis) may be present in patients with nephrotic syndrome (i.e., proteinuria, hypoalbuminemia, hypercholesterolemia and ascites/peripheral edema). Occurrence of clinical signs may depend on the stage of CKD at diagnosis. Dogs and cats with stage 1 CKD generally have no or minimal clinical signs. However, polyuria/polydipsia may occur in some patients during this stage. Systemic clinical signs become more obvious in stages 3 and 4.

Physical Examination

A thorough physical examination is indicated for patients with suspected CKD, with emphasis on those items listed in **Table 37-3**. Dehydration (70%) and decreased body condition (58%) were the most common abnormal physical examination findings in a clinical series of cats with CKD (Lulich et al, 1992). An abnormally large kidney was detected by palpation in 25% of cases and an abnormally small kidney in 16% of cases in this series. Gingivitis, halitosis and oral ulcers were occasionally reported. Firm swellings in the nasomaxillary region, including the maxillary and mandibular gingival surfaces and extending to frontal sites, may be present in young dogs with stage 4 CKD. These changes result from renal osteodystrophy. Ascites or peripheral edema may be identified in patients with nephrotic syndrome; this finding is more common in dogs than cats.

The primary abnormal findings in some patients with CKD are due to ocular changes (e.g., retinal hemorrhage and detachment) associated with hypertension. In one study, 15 of 23 cats (65%) with CKD had indirect blood pressure measurements

consistent with systemic hypertension (Stiles et al, 1994). Twelve of the 15 cats (80%) with hypertension had active hypertensive retinopathy including increased tortuosity of arteries, retinal edema and focal detachments. In a larger study of cats with CKD in a primary care practice setting, prevalence of hypertension in cats with CKD was about 20% (Syme et al, 2002). Hypertensive retinopathy has been reported to occur in dogs with CKD, but it appears to be less common than in cats (Jacob et al, 2003).

Routine Laboratory Evaluation

Most major renal functions can be evaluated diagnostically by routine laboratory tests including complete blood counts (CBC), serum biochemistry profiles and urinalyses (DiBartola, 2005). **Table 37-4** lists diagnostic tests that are recommended for patients with suspected CKD. CBC results are useful in dogs and cats with CKD to evaluate the presence of anemia and concurrent disorders such inflammation from systemic infection. Azotemia is increased serum urea nitrogen or creatinine concentrations. Increased serum concentrations of urea nitrogen or creatinine may result from prerenal, renal or postrenal disorders. (See Glomerular Filtration and Localization of Azotemia below.) Results of serum biochemistry profiles reveal renal azotemia from reduced GFR in patients in stages 2 to 4 CKD. Dogs and cats with stage 1 CKD do not have azotemia. Dogs and cats with CKD have impaired urine concentrating ability and usually have urine specific gravity values <1.030 (dogs) or <1.040 (cats), with concurrent clinical dehydration or azotemia. Some cats with stage 2 CKD may retain urine concentrating ability (urine specific gravity values >1.040). However, these patients have gradually decreasing urine specific gravity values as CKD progresses (e.g., over a period of 18 months) (Polzin et al, 2005). Additional notable urinalysis findings may include proteinuria (See Altered Membrane Permselectivity below.), glucosuria from tubular dysfunction or pyuria associated with urinary tract infection.

Diagnostic Imaging

Radiography and ultrasonography are complementary imaging modalities that help assess renal structure and localize disease within the urinary tract (Rivers and Johnston, 1996). Survey radiographs can assess renal size by comparing the length of the kidneys with the length of the second lumbar vertebral body on the ventrodorsal view. In a retrospective series of cats with CKD, 33% had small kidneys, 40% had kidneys of normal size and 27% had larger than normal kidneys as determined by imaging procedures (Dibartola et al, 1987). Polycystic kidney disease and lymphoma were the most common causes of renomegaly in cats. Feline polycystic kidney disease can be diagnosed ultrasonographically with a high level of confidence, although extensive polycystic disease must be differentiated from severe hydronephrosis and perirenal pseudocysts (Walter et al, 1988). Excretory urography can be used to qualitatively assess renal function and detect evidence of upper urinary tract obstruction.

Ultrasonography provides information about intrarenal architecture even when reduced renal function makes excretory urography impractical (Walter et al, 1987, 1988). It also can provide images of the kidneys when abdominal effusion or loss of abdominal fat reduces radiographic contrast. Ultrasonographic patterns are not specific for histologic lesions. However, it is possible to differentiate solid lesions from fluid-filled lesions and to assess distribution patterns. Ultrasonography also may be used to detect renal pelvic dilatation secondary to obstruction of the ureter by ureteroliths or nephroliths.

Radiography also is useful in the diagnosis of renal osteodystrophy. In young dogs with advanced CKD, radiographs of the skull reveal generalized osteopenia, irregular mineralization and dense soft-tissue swelling of the mandibles, maxillae and zygomatic arches. The most striking radiographic finding is demineralization of lamina dura dentes (i.e., bone surrounding the teeth). Radiographs of long bones reveal normal-appearing cortices with a coarse trabecular pattern of the metaphyseal and epiphyseal regions, suggesting demineralization. Spontaneous fractures may be evident. The radiographic diagnosis of fibrous osteodystrophy is applied to this constellation of findings.

Blood Pressure Measurement

Systemic blood pressure varies markedly in healthy pets and may be compounded further by effects of anxiety associated with blood pressure measurement in a hospital environment, and other factors (Bodey and Michell, 1996; Remillard et al, 1991; Brown et al, 2007). Several studies have evaluated different techniques for measuring blood pressure in dogs and cats. In the clinical setting, however, blood pressure is most often measured indirectly (e.g., Doppler ultrasonography, oscillometry). Follow a standard protocol to obtain reliable blood pressure values (**Table 37-5**) (Brown et al, 2007).

About 10% of apparently healthy dogs (Remillard et al, 1991) and 9 to 93% of dogs with CKD are hypertensive (Brown et al, 2007); whereas, 19 to 65% of cats with CKD are hypertensive (Syme et al, 2002; Brown et al, 2007). Depending on measurement techniques and methods used to determine reference ranges, indirect systolic arterial blood pressures greater than 141, 160, 170 or 185 mm Hg have been used to indicate systemic hypertension. Despite difficulties measuring blood pressure and confusion regarding diagnostic criteria, hypertension is a clinically important problem because of its apparent prevalence and potential for associated end-organ damage (e.g., retinal hemorrhage and left ventricular hypertrophy) (Morgan, 1986; Littman, 1994; Elliott et al, 2006a; Brown et al, 2007).

The IRIS has proposed that dogs and cats with CKD should be substaged on the basis of risk of hypertensive injury as determined by serial blood pressure measurements (**Table 37-1**). Dogs and cats with CKD with indirect systolic blood pressures less than 150 mm Hg are considered to have minimal risk of hypertensive injury. Patients with CKD and moderate or high risk of hypertensive injury or with overt evidence of hypertensive injury (e.g., hypertensive retinopathy) should be treated with appropriate antihypertensive medications.

Table 37-5. Standard protocol for measuring blood pressure in dogs and cats.*

Calibrate the blood pressure measurement device twice yearly. Standardize the procedure used.

- Obtain measurements in an environment that is quiet, located away from distractions (e.g., other patients) and with the owner present.
- Restrain patients in a comfortable position, ideally in ventral or lateral recumbency to limit the distance from the base of the heart to the measurement cuff. Patients should be calm and motionless during the procedure.
- Use a cuff that is approximately 30 to 40% of the circumference of the measurement site in cats and 40% in dogs.
- Have the same trained individual, ideally a technician, perform blood pressure measurements each time.
- Determine and record five to seven consecutive and consistent (<20% variability) values.
- Discard the first measurement and determine the mean of all remaining values to obtain the patient's blood pressure measurement.
- Record the cuff size and site of placement (e.g., limb, tail), values for all measurements obtained, final (mean) value, details of any additional information (e.g., nervous patient) and interpretation of results by a veterinarian.

*Adapted from Brown S, Atkins C, Bagley R, et al. Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. Journal of Veterinary Internal Medicine 2007; 21: 542-558.

Evaluation of Renal Function

The primary functions of the kidneys are to excrete metabolic wastes (e.g., urea, creatinine), regulate fluid, electrolyte and acid-base balance and produce or activate several hormones including erythropoietin, calcitriol and renin. Anatomically, these functions occur in glomeruli (i.e., glomerular filtration and membrane permselectivity), renal tubules (i.e., urine concentration and tubular resorption) and other areas of the kidney (i.e., erythropoietin, calcitriol, renin). CKD may be associated with generalized renal dysfunction or it may involve only one function (e.g., tubular resorptive defect in Fanconi syndrome).

Glomerular Filtration

The most commonly evaluated renal function is glomerular filtration, which is determined by estimating or measuring GFR. Under steady state conditions, serum concentrations of urea nitrogen and creatinine are the time-honored methods for indirectly estimating GFR. These tests are useful for detecting large decreases in GFR (75% or greater), but lack sensitivity for detecting smaller decreases in glomerular filtration (**Figure 37-1**). In addition, serum urea nitrogen and creatinine values are affected by nonrenal factors, which contribute to the broad ranges for normal values.

Urea is produced in the liver from ammonia derived from the ornithine cycle, which catabolizes amino acids. The catabolized amino acids come from exogenous (dietary) and endogenous proteins. Urea is distributed throughout intracellular and extracellular water and is freely diffusible; therefore, it is common to use the terms blood urea nitrogen, serum urea nitrogen and plasma urea nitrogen interchangeably. The kidneys excrete urea by glomerular filtration, and serum urea nitrogen concentrations are inversely proportional to GFR. However, because urea is passively reabsorbed in the tubules, especially at reduced tubular flow rates, urea clearance is not an accurate measure of GFR. Clinical conditions that can increase serum urea nitrogen concentration include gastrointestinal hemorrhage, consumption of high-protein foods and catabolic drugs (e.g., glucocorticoids). Severe hepatic disease (e.g., portosystemic vascular shunts), feeding a low-protein food and conditions causing increased urine volume (e.g., intravenous fluid therapy) can decrease serum urea nitrogen concentrations independent of renal function.

Creatinine results from the nonenzymatic breakdown of muscle phosphocreatine. During steady states, creatinine production is constant and related to muscle mass. Serum creatinine concentration is less influenced by feeding than serum urea nitrogen concentration. However, it may be affected by breed and body size (Gleadhill, 1995). In a study of retired racing greyhounds, mean values for serum creatinine concentration (1.8 ± 0.1 mg/dl) and GFR (3.0 ± 0.1 ml/min./kg) were significantly greater than values from control dogs. However, blood urea nitrogen values were not different (Drost et al, 2006). Increased serum creatinine levels in greyhounds may be due to increased muscle mass in this breed. In contrast, it is possible for serum creatinine concentration to remain lower than expected or to not be increased in proportion to the decrease in GFR in older patients with decreased muscle mass and kidney disease.

When considering the magnitude of azotemia it's important to recognize that the relationship between serum urea nitrogen and creatinine concentrations and GFR is not linear (**Figure 37-1**). Thus, very large changes in GFR early in the natural course of CKD cause only small changes in serum urea nitrogen and creatinine concentrations. These small changes may not exceed the upper limit of the laboratory reference range and thus may go unrecognized throughout most of stage 1 CKD. Small decreases in GFR cause disproportionately large increases in serum urea nitrogen and creatinine concentrations in more advanced CKD (stages 3 and 4).

Evaluation of serum urea nitrogen and creatinine is used to indirectly assess GFR in most patients; however, measuring GFR is helpful for identifying kidney dysfunction that occurs before the onset of azotemia (e.g., breeds known to have familial kidney disease, patients with polyuria/polydipsia due to kidney disease, when potentially nephrotoxic treatment will be used). Urinary clearance of infused inulin is the gold standard for measuring GFR. However, this technique is limited to research settings because it requires collection of multiple, timed blood and urine samples and a constant rate infusion of inulin. Other methods have been used to estimate GFR but each has disadvantages. Endogenous creatinine clearance underestimates GFR because non-creatinine chromogens are present in plasma. Exogenous administration of creatinine reduces this potential problem by decreasing the proportion of non-creatinine chromogens in plasma. A newer creatinine-specific enzymatic analytical method eliminates the problem

(Finco et al, 1993). However, in cats, exogenous creatinine clearance does not accurately estimate GFR (Finco et al, 1996). In addition, factors other than GFR (e.g., hydration status) can affect creatinine clearance and serum creatinine concentration. Clearance of iohexol, a readily available radiographic contrast medium, has been used to reliably estimate GFR in dogs and cats and is a convenient method that can be used in clinical practice (Finco et al, 2001; Miyamoto 2001, 2001a; Goy-Thollot et al, 2006; Sanderson, 2009).

Altered Membrane Permselectivity

Proteinuria is the hallmark of altered glomerular membrane permselectivity. In patients with glomerular disease, permselective properties of the glomerular capillary wall are altered and increased amounts of protein are present in urine. Glomerulopathies are the most common cause of severe (heavy) proteinuria in dogs and cats although they appear to be more common in dogs than cats. Glomerulopathies can be primary (e.g., renal amyloidosis in dogs or idiopathic membranous nephropathy) or secondary to systemic infectious, inflammatory or neoplastic diseases (e.g., lupus erythematosus, heartworm disease, ehrlichiosis, lymphoma).

Proteinuria is defined as excretion of greater than normal amounts of protein in urine. Potential causes include urinary tract hemorrhage or inflammation, tubular resorptive defects, "overflow" proteinuria and altered glomerular permselectivity. Clinical significance of proteinuria depends on its severity and persistence. In the absence of hyperproteinemia, hematuria and urinary tract inflammation, persistent proteinuria usually indicates kidney disease and severe proteinuria (urine protein-creatinine ratio [UPC] ≥2) is generally associated with glomerular disease. The magnitude of proteinuria does not predict reversibility of the underlying disease, however. Serial quantitative evaluation of proteinuria is necessary for prognosis and assessment of response to treatment. Clinicians should confirm the persistence of proteinuria and attempt to localize its source before performing invasive and expensive diagnostic tests such as renal biopsy. Significance of proteinuria should always be interpreted in context of other laboratory and clinical findings (e.g., microscopic urine sediment examination).

Qualitative techniques for measurement of proteinuria include dipstick methods and precipitation techniques such as the sulfosalicylic acid (SSA) test. Urine concentration (refractive index, specific gravity) should be considered when interpreting results of these qualitative techniques (Finco, 1995). The most commonly used qualitative test is the colorimetric dipstick test. The test depends on ability of proteins, especially albumin, to alter the color reaction in paper impregnated with a pH-sensitive dye, tetrabromophenol blue. The test pad is buffered so that color changes reflect changes in protein concentration. In one study, sensitivity of the urine protein test strip for albuminuria in canine and feline urine was 54 and 60%, respectively. This means that 46 and 40% of dogs and cats, respectively, had proteinuria that was not detected by the dipstick (Grauer et al, 2004). Urine protein test strip specificity for canine and feline albuminuria was 69 and 31%, respectively. Therefore, 31 and 69% of dogs and cats, respectively, with a positive dipstick reaction for protein did not have proteinuria. Based on this, false positive reactions are common, especially in cats, and may occur with concentrated or alkaline urine, hematuria, pyuria, urine contaminated with quaternary ammonium compounds or with excessive urine contact time with the dipstick pad (Grauer et al, 2004). Observer variation is a documented and unavoidable source of error with dipstick tests. All positive dipstick reactions for proteinuria should be followed up with additional testing such as the SSA test or testing for microalbuminuria (Lees et al, 2005). The SSA test is used by most commercial laboratories and can be performed in-house by mixing equal volumes of centrifuged urine and 5% SSA,[a] available from chemical supply companies. Resulting turbidity of urine is graded on a scale of 0 (no turbidity) to 4+ (completely opaque). Microalbuminuria can be detected in-house using a species-specific point-of-care test.[b]

In patients with stable renal function, the UPC ratio is a semiquantitative method for assessing proteinuria. The UPC ratio is calculated by dividing urinary protein concentration by urinary creatinine concentration. Urinary protein is measured by a quantitative analytical technique rather than by dipstick. It may be determined in commercial laboratories or by using an in-house kit.[c] Because urinary excretion of creatinine and protein is presumed constant in the presence of stable GFR, the UPC ratio in a single urine sample can be used to estimate 24-hour urinary protein loss. The time of day and method of urine sample collection are not critical. The UPC ratio eliminates the potentially confounding effect of urine concentration on interpretation of urinary protein concentration. A UPC ratio less

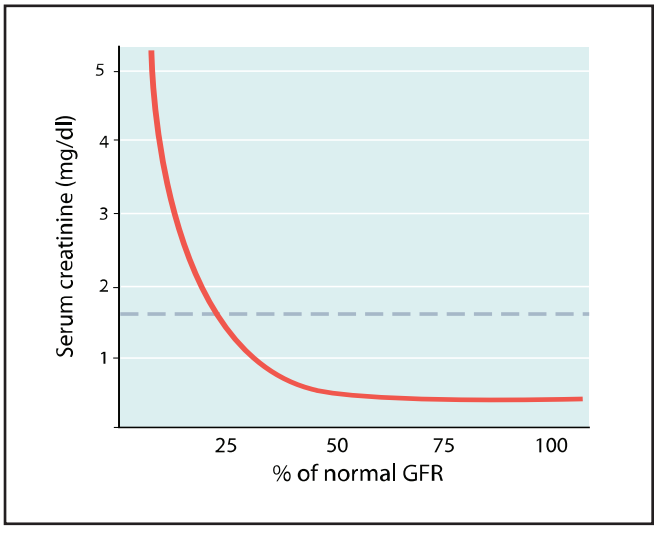


Figure 37-1. The relationship between serum creatinine concentration and % of normal glomerular filtration rate (GFR) or % of remaining functional nephrons is not linear. Therefore, small changes in GFR during early chronic kidney disease do not result in increased serum creatinine concentrations. Notice that values for serum creatinine do not exceed the upper reference range (broken line) until kidney dysfunction is marked (i.e., when 75% of nephrons are nonfunctional).

than 0.5 was found in the majority of non-proteinuric dogs studied (Grauer et al, 1985; White et al, 1984; Center et al, 1985). The upper limit of the reference range for UPC ratios in cats is 0.2 (Monroe et al, 1989; Adams et al, 1994). However, in one study of healthy male cats, the 24-hour urinary protein loss was greater in males than females and UPC values up to 0.6 were observed. This difference may be attributable to secretions of secondary sex glands in male cats (Monroe et al, 1989). Dietary protein intake significantly affected UPC values in normal cats and cats with surgically induced CKD (Adams et al, 1994). Consequently, dietary protein levels should be considered when interpreting UPC values because high protein intake may increase proteinuria.

UPC ratios should be performed on all dogs and cats with CKD to allow for substaging based on severity of proteinuria (**Table 37-1**). Studies in dogs and cats with CKD indicate that proteinuria is an important predictor of survival (Syme et al, 2006; Jepson et al, 2007; Jacob et al, 2005). Cats with UPC values consistently less than 0.2 have significantly longer survival than cats with UPC values greater than 0.4 (Syme et al, 2006; Jepson et al, 2007). Similarly, dogs with CKD and UPC values above 1.0 had significantly shorter survival than dogs with UPC values less than 1.0 (Jacob et al, 2005). Despite correlation of survival with proteinuria in cats with CKD, there is considerable overlap of survival times across the severity range of proteinuria. Accurate prediction of survival time for individual patients is not possible based on severity of proteinuria (Syme et al, 2006).

Urine Concentration

Disorders of urine concentrating ability generally involve abnormalities in the secretion of, or response to, antidiuretic hormone. Loss of concentrating ability can be one of the earliest indicators of kidney dysfunction, which is generally recognized when two-thirds of nephrons are nonfunctional. In CKD, the renal interstitial osmolality gradient is decreased because of increased urine flow per nephron or because of inability to establish and maintain the medullary concentration gradient. The resultant decrease in responsiveness to antidiuretic hormone leads to excretion of urine with osmolality or specific gravity values similar to those of plasma (i.e., isosthenuria).

Estimation of urine concentrating ability from urine specific gravity or refractive index is most often used for clinical purposes. The physiologic range for urine specific gravity is 1.001 to 1.070 in dogs and 1.001 to 1.080 in cats. Any urine specific gravity value may be normal; therefore, it's important to interpret specific gravity in the context of clinical findings including hydration status, concurrent disease and medications. (See Diagnosis of Chronic Kidney Disease.) In a retrospective series of cats with CKD, 37% had urine specific gravity values between 1.008 to 1.012 and 60% were between 1.013 and 1.034 (Lulich et al, 1992). However, some cats with CKD may have urine specific gravity values greater than 1.040 and remain persistently azotemic (up to 18 months) before losing concentrating ability (Polzin et al, 2005). In a study of cats with induced kidney disease (5/6 reduction of renal mass), mean urine specific gravity was 1.050 ± 0.015 in cats fed a 27.6% protein food and 1.038 ± 0.013 in a group fed a 51.7% protein food (Adams et al, 1994). However, the majority of cats with spontaneously occurring CKD have urine specific gravity values less than 1.035 (Polzin et al, 2005). Although it has not been reported, it is generally accepted that urine specific gravity in dogs with naturally occurring CKD is less than 1.030.

Tubular Resorption

Water and many solutes are reabsorbed from the tubular lumen into the peritubular interstitial fluid and ultimately the blood. In general, tubular resorption conserves substances that are essential for normal function (e.g., electrolytes, water, glucose and amino acids). Alterations in the renal handling of solutes may indicate kidney dysfunction. Abnormalities in tubular resorption may be generalized or limited to one or more tubular transport processes. Clinical syndromes are defined by the particular transport process involved. These syndromes include diverse disorders such as nephrogenic diabetes insipidus, renal tubular acidosis, renal glucosuria and aminoaciduria (e.g., cystinuria). Diagnosis is based on urinalysis findings (e.g., cystine crystalluria) or other tests such as quantitation of urinary amino acid concentrations.

Endocrine Function

Renal endocrine function can be evaluated by directly measuring the plasma concentration of the hormone or by indirectly assessing the action of that hormone. Erythropoietin concentration can be measured, but it is more practically assessed by serial monitoring of CBCs to detect progressive non-regenerative anemia that may occur in patients with stages 2 to 4 CKD. In CKD, reduced renal excretion of phosphorus causes phosphorus retention, which in turn stimulates increased parathyroid hormone (PTH) production and secretion. Phosphorus retention and hyperphosphatemia also inhibit renal tubular activity of 1-α hydroxylase, the enzyme responsible for renal conversion of inactive vitamin D to its active form, calcitriol. Decreased calcitriol concentrations, along with hypocalcemia (decreased ionized calcium) and hyperphosphatemia, contributes to development of hyperparathyroidism. Diagnosis of hyperparathyroidism is based on increased plasma concentrations of intact PTH. Although measurement of PTH is not routinely performed for patients with CKD, it should be measured (with serum calcium, phosphorus and ionized calcium) when calcitriol is administered for management of CKD. In the future, it may be recommended to monitor serum PTH concentrations in all patients with CKD, before the onset of hyperphosphatemia, so that treatment (e.g., dietary phosphorus restriction) can be adjusted to control secondary renal hyperparathyroidism earlier.

Diagnosis of Chronic Kidney Disease

Most routine tests used to diagnose CKD do not identify abnormal findings until there is advanced disease (stage 2 or higher). At present, the most common way to diagnose CKD

is by first detecting evidence of changes in renal function (e.g., azotemia, proteinuria) that arise as a result of renal lesions (Lees, 2004). Looking for subtle changes (e.g., gradually increasing serum creatinine over time, progressive decline in urine concentrating ability or presence of mild proteinuria) is helpful for identifying CKD at earlier stages (Lees, 2004). Earlier diagnosis of CKD allows earlier therapeutic intervention, which could slow or halt disease progression.

Localizing Azotemia

Azotemia is present by the time CKD is diagnosed in most dogs or cats. Increased serum concentrations of urea nitrogen or creatinine may result from prerenal, renal or postrenal disorders. Prerenal azotemia may be caused by catabolic states (e.g., treatment with corticosteroids), consumption of a high-protein food, gastrointestinal hemorrhage, dehydration, hypovolemia or decreased cardiac output. Renal structure remains normal and the kidneys are capable of normal function if the prerenal insult is corrected before permanent damage occurs. Renal azotemia is caused by kidney disease and generally occurs when 75% of nephrons are nonfunctional. Renal azotemia should be further classified as either acute or chronic because of differences in treatment and prognosis. Postrenal azotemia is caused by disorders that impair elimination of urine from the body (e.g., urinary tract obstruction or rupture). Sites most often affected are the urethra and urinary bladder, and less often, ureters and kidneys. For upper urinary tract disease to cause postrenal azotemia, bilateral renal or ureteral disease must be present (unless the patient has concomitant kidney disease). As with prerenal disorders, renal function in patients with postrenal azotemia is normal initially; development of irreversible renal injury depends on severity, duration and nature of the disorder impairing urine outflow.

One of the most useful tests for distinguishing between prerenal and renal azotemia is analysis of urine obtained before any treatment, especially fluid therapy. Patients with azotemia and evidence of adequate urine concentration (i.e., specific gravity >1.030 in dogs and >1.040 in cats) usually have prerenal disorders. There are two exceptions to this rule: 1) some cats with CKD may have renal azotemia and still retain urine concentrating ability (specific gravity >1.040); it may be many months before they finally develop concurrent azotemia and inadequate concentrating ability, 2) some dogs with glomerular disease may develop azotemia initially and then lose concentrating ability; this "glomerulotubular imbalance" should be suspected in dogs that have significant proteinuria, azotemia and urine specific gravity values greater than 1.030. When azotemia is initially identified, it's important to determine if the patient has received any treatment that may interfere with urine concentrating ability such as intravenous fluids, diuretics or corticosteroids. Also, disorders that may cause prerenal azotemia but concomitantly decrease urine specific gravity must be excluded; examples include hypoadrenocorticism, diabetic ketoacidosis, hypercalcemia, hepatic disease and pyometra. Hypoadrenocorticism may be easily misdiagnosed as acute kidney failure because of similar clinical and laboratory findings. Dogs and cats with renal azotemia usually have either isosthenuria (urine specific gravity of 1.008 to 1.013) or minimally concentrated urine (specific gravity <1.025). However, as previously noted, some patients with CKD may retain the ability to produce concentrated urine.

Postrenal azotemia should be suspected in patients with stranguria, dysuria, pollakiuria, abdominal pain, ascites, firm/painful urinary bladder, subcutaneous swelling or discoloration of the perineum or a history of recent abdominal trauma. Palpable urethroliths or masses in the urethra, urinary bladder or prostate gland also suggest a postrenal cause of azotemia. Complete absence of urine production (i.e., anuria) most often is caused by lower urinary tract obstruction, although it may occur in some cases of acute kidney disease (e.g., ethylene glycol toxicosis). An attempt should be made to pass a urinary catheter if there is any question regarding patency of the lower urinary tract. However, the ability to pass a urinary catheter does not definitively exclude urethral obstruction. Urine specific gravity often is not helpful for distinguishing between renal and postrenal azotemia because urinary tract obstruction may cause renal tubular dysfunction and interfere with urine concentrating ability. Abdominal ultrasonography is helpful for detecting masses and accumulation of fluid when urinary tract obstruction or rupture is suspected. Abdominal fluid analysis in patients with uroabdomen reveals a modified transudate or exudate characterized cytologically by neutrophils, macrophages and mesothelial cells; bacteria may be seen if there is urinary tract infection. If uroabdomen is suspected, a sample of abdominal fluid should be submitted for measurement of creatinine and potassium concentrations so these values can be compared to concomitant serum concentrations. Measurement of urea nitrogen concentration in abdominal fluid often equals that of serum or blood and is therefore not helpful in patients with uroabdomen. Contrast urethrocystography is indicated when rupture or obstruction of the urethra or urinary bladder is likely; whereas, excretory urography is indicated when rupture of the upper urinary tract is suspected. If available, urethrocystoscopy may also be used to confirm rupture of the bladder or urethra.

Response to treatment may help localize azotemia. In general, pre- and postrenal azotemia resolve rapidly within one to three days after the underlying cause is corrected. In contrast, renal azotemia usually decreases more slowly, persists after appropriate treatment or recurs soon after discontinuation of treatment. Note that severe or prolonged pre- or postrenal azotemia may cause renal injury, which eventually leads to permanent kidney disease. It is also possible for renal azotemia to exist concomitantly with either pre- or postrenal disorders; this possibility should be suspected in patients that do not respond to treatment as expected.

Differentiating Between Acute and Chronic Kidney Disease

After renal azotemia is confirmed, additional evaluation is indicated to distinguish between acute and CKD (Vaden, 2000). Careful review of history, physical examination findings and laboratory evaluation results usually distinguishes between acute and CKD (**Table 37-6**). Acute kidney disease is a rapid

Table 37-6. Distinguishing between acute and chronic kidney disease in dogs and cats on the basis of clinical and laboratory findings.*

Findings	Acute kidney disease	Chronic kidney disease
Clinical findings	Acute onset of clinical signs (usually <seven days)	Vague onset of clinical signs (often over weeks to months)
	Usually moderately to severely depressed	Alert, responsive or only slightly depressed
	Urine volume often decreased	Polyuria/polydipsia more likely
	Often good body condition	May be thin
	Kidneys enlarged, painful or may be normal	Kidneys small, irregular or may be normal
Laboratory and diagnostic imaging findings	Normal or increased hematocrit; anemia may result from blood loss (e.g., gastrointestinal hemorrhage)	Nonregenerative anemia typical; hematocrit decreases progressively over time
	Serum urea nitrogen and creatinine previously normal but increase progressively	Serum urea nitrogen and creatinine previously increased and typically remain stable
	Normal to increased serum potassium	Normal to decreased serum potassium, especially in cats
	Moderate to severe metabolic acidosis	Mild to moderate metabolic acidosis
	Urinary casts in some patients	Usually no urinary casts
	Proteinuria or glucosuria may result from acute tubular necrosis	Proteinuria often present, more likely due to glomerular disease
	Bone density normal	Bone density may be decreased

*Modified from Vaden SL. Differentiation of acute from chronic renal failure. In: Bonagura JD. Kirk's Current Veterinary Therapy XIII. Philadelphia, PA: WB Saunders Co, 2000; 856-858.

Table 37-7. Potential mechanisms in the pathogenesis of chronic kidney disease.

Altered lipid metabolism
Amyloidosis
Compensatory renal growth (hypertrophy)
Effects of renal aging
Glomerular hyperfiltration
Glomerular hypertension
Hyperphosphatemia and secondary renal hyperparathyroidism
Inadequate urinary concentration
Increased renal ammoniagenesis
Metabolic acidosis
Renal oxidative stress
Systemic hypertension
Tubulointerstitial changes

deterioration of renal function that occurs over a period of hours to days, whereas CKD occurs over a period of months to years. A careful medical history may reveal causes of acute kidney disease (e.g., ingestion of a nephrotoxin such as ethylene glycol). Patients with acute kidney disease generally are healthy before sudden onset of lethargy, depression and vomiting, whereas clinical signs in CKD such as inappetence, weight loss and polyuria/polydipsia occur more gradually. Patients with acute exacerbation of CKD are common and may present a diagnostic challenge. However, careful questioning of owners in these cases usually establishes a more chronic history. If it is still not possible to distinguish between acute and chronic disease, renal biopsy may be helpful, particularly if results will alter treatment or provide prognostic information that would help owners decide on a course of action.

Etiopathogenesis of Chronic Kidney Disease

A variety of compensatory and adaptive responses are likely involved in the pathogenesis and progression of naturally occurring CKD (**Table 37-7**). In addition, sequelae of CKD (e.g., hypertension, proteinuria, metabolic acidosis and tubulointerstitial injury), changes in lipid metabolism and coagulation and normal renal aging may contribute to progression. Although some of these mechanisms initially are adaptive when renal function declines, they may ultimately lead to progressive renal injury (**Figure 37-2**). In addition, these etiopathogenic mechanisms are not mutually exclusive and in some instances may act synergistically. Understanding these mechanisms helps guide selection of treatment for patients with CKD.

Much of what we currently know about etiopathogenic mechanisms in CKD comes from studies in which kidney disease was induced by reduction or ablation of renal mass. This "remnant kidney model" causes progressive azotemia, mild proteinuria and arterial hypertension. In rats, this model is characterized by relentless progression to endstage kidney disease following the loss of a critical number of functioning nephrons (i.e., approximately three-fourths of the functional renal mass). Similarly, in human patients, progression from early to late stages of CKD has been reported regardless of the inciting renal injury and whether the initiating cause is present or not (Ihle et al, 1989).

Some controversy has existed about whether similar progressive renal injury occurs in other species, because the remnant kidney model has not been uniformly progressive in dogs and cats. Reduction of renal mass by 7/8 or less did not result in a consistently progressive decline in GFR in studies in dogs and cats (Polzin et al, 1991; Adams et al, 1994; Finco et al, 1998). It is possible that progression was not observed in these studies because the extent of the induced renal injury was insufficient to alter glomerular hypertension or renal autoregulation or perhaps because only mild proteinuria occurred. In experimental studies in dogs, reduction of renal mass resulted in glomerular changes and proteinuria; the severity of these changes appeared

to correlate with the amount of renal tissue ablated (Bourgoignie et al, 1987). In a remnant kidney model in which renal mass was reduced by 15/16 in dogs, GFR progressively declined, providing evidence that progressive kidney disease occurs in dogs if adequate renal tissue is ablated (Brown et al, 1991; Finco et al, 1992). It is generally accepted that naturally occurring CKD (stages 2 through 4) in dogs and cats tends to be progressive (Allen et al, 1987; Jacob et al, 2002; Ross et al, 2006; Polzin et al, 2005). Therefore, it appears that after a critical mass of nephrons becomes nonfunctional in dogs and cats, either due to renal ablation or natural causes, disease characterized by several pathophysiologic adaptations progresses. See sections below for more detailed information about specific mechanisms and how they may contribute to progression of CKD in dogs and cats.

Glomerular Hypertension and Hyperfiltration

In normal kidneys, single-nephron GFR and single-nephron plasma flow are submaximal under basal conditions. Reduction of nephron mass leads to hypertrophy of the residual nephrons with increases in filtration and perfusion of surviving nephrons to maintain total GFR (Polzin et al, 2005). Although these compensatory increases in single-nephron GFR and renal plasma flow initially help maintain homeostasis, eventually they contribute to progressive kidney damage. Single-nephron GFR increases are accompanied by glomerular hyperfiltration and intraglomerular hemodynamic changes, which increase flux of plasma proteins through the glomerular mesangium. These proteins stimulate mesangial cell proliferation and matrix production and eventually lead to glomerulosclerosis (**Figure 37-3**). Glomerular capillary hypertension is the critical intraglomerular hemodynamic factor responsible for promoting glomerular injury, perhaps through increasing proteinuria. Decreased dietary protein intake prevents these hemodynamic changes and preserves normal glomerular structure in rats (Brenner et al, 1982). The impact of dietary protein intake on glomerular hemodynamics and structure in dogs and cats is less certain.

As kidney disease develops, the afferent renal arterioles dilate, directly exposing glomeruli to systemic blood pressure; this causes glomerular hypertension, which distends the capillaries. The resultant mesangial stretch stimulates accumulation of collagen and progressive loss of glomerular function (**Figure 37-4**) (Riser et al, 1992). Continued strain on mesangial cells is a stimulus for cytokine release and extracellular matrix production (Polzin et al, 2005). Mesangial cells are stretched because of their relationship to capillaries and their attachment to the glomerular basement membrane. When mesangial cells in culture are stretched and relaxed repeatedly, stretch-induced release of transforming growth factor-β mediates production of collagen (Cortes et al, 1994). Intraglomerular hypertension also may lead to decreased glomerular permselectivity with resultant proteinuria (Polzin et al, 2005). Proteinuria, in turn, may mediate progressive injury of glomeruli and the renal tubulointerstitium (Lees et al, 2005; Polzin et al, 2005). Proteinuria has been associated with more rapid progression of CKD in dogs (Jacob et al, 2005) and cats (Syme et al, 2006).

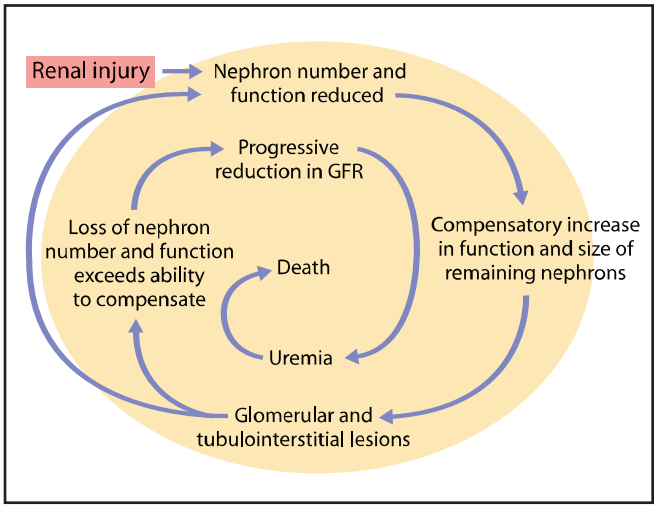


Figure 37-2. Vicious cycle of relentless progression of chronic kidney disease. After a critical amount of damage has occurred, compensatory mechanisms, which are initially beneficial, are activated and ultimately contribute to progressive injury. The amount of damage required to trigger progression probably varies from species to species and from individual to individual. (Adapted from Churchill J, Polzin DJ, Osborne CA, et al. The influence of dietary protein intake on progression of chronic renal failure in dogs. Seminars in Veterinary Medicine and Surgery: Small Animal 1992; 7: 246.)

Proteinuria

Proteinuria may mediate progressive renal injury through several mechanisms (Polzin et al, 2005; Elliott and Syme, 2006). Impaired glomerular permselectivity allows passage of proteins that are not normally filtered including albumin, transferrin and complement (Polzin et al, 2005). Proteinuria may result in direct mesangial cell toxicity, fibrosis of glomeruli and subsequent glomerulosclerosis. Progression of CKD in experimental models more closely relates to the degree of tubulointerstitial disease than to the severity of glomerular lesions. Proteinuria may injure tubular cells through overloading tubular reabsorptive mechanisms or by receptor-mediated mechanisms (Polzin et al, 2005). Proximal tubular cells reabsorb abnormally filtered proteins such as albumin through endocytosis and lysosomal degradation. Excessive albuminuria can overload this resorptive capacity, causing lysosomal swelling and rupture, leading to lysosomal enzyme-mediated injury of tubular cells. Excessive albuminuria also increases oxidative stress, which appears to be an important mechanism of progressive renal injury. (See Renal Oxidative Stress.)

Abnormally filtered transferrin, a plasma protein that transports iron, increases absorption of iron by proximal tubular cells. Increased intracellular iron concentration of tubular cells produces reactive oxygen species (ROS) leading to oxidative injury. Complement binds to the luminal membrane of tubular cells and activates the membrane attack complex, culminating in cellular injury and lysis. These mechanisms contribute to loss of tubular cells and ultimately loss of nephrons. Cellular activation of inflammatory genes also stimulates secretion of inflammatory mediators into the interstitium, which promotes inter-

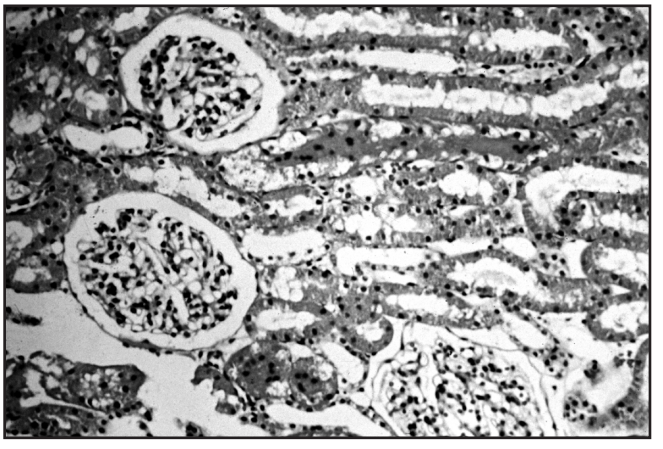
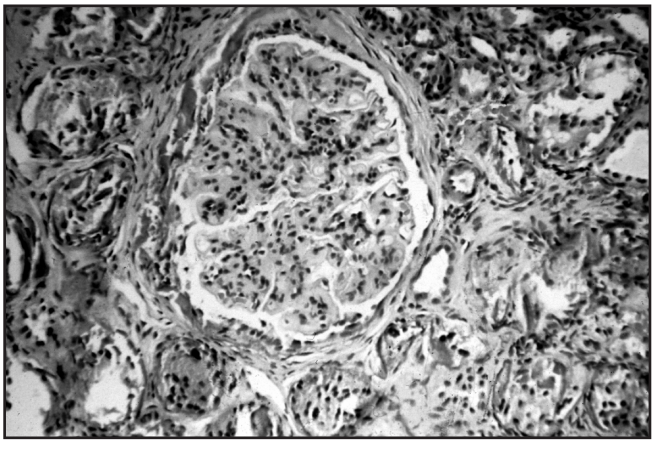


Figure 37-3. Microscopic view of early stages of kidney disease. (Above) Photomicrograph (hematoxylin-eosin stain) showing normal glomeruli, tubules and interstitium. (Below) Early progressive chronic kidney disease. Photomicrograph (hematoxylin-eosin stain) showing increased mesangial matrix, increased glomerular cellularity and increased interstitial infiltrates.



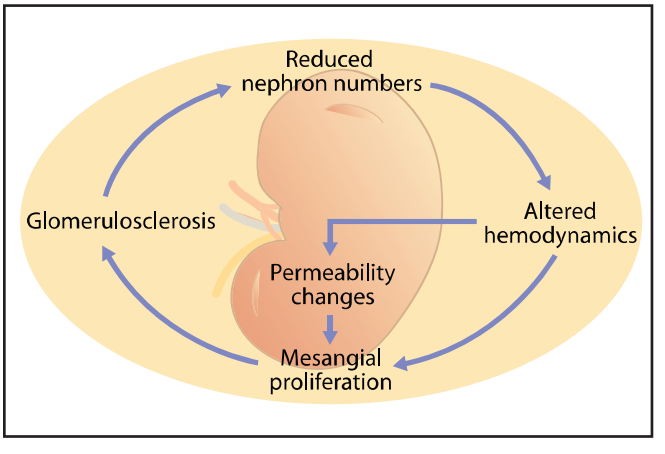


Figure 37-4. Schematic showing the progressive effect of glomerular capillary hypertension.

stitial fibrosis. These mechanisms of glomerular and tubular injury explain why even modest levels of proteinuria are associated with more rapid progression of CKD in dogs (Jacob et al, 2005) and cats (Syme et al, 2006).

Systemic Hypertension

In dogs and cats, hypertension usually occurs secondary to other diseases including kidney disease, obesity, hyperadrenocorticism, hyperthyroidism, pheochromocytoma and diabetes mellitus (Kobayashi et al, 1990; Rocchini et al, 1987; Brown et al, 2007). However, CKD appears to be the disease most commonly associated with systemic hypertension (Brown et al, 2007). When considering hypertension in CKD, it is important to note that CKD may cause hypertension and hypertension can promote progression of CKD. Systemic hypertension can also damage a number of other end organs, including the eyes, central nervous system and cardiovascular system (Morgan, 1986). The IRIS scheme for staging CKD in dogs and cats identifies substages based on magnitude of systemic blood pressure and risk of end-organ damage (**Table 37-1**).

Impaired autoregulation occurs in dogs with ischemic acute kidney failure and reduced renal mass. In normal dogs, the renal autoregulatory mechanism limits the effect of systemic blood pressure changes on renal blood flow and GFR. This protection is achieved by adjusting preglomerular resistance so that renal hemodynamics remain stable between mean systemic arterial blood pressures of 70 to 150 mm Hg. Dogs with severe reductions in functional mass have impaired renal autoregulation with elevations in renal arterial pressure. Impaired autoregulation may lead to renal injury during systemic hypertensive episodes and contribute to a progressive decline in kidney function (Brown et al, 1995; Polzin et al, 2005). Hypertension has been associated with increased risk of uremic crisis and death in dogs with CKD (Jacob et al, 2003).

Hyperphosphatemia and Secondary Renal Hyperparathyroidism

Hyperphosphatemia and secondary renal hyperparathyroidism have been incriminated as causes of progressive renal injury (Felsenfeld and Llach, 1993; Lumlertgul et al, 1986). Secondary renal hyperparathyroidism, characterized by increased PTH concentration, is an inevitable consequence of CKD (Nagode and Chew, 1992; Nagode et al, 1996; Barber and Elliott, 1998; Barber et al, 1999) (**Figure 37-5**). A study of cats with spontaneous CKD found an overall prevalence of secondary renal hyperparathyroidism of 84% (Barber and Elliott, 1998). Hyperparathyroidism was present in 100% of cats with endstage CKD and 47% of cats with biochemical evidence of CKD, but no clinical signs. Secondary renal hyperparathyroidism may be present based on increased PTH concentrations, even if serum phosphorus concentrations are within the reference range.

The inciting event in the pathogenesis of secondary renal hyperparathyroidism is phosphate retention (**Figure 37-6**). Destruction of nephrons decreases phosphorus filtration with a subsequent increase in serum phosphate, which stimulates PTH release from the parathyroid gland (Burkholder, 2000; Polzin et al, 2005). Hyperphosphatemia also decreases ionized calcium concentration, which stimulates PTH secretion. In a normal kidney and in early CKD, one effect of PTH is to decrease phosphate resorption in the proximal tubules so that

more phosphate is excreted and serum phosphorus concentration is maintained within the normal range. However, as CKD progresses and more nephrons become nonfunctional, a greater concentration of PTH is required to maintain serum phosphorus concentration and eventually hyperphosphatemia develops. The primary consequence of hyperphosphatemia is development and progression of hyperparathyroidism. Although hyperparathyroidism helps maintain serum phosphorus concentrations initially, it has other effects that may be harmful. PTH stimulates resorption and release of minerals (e.g., phosphate) from bone, which increases the amount of phosphate that remaining nephrons must excrete. Increased PTH concentration correlates with histologic evidence of renal tissue inflammation and mineralization; therefore, hyperparathyroidism may damage the kidneys (Finco et al, 1992, 1992a; Ross et al, 1982; Brown et al, 1991).

Chronic Renal Hypoxia

The kidney has a very high rate of oxygen consumption, the majority of which is expended reabsorbing sodium. With kidney damage, surviving nephrons increase sodium resorption and correspondingly increase oxygen consumption. The renal medulla concentrates urine by means of the countercurrent system of blood vessels and tubules that actively absorb sodium. The major determinant of medullary oxygen demand is the rate of active absorption in the medullary thick ascending loop, which is a relatively hypoxic environment. Hypoxia of the renal medulla can predispose to acute and chronic renal injury because the kidneys are extremely susceptible to hypoxic injury (O'Connor, 2006; Eckardt et al, 2005; Brezia and Rosen, 1995).

In CKD, increased fibrosis in the kidneys may result from intrarenal hypoxia due to increased oxygen consumption by surviving nephrons. Acute kidney injury often is associated with altered intrarenal microcirculation and oxygenation (Rosenberger et al, 2006). Hypoxia deprives tissues of energy and induces various regulatory mechanisms. The transcription factor, hypoxia-inducible factor, is involved in cellular regulation of development of new blood vessels, blood vessel tone, glucose metabolism and cell death. Kidney disease activates hypoxia-inducible factor, which presumably is renoprotective during oxygen deprivation (Eckardt et al, 2005). Hypoxia induces profibrogenic changes in proximal tubular epithelial cells and interstitial fibrosis (Norman and Fine, 2006). Hypoxia causes release of cytokines such as TGF-β and platelet derived growth factor, which stimulate intrarenal production of collagen. Furthermore, anemia may contribute to progression of CKD because anemia reduces oxygen delivery within the kidney, further promoting hypoxia and progressive renal damage (Rossert and Froissart, 2006).

A variety of mechanisms regulate medullary oxygen homeostasis; these include medullary vasodilators (e.g., nitric oxide, prostaglandin E_2, adenosine, dopamine and urodilatin) and vasoconstrictors (e.g., endothelin, angiotensin II and vasopressin). Tubuloglomerular feedback controls glomerular filtration and, indirectly, medullary oxygen demand. Reduced resorption of sodium activates signals that constrict the glomerulus, reducing glomerular filtration and subsequent delivery and resorption of sodium from the tubule. A related

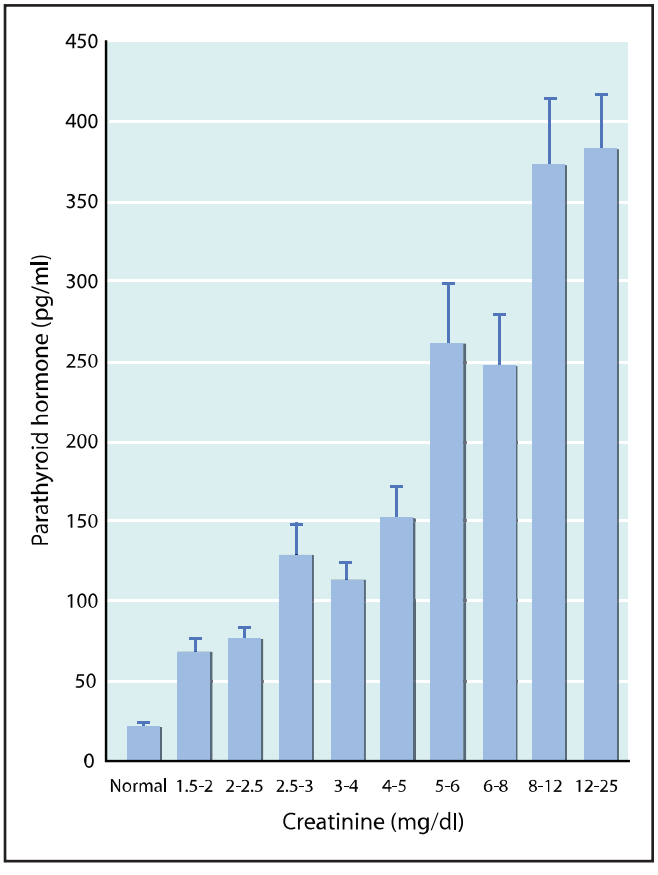


Figure 37-5. Relationship of serum parathyroid hormone concentrations to serum creatinine concentrations in 35 normal dogs and 333 dogs with uremia. (Adapted from Nagode LA, Chew DJ. Nephrocalcinosis caused by hyperparathyroidism in progression of renal failure: Treatment with calcitriol. Seminars in Veterinary Medicine and Surgery: Small Animal 1992; 7: 206.)

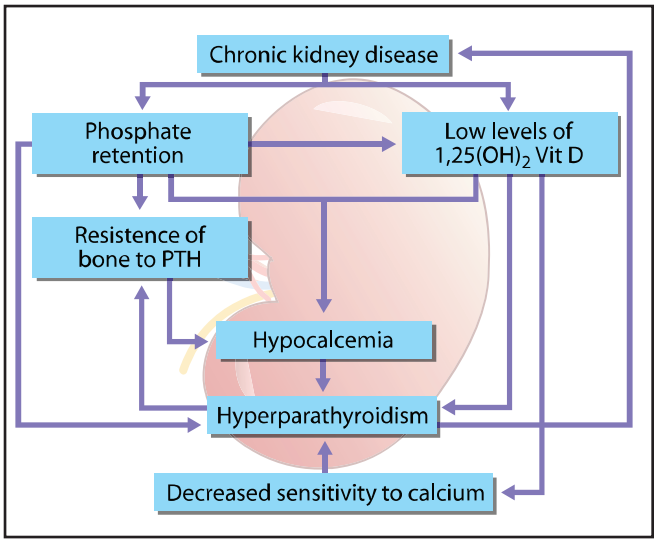


Figure 37-6. The pathogenesis of secondary renal hyperparathyroidism. Key: PTH = parathyroid hormone, $1,25(OH)_2$ Vit. D = 1,25-dihydroxycholecalciferol.

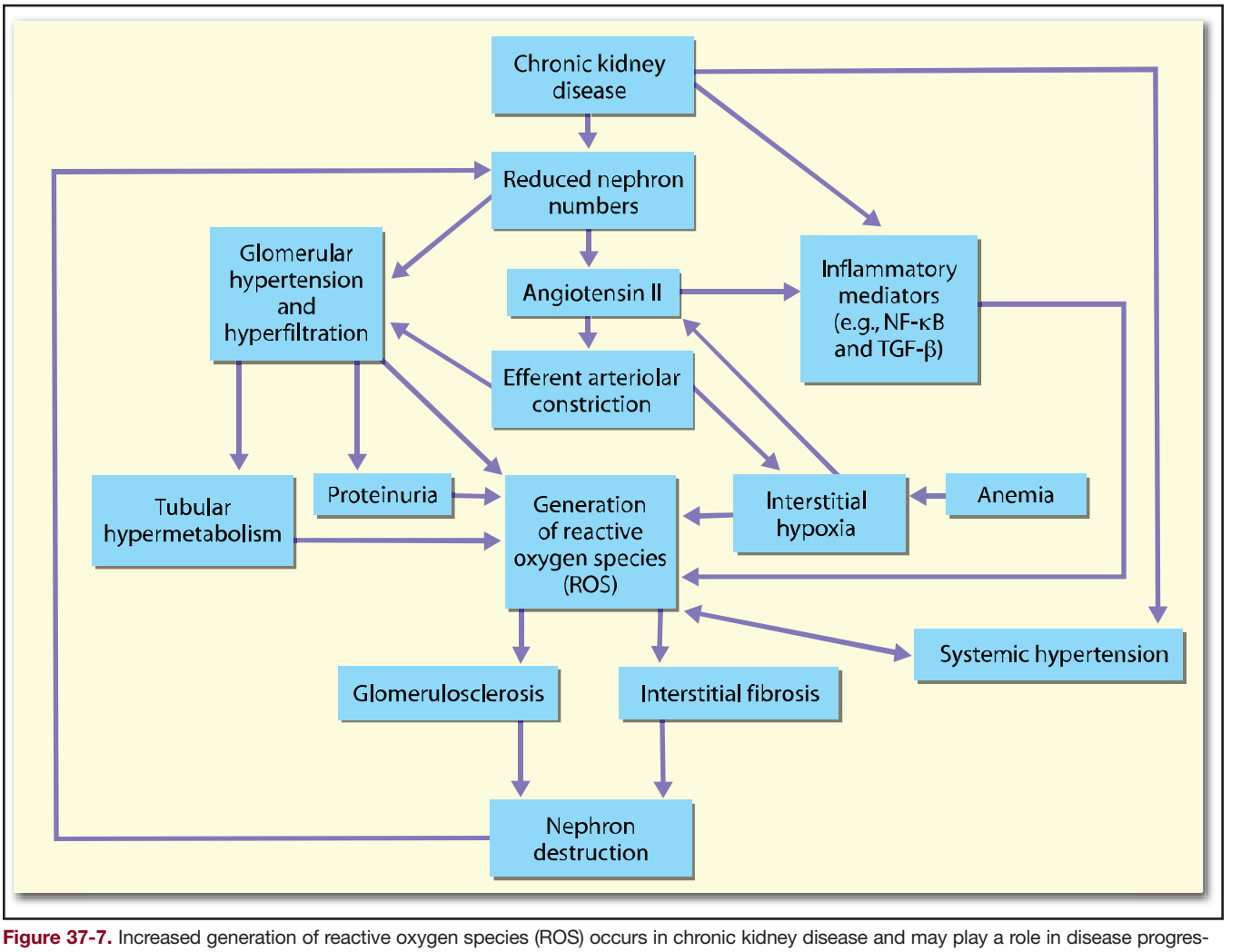


Figure 37-7. Increased generation of reactive oxygen species (ROS) occurs in chronic kidney disease and may play a role in disease progression. (Adapted from Brown SA. Oxidative stress and chronic kidney disease. Veterinary Clinics of North America: Small Animal Practice 2008; 38: 157-166).

reaction is shifting of the corticomedullary blood flow to the medulla when renal blood flow is reduced. Because the work of concentrating urine predisposes a patient to medullary hypoxic injury, reducing the need for concentration of urine may prevent medullary injury. Reducing transport activity protects medullary tubules from hypoxic injury. Dehydration, volume depletion and renal hypoperfusion stimulate urine concentration; avoiding these conditions reduces the work of urine concentration and stimulates intrarenal protective mechanisms, such as prostaglandin and dopamine production.

Renal Oxidative Stress

ROS are examples of free radicals that are produced at low levels by normal aerobic metabolism in the kidney (Brown, 2008). Examples of ROS produced in the kidney include hydrogen peroxide (H_2O_2), hydroxyl radical (OH), superoxide anion (O_2^-), lipid peroxy radicals, lipid and DNA hydroperoxides, hypochlorous acid and peroxynitrite. These ROS may damage proteins, lipids, DNA and carbohydrates, resulting in structural and functional abnormalities and progressive renal injury. Antioxidant defense mechanisms are designed to minimize damage by ROS including superoxide dismutase, catalase, nitric oxide synthase, glutathione peroxidase, vitamins E and C and carotenoids (Brown, 2008). Erythrocytes and albumin may also play important roles in minimizing oxidative injury to tissues (Agarwal, 2003; Brown, 2008; Rossert and Froissart, 2006). Erythrocytes represent a major antioxidant component of blood through enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Also, erythrocyte glutathione reductase can regenerate reduced glutathione from its oxidized form (Rossert and Froissart, 2006).

Renal tissue damage occurs when production of ROS exceeds capacity of antioxidant defense mechanisms and is called renal oxidative stress (Brown, 2008). Oxidative damage has been incriminated as a cause of progressive renal injury in several types of kidney disease (Diamond et al, 1986; Agarwal, 2003; Vasavada and Agarwal, 2005; Brown, 2008) (**Figure 37-7**). In rats with remnant kidneys, increased oxygen consumption associated with increased dietary protein is accompanied by increased urinary clearance of oxidative products (Nath et al,

1994). The role of ROS in progressive renal injury has also been evaluated in studies using vitamin E and selenium-deficient diets (Nath et al, 1994). Vitamin E is a major scavenger of ROS in lipid bilayers and selenium is required for glutathione peroxidase activity. Glutathione peroxidase is the enzyme that degrades hydrogen peroxide. Deficiency of vitamin E or selenium favors hydrogen peroxide accumulation and its associated oxidative effects. Increased renal oxidative stress has been linked to proteinuria as a potential mediator of tubulointerstitial damage and to progression of CKD (Brown, 2008; Agarwal, 2003; Agarwal et al, 2004; Vasavada and Agarwal, 2005). Overloading tubular mechanisms for resorption of filtered albumin by proximal tubular cells can stimulate production of proinflammatory and profibrotic cytokines by activation of the redox-sensitive gene nuclear factor-κB thereby contributing to tubulointerstitial damage (Agarwal, 2003; Rossert and Froissart, 2006).

Hypokalemia

Several investigators have recognized an association between CKD and hypokalemia in cats (Lulich et al, 1992; Dow and Fettman, 1992; DiBartola, 1994). Hypokalemia occurred in 19% of cats with spontaneous CKD in one study and was moderate to severe in more than half (DiBartola et al, 1987). In cats with CKD and hypokalemia, renal function may improve after potassium supplementation and restoration of normokalemia, suggesting that hypokalemia may be associated with a reversible, functional decline in GFR. Renal function adversely affected normal cats when an acidified, low-potassium food was fed (Dow et al, 1990). In this study, potassium depletion and acidosis appeared to have additive effects on impairing renal function.

Limited evidence suggests; however, that hypokalemia is a cause of, and contributing factor to, CKD in cats rather than simply a consequence of the disease. In an uncontrolled study, renal lesions and dysfunction developed in three of nine cats fed a potassium-restricted, acidifying food for several months (DiBartola et al, 1993). However, it was not clear whether potassium depletion or hypokalemia preceded the onset of kidney disease. In another study, four of seven cats with induced CKD fed a food containing 0.3% dry matter (DM) potassium developed hypokalemia, but four cats with normal renal function fed the same food did not develop hypokalemia (Adams et al, 1993). Muscle potassium content is decreased in normokalemic cats with spontaneous CKD, indicating that a total body deficit of potassium may develop well before the onset of hypokalemia (Theisen et al, 1997). The latter findings support the concept that reduced renal function precedes the development of hypokalemia.

Metabolic Acidosis and Renal Ammoniagenesis

Metabolic acidosis appears to be a common complication of CKD in dogs and cats (DiBartola et al, 1987; Lulich et al, 1992; Jacob et al, 2002). In one report, six of 38 dogs with CKD had metabolic acidosis of sufficient severity to warrant treatment (Jacob et al, 2002). A cross-sectional study involving 59 cats with CKD showed that more than half of patients with severe CKD had acidemia and low plasma bicarbonate concentrations (Elliott et al, 2003, 2003a). These data also suggested that biochemical evidence of severe metabolic acidosis does not generally occur in cats until late in the course of CKD (Elliott et al, 2003). Patients with CKD tend to develop metabolic acidosis because of impaired ability of the failing kidneys to excrete the daily net acid load. The kidney eliminates hydrogen ions by three major mechanisms: reclaiming filtered bicarbonate, buffering secreted hydrogen ions with filtered phosphate and sulfate (titratable acidity) and renal ammoniagenesis. Of these three mechanisms, renal ammoniagenesis can be markedly upregulated to increase net acid secretion by the kidneys. As functional renal mass decreases in CKD, ammonia production per surviving nephron is increased several-fold, although total ammonia production is still reduced. Because ammonia is nonpolar, it diffuses into the tubular lumen and the surrounding interstitium.

Ammonia activates the alternate complement cascade, which may lead to renal injury by several mechanisms including: release of cytokines, prostanoids and ROS, cell lysis and stimulation of collagen synthesis. In studies involving rats, supplementation with bicarbonate reduced concentrations of complement components (i.e., C_3 and $C_{5b\text{-}9}$) (Nath et al, 1985). Bicarbonate administration also reduced cortical levels of ammonia, decreased proteinuria, reduced structural damage and improved tubular function. The interaction of ammonia and complement in the etiopathogenesis of tubulointerstitial disease has also been demonstrated in studies of hypokalemic nephropathy in rats (Nath et al, 1985). Studies in rats, however, failed to demonstrate a role for acidemia and increased renal ammoniagenesis as a cause of renal injury and progression of kidney disease (Throssell et al, 1995). In an investigation of cats with induced CKD, those fed an acidifying food for six months did not develop progressive glomerular dysfunction or renal tubulointerstitial injury vs. cats fed a non-acidifying food (James, 2001). Therefore the relative importance of renal ammoniagenesis in progressive renal injury in dogs and cats with CKD is unknown.

Lipid Disorders

Cholesterol, triglycerides and possibly some classes of lipoproteins are cytotoxic to endothelial cells and stimulate glomerular mesangial cell proliferation and production of excess mesangial matrix. Abnormalities of lipid metabolism in dogs with kidney disease generally include increased serum concentrations of total cholesterol, low-density lipoproteins and triglycerides (Brown et al, 1991). Cats with experimentally induced renal dysfunction demonstrate hypercholesterolemia compared with normal cats. Despite occurrence of lipid abnormalities in dogs and cats with CKD, there is little evidence to show they play a role in causing progression of disease.

Tubulointerstitial Changes

Endstage kidney disease is characterized by glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy (Wolf, 2006; Polzin et al, 2005). Tubulointerstitial changes are a consistent feature in CKD, irrespective of the cause or initial structure

Table 37-8. Potential etiopathogenic mechanisms in chronic kidney disease and therapeutic approaches for each.

Factors	Therapeutic approaches
Chronic renal hypoxia	Maintain hydration (increased water intake) Avoid excessive sodium intake ACE inhibitors Control anemia (erythropoietin)
Glomerular hypertension and hyperfiltration	Avoid excessive dietary protein and sodium Increased dietary omega-3 fatty acids ACE inhibitors
Hyperphosphatemia and secondary renal hyperparathyroidism	Limit dietary phosphorus Intestinal phosphate binders Calcitriol (after normophosphatemia is achieved)
Hypokalemia	Potassium supplementation
Metabolic acidosis	Avoid excessive dietary protein Alkalinizing foods (therapeutic renal foods) Alkalinizing agents (bicarbonate, potassium citrate)
Proteinuria	Avoid excessive dietary protein Increased dietary omega-3 fatty acids ACE inhibitors
Renal oxidative stress	Avoid excessive dietary protein, phosphorus and sodium Increased dietary antioxidants Omega-3 fatty acid supplementation
Systemic hypertension	Avoid excessive dietary sodium ACE inhibitors Calcium-channel antagonists (amlodipine)
Tubulointerstitial inflammation/fibrosis	Increased dietary omega-3 fatty acids Avoid excessive dietary phosphorus and protein

Key: ACE = angiotensin-converting enzyme.

involved (Eddy, 1994). The extent of tubulointerstitial injury correlates with the decline in renal function, whereas the severity of glomerular injury does not correlate well with progression of CKD models. It appears that GFR is influenced to a greater degree by interstitial fibrosis than by glomerulosclerosis (Nath, 1992).

Although chronic, progressive tubulointerstitial disease plays a critical role in progression of renal lesions, the basic mechanisms that generate the tubulointerstitial damage remain unclear. There appears to be a clinically silent acute phase that is characterized by inflammation and tubular cell injury. Possible mediators of tubular injury include antibodies, ROS, obstruction, complement and lysosomal enzymes (Eddy, 1994). Damaged tubular cells can regenerate or die. Factors responsible for recruitment of mononuclear cells to the interstitium are important because of evidence that monocytes and macrophages play a key role in interstitial fibrosis (Eddy et al, 1991). Recruitment is probably mediated by the release of fibrosis-promoting cytokines, such as TGF-β (Wolf, 2006). TGF-β directly stimulates transcription of many extracellular matrix genes in renal cells including mesangial, endothelial and tubular cells. TGF-β also appears to trigger increased matrix production by perivascular and interstitial fibroblasts. Dietary protein restriction inhibits secretion of TGF-β and glomerular scarring in rats with glomerulonephritis (Fukui et al, 1993). Furthermore, the renin-angiotensin-aldosterone system is linked to activation of the TGF-β pathway, which in turn promotes interstitial fibrosis (**Figure 37-7**) (Wolf, 2006).

Tubulointerstitial injury can impair renal function by a number of mechanisms: 1) vascular effects, 2) glomerular injury, 3) interstitial and tubuloepithelial processes, 4) nephron obstruction and 5) deposition of crystals (Nath, 1992). Postglomerular blood flow is decreased when the cortical interstitium expands due to fibrosis and mononuclear infiltration. Decreased blood supply also results from release of vasoactive cytokines, growth factors and ROS produced by the interstitial infiltrate and damaged tubules. Decreased postglomerular blood flow decreases tubular blood flow and changes glomerular size and pressure. Decreased tubular blood flow may impair tubular function and glomerular size and pressure changes may lead to glomerular injury (Nath, 1992).

As discussed above, abnormal glomerular function can incite tubulointerstitial injury (Diamond and Anderson, 1990). Loss of glomerular permselectivity and resultant proteinuria are accompanied by tubulointerstitial damage. Increased trafficking of protein in the proximal tubules may cause cellular damage. Filtered protein is endocytosed in the proximal tubules and subsequently degraded by lysosomal action. Excessive release of lysosomal enzymes may be one of the pathways for tubular damage. Tubular damage may also be induced by plasma proteins that have escaped into the urine. Incriminated plasma proteins include albumin, lipoproteins, complement components and transferrin. Studies in cats with spontaneously occurring CKD demonstrated that progression of CKD is most closely linked to severity of proteinuria, which may be explained by tubular damage during tubular resorption of leaked proteins (Syme et al, 2006; Jepson et al, 2007). Progression of spontaneously occurring CKD in dogs is also related to severity of proteinuria (Jacob et al, 2005).

Effects of Renal Aging

The kidney is one of the most vulnerable organs to age-associated changes. Renal changes associated with aging are manifested by significant structural and functional alterations. Functional changes include decreased GFR, decreased renal blood flow, decreased urine concentrating ability and decreased ability to maintain sodium, water, endocrine and acid-base homeostasis. Structural changes include alterations in renal weight, volume and histologic appearance. Fibroconnective tissue replaces functionally active parenchyma in aging kidneys. In a study of dogs with spontaneous glomerulonephritis, the incidence of interstitial nephritis increased with increasing age. Interstitial nephritis was present in 10% of dogs less than one year of age, in 60% of dogs between one and five years of age and in 85% of dogs more than five years of age (Muller-Peddinghaus and Trautwein, 1977). In another study, 59% of the dogs older than four years had evidence of interstitial nephritis (Shirota et al, 1979). Glomerular lesions were noted in 43 to 78% of these dogs. Based on these reports, interstitial

nephritis and glomerulosclerosis apparently are common and occur with increased frequency in aging dogs.

It is possible that CKD occurs as a consequence of life-preserving adaptive mechanisms that accompany the aging process (Lawler et al, 2006). A study of postmortem data collected from 1979 to 2001 revealed that of 676 cats living in a research colony, cats that died from kidney disease most often had renal histologic changes (i.e., progressive tubular deletion and peritubular interstitial fibrosis); however, their mean lifespan was longer than cats that died from other causes (Lawler et al, 2006). In addition, among cats that died from causes other than kidney disease, those with renal histologic changes had a longer mean lifespan compared with cats that had no changes in their kidneys. It was hypothesized that these renal changes may represent an intrinsic mechanism that is protective until the point of failure. Regardless of the initiating cause, CKD often is characterized by irreversible loss of renal functional mass. After a critical amount of kidney damage occurs, CKD tends to be a progressive condition that often terminates with uremia-associated death.

Key Nutritional Factors

The goals of managing patients with CKD are to: 1) control clinical signs of uremia, 2) minimize disturbances associated with fluid, electrolyte and acid-base balance, 3) support adequate nutrition and 4) modify progression of CKD (Polzin et al, 2005). Nutritional management plays a role in all of these goals and is indicated to address the etiopathogenic mechanisms that occur in CKD (**Table 37-8**). In addition, the use of an appropriately formulated commercial veterinary therapeutic renal food is the only treatment that has been shown in randomized, controlled clinical studies to prolong survival time and improve quality of life in dogs and cats with CKD (Polzin et al, 2009; Roudebush et al, 2009; Jacob et al, 2002, 2004; Ross et al, 2006). Therefore, nutritional intervention should be considered a critical component of managing patients with CKD.

When designing a therapeutic regimen for dogs and cats with CKD, it is helpful to consider a food's key nutritional factors. Recommended ranges of these key nutritional factors were determined by considering nutrient levels in foods evaluated in dogs and cats with naturally occurring CKD and experimentally induced kidney disease (**Table 37-9**). Although numerous studies have been published about dogs and cats regarding the benefits of various combinations of these factors, little work has been done to isolate effects of individual nutrients (Adams et al, 1993; Barber et al, 1999; Bovee, 1991; Brown et al, 1991, 1998, 2000; Burkholder, 2000; Burkholder et al, 2004; Elliott et al, 2000; Finco et al, 1985, 1992, 1992a, 1998; Jacob et al, 2002; McCarthy et al, 2001; Polzin et al, 1982, 1983, 1983a, 1984, 1991, 1991a, 2000; Robertson et al, 1986; Ross et al, 1982, 2006; Valli et al, 1991). Commercially available veterinary therapeutic foods for dogs and cats with CKD are usually designed with these key nutritional factors in mind. Compared with typical maintenance pet foods, appropriately formulated veterinary therapeutic foods for dogs and cats with CKD generally contain less protein, phosphorus and sodium and have increased fat, omega-3 fatty acids and buffering capacity. Feline renal foods contain increased potassium to help prevent hypokalemia. In addition to key nutritional factors, it is important to consider available evidence supporting effectiveness of specific veterinary therapeutic renal foods and other treatments for CKD (**Table 37-10**). Finally, individual patient needs and responses and owner preferences must be considered to design an optimal therapeutic regimen.

Table 37-9. Key nutritional factors for dogs and cats with chronic kidney disease.*

Factors	Dietary recommendations
Water	Parenteral fluid therapy if dehydration, blood volume contraction or renal hypoperfusion is clinically significant
	Offer water free choice at all times
	Recommend moist foods
Protein	14 to 20% in foods for dogs
	28 to 35% in foods for cats
Phosphorus	0.2 to 0.5% in foods for dogs
	0.3 to 0.6% in foods for cats
Sodium	≤0.3% in foods for dogs
	≤0.4% in foods for cats
Chloride	1.5 x sodium levels in foods for dogs
	1.5 x sodium levels in foods for cats
Potassium	0.4 to 0.8% in foods for dogs
	0.7 to 1.2% in foods for cats
	If patient becomes hyperkalemic, switch to a lower potassium food
Omega-3 fatty acids	0.4 to 2.5% in foods for dogs and cats
	Omega-6:omega-3 fatty acid ratio of 1:1 to 7:1
Antioxidants	
Vitamin E	≥400 IU vitamin E/kg of food for dogs
	≥500 IU vitamin E/kg of food for cats
Vitamin C	≥100 mg vitamin C/kg of food for dogs
	100 to 200 mg vitamin C/kg of food for cats

*All values expressed on a dry matter basis, unless otherwise indicated.

Water

Kidney disease causes a progressive decline in urine concentrating ability, and maximal urine osmolality approaches that of plasma (300 mOsm/kg) (i.e., isosthenuria). As CKD progresses; these changes may be observed in patients with stage 1 CKD. If total solute excretion remains normal, but the maximal achievable urine osmolality decreases, obligatory water loss occurs to eliminate the osmolar load. This obligatory water loss may lead to development of polyuria. Compensatory polydipsia occurs to maintain fluid balance. Dehydration, volume depletion, renal hypoperfusion and dietary salt (sodium) intake stimulate urine concentration. Concentrating urine solutes represents "osmotic work" for the kidneys and represents a burden for diseased kidneys. Reducing the amount of solutes to be concentrated by decreasing dietary protein and sodium intake or by providing more water for the excretion of the same amount of solutes independently reduces the amount of osmotic work. Patients with CKD should have unlimited access to fresh water for free-choice consumption. If readily consumed by the patient, moist foods are preferred because their consumption gen-

Table 37-10. Summary of evidence for treatments of chronic kidney disease.

Dogs	Cats
Grade I	**Grade I**
Some therapeutic renal foods (for prolonging survival time and increasing quality of life when serum creatinine [SCr] >2 mg/dl)	Some therapeutic renal foods (for prolonging survival time and increasing quality of life when SCr >2 mg/dl)
Calcitriol (for prolonging survival)	ACE inhibitor (benazepril) (for reducing proteinuria; increasing appetite in cats with urine protein-creatinine ratios ≥1)*
ACE inhibitor (enalapril) (for reducing proteinuria)*	
Grade II	**Grade II**
ACE inhibitor (enalapril) (for delaying progression)*	–
Grade III	**Grade III**
Recombinant human erythropoietin (for correcting anemia)	Some therapeutic renal foods (for prolonging survival time)
Dietary phosphorus restriction (IRIS stages 3 and 4)	Dietary phosphorus restriction (IRIS stages 3 and 4)
Omega-3 fatty acid supplementation (IRIS stages 3 and 4)	Recombinant human erythropoietin (for correcting anemia)
	Amlodipine (for controlling hypertension)
	Potassium supplementation (for correcting hypokalemia)
Grade IV	**Grade IV**
Therapeutic renal foods (for delaying progression when SCr is <2 mg/dl)	Therapeutic renal foods (for delaying progression when SCr is <2 mg/dl)
Subcutaneous fluid therapy (for maintaining hydration)	Subcutaneous fluid therapy (for maintaining hydration)
ACE inhibitors (non-proteinuric) (for delaying progression)	ACE inhibitor (benazepril) (for cats without proteinuria)
Antihypertensive therapy (confirmed hypertension)	Alkalinizing therapy (acidemia)
Alkalinizing therapy (acidemia)	Assisted feeding (anorexia and malnutrition)
Assisted feeding (anorexia and malnutrition)	Calcitriol therapy
Phosphate binders (for hyperphosphatemia)	Phosphate binders (for hyperphosphatemia)
Others (e.g., enteric dialysis)	Potassium supplementation (for cats with normokalemia)
Others (e.g., enteric dialysis)	

Key: ACE = angiotensin-converting enzyme, IRIS = International Renal Interest Society, SCr = serum creatinine.
*Combined with feeding a veterinary therapeutic renal food. See Chapter 2 and Table 46-20 for more information about evidence grades I through IV.

erally results in increased total water intake compared with dry food consumption.

Protein

There is general consensus that avoiding excessive dietary protein intake is indicated to control clinical signs of uremia in dogs and cats with CKD; uremic signs most often occur in stage 4 disease but may be observed earlier (Polzin et al, 2005; Elliott et al, 2006). Many of the extrarenal clinical and metabolic disturbances associated with uremia are direct results of the accumulated waste products derived from protein catabolism. Early studies in laboratory animals showed rapid improvement when dietary protein was reduced (Klahr et al, 1983; Brenner, 1983). However, urea by itself does not account for all, if any, of the clinical signs of uremia. Serum urea nitrogen generally is considered to simply be a marker for other more important uremic toxins. Excessive dietary protein is catabolized to urea and other nitrogenous compounds that normally are excreted by the kidneys. And, as mentioned above, endogenous proteins will be degraded if amino acid intake is insufficient to maintain nitrogen balance. The goal of managing patients with CKD is to achieve nitrogen balance and limit accumulation of nitrogenous waste products by proportionally decreasing protein intake as renal function declines.

The role of decreased dietary protein intake is less clear in patients with CKD that do not have clinical signs of uremia (Polzin et al, 2005). Limiting protein intake has been advocated to slow progression of CKD on the basis of studies in rats, which revealed that excessive dietary protein consumption was associated with glomerular capillary hypertension and hyperfiltration (Brenner et al, 1982). Decreased dietary protein intake prevents these hemodynamic changes and preserves normal glomerular structure in rats (Brenner et al, 1982). The role of decreased dietary protein in delaying progression of CKD in dogs and cats is less clear and has been the subject of numerous studies and a topic of considerable debate (Polzin et al, 2000; Finco et al, 1998a) (**Box 37-1**).

Despite the lack of clarity about the effects of dietary protein on progression of CKD in dogs and cats, potential benefits should be considered. Decreased dietary protein intake inhibits secretion of TGF-β, a cytokine that may be involved in progression of kidney disease (Fukui et al, 1993). (See Etiopathogenesis of Chronic Kidney Disease, Tubulointerstitial Changes.) Decreased protein intake potentially reduces tubular hyperfunction by decreasing the renal acid load and decreasing renal ammoniagenesis. In general, protein metabolism is the major source of hydrogen ions. Consequently, avoiding excess dietary protein and decreasing endogenous protein catabolism for energy contribute markedly to the maintenance of acid-base balance (Relman et al, 1961). Primary dietary protein contributions to the renal acid load are from the sulfur-containing amino acids (methionine and cysteine). Animal proteins tend to be higher in sulfur-containing amino acids than plant protein sources. This is true whether the source of the animal pro-

Box 37-1. Role of Dietary Protein in Progression of Chronic Kidney Disease.

There has been considerable debate about the effects of dietary protein on the progression of chronic kidney disease (CKD) in dogs and cats. Studies that have attempted to evaluate the role of protein intake alone (vs. other nutrients such as phosphorus) have been conducted in dogs and cats with experimentally induced CKD (i.e., remnant kidney model or renal ablation); however, none have been performed in patients with naturally occurring disease. Feeding a veterinary therapeutic renal food, with decreased protein, significantly prolongs survival time, decreases uremic episodes and delays disease progression in dogs and cats with naturally occurring CKD. However, compared with typical maintenance pet foods, veterinary therapeutic renal foods have other features in addition to less protein (i.e., decreased phosphorus, increased fat, increased omega-3 fatty acids), which likely contribute to their effectiveness. When evaluating the evidence for or against limiting dietary protein intake, factors to consider include mechanism(s) by which protein may exert its effect(s), experimental design of previously conducted studies and appropriateness of the remnant kidney model as a predictor of what occurs in dogs and cats with naturally occurring CKD. Practically speaking, it's also important to consider what foods are readily available for patients with CKD.

When evaluating conclusions from reported studies, it is necessary to critically evaluate the research methods and results, which could affect interpretation of data. For example, in a study widely cited to support the position that feeding less protein is ineffective in slowing progression of kidney disease, some dogs in the high-protein groups, but not the low-protein groups, were supplemented with potassium citrate to correct metabolic acidosis observed with high dietary protein intake. Metabolic acidosis may contribute to renal injury by increasing renal ammoniagenesis and may increase renal oxygen consumption. Thus, conclusions regarding the effect of dietary protein on progression based on this study may be invalid because the study neutralized one mechanism by which protein may exert its beneficial effect. In the same study, some dogs developed "diet-related uremia" when they were abruptly switched to the high-protein food following renal ablation. Those dogs were removed from the study, which could have resulted in selecting for study dogs that were "resistant" to the effects of protein.

Another question that is not typically addressed in the debate on the effect of dietary protein intake on progressive renal injury is whether studies had sufficient statistical power. Before declaring that there is no treatment effect, it is useful to consider whether the group size studied was sufficient to detect an effect if one truly existed. At the conclusion of one frequently cited study, there were four dogs evaluated in the high-protein group, three dogs in the moderate-protein group and four dogs in the low-protein group. However, this study did not address the question of whether group sizes were adequate to support the conclusions made. Another study that did not show an effect of dietary protein levels on glomerular lesions in uninephrectomized dogs did mention low power in their study (i.e., power calculations of 15 and 20%). The authors indicated that factors responsible for the low power included small sample size and large inter-dog differences.

Finally, in evaluating the role of protein in CKD most veterinary investigators have used the remnant kidney model. Although this model eliminates some of the variability associated with clinical trials, it does not exactly mimic naturally occurring kidney disease and all conclusions drawn from this model may not be applicable to clinical patients. For example, in a study evaluating effects of different dietary protein levels in dogs with 75% nephrectomy, mean plasma creatinine concentrations during the four-year study ranged from 0.8 to 0.9 mg/dl in all diet groups; these values are much lower than expected in clinical patients with progressive CKD. Although it may be appropriate to conclude that feeding high levels of protein to dogs with 75% reduction in renal mass was not associated with a progressive decline in renal function, it would not be valid to state that similar dietary protein levels have the same effect in dogs with naturally occurring CKD. Several studies evaluating the role of dietary protein in limiting progression of CKD have been performed in dogs and cats that maintained stable renal function throughout the entire study period; the stable nature of renal dysfunction in such studies does not permit assessment of the role of dietary protein in limiting progression of CKD.

The Bibliography for **Box 37-1** can be found at www.markmorris.org.

tein is from food or catabolism of a patient's body tissue. Catabolism of a patient's protein stores can occur if insufficient energy (carbohydrates and fats) and/or protein are consumed. In the case of inadequate energy intake, the body's amino acids stores (tissue protein) are used for gluconeogenesis to meet glucose needs. Avoiding dietary protein excess, without imposing dietary protein deficiency can help limit the acid load imposed on patients with CKD (Burkholder, 2000).

Another potential benefit of limiting dietary protein is its effects on proteinuria. Results of studies in rats with experimentally induced nephrotic syndrome suggest that the permselective properties of the filtration barrier are altered as a consequence of increasing dietary protein intake, permitting albumin to cross the capillary wall more readily (Kaysen et al, 1984; Hutchison et al, 1987, 1990). In healthy dogs and in dogs with kidney disease, increasing dietary protein intake increases renal blood flow and GFR, which may increase filtration of plasma proteins through the glomerular membrane, resulting in proteinuria (Polzin et al, 1983a, 1984; Devaux et al, 1996; Bovee, 1991; Brown et al, 1992; Bovee et al, 1981). Proteinuria may result in direct mesangial cell toxicity, glomerular fibrosis and eventual glomerulosclerosis (**Figure 37-3**). Excessive albuminuria and abnormally filtered transferrin may lead to increased oxidative stress, which appears to be an important mechanism of progressive renal injury (**Figure 37-7**). (See Renal Oxidative Stress.) The end result of proteinuric-induced glomerulosclerosis and tubular damage is further loss of nephrons. This reduction of functional renal mass and subsequent increase in single-nephron GFR further increase proteinuria and progression of renal damage. The impact of varying dietary protein intake on glomerular hemodynamics and structure in dogs and cats with CKD is less certain; however, studies in dogs have shown that feeding a vet-

Box 37-2. Nutritional Management of Patients with Proteinuria.

Previously, it was recommended to estimate urinary protein loss and replace a similar amount by increasing dietary protein intake (e.g., supplementing with hard-boiled eggs) in patients with glomerular disease. This recommendation seemed prudent based on pathophysiologic rationale, but was not validated. Investigations in people and laboratory animals with protein-losing glomerulonephropathy indicate that reductions in dietary protein limit proteinuria and preserve serum albumin concentrations without impairing protein nutriture. The advisability of replacing persistent, severe renal protein loss has therefore been questioned.

Two studies have evaluated the effects of limiting dietary protein intake in dogs with X-linked hereditary nephritis, a glomerular disease that causes proteinuria. Male dogs have rapid progression of disease during the first year of life whereas females typically have stable disease characterized by proteinuria that may progress to advanced stages of CKD after five years of age.

In one study, effects of feeding a veterinary therapeutic renal food[a] were evaluated in male and female dogs with X-linked hereditary nephritis. One group of dogs was fed the therapeutic food with reduced protein (13.5% dry matter [DM]), phosphorus and sodium and the other group was fed a maintenance food (23% DM protein). Onset and progression of kidney disease were delayed and severity of glomerular basement membrane splitting was reduced in affected male dogs eating the commercial veterinary therapeutic renal food. In addition, these dogs lived 53% longer (362 ± 17 days vs. 239 ± 14 days) than dogs fed the regular maintenance food.

Effects of decreased dietary protein intake on proteinuria have also been studied in female dogs with heterozygous X-linked hereditary nephropathy. Dogs were blocked by urine protein-creatinine (UPC) ratios and randomly assigned to receive either a high-protein food (HP) (34.6% DM) or a veterinary therapeutic renal food[b] with less protein (LP) (14.1% DM). Phosphorus, sodium, chloride and potassium levels were essentially the same in both foods; the first three of these nutrients were decreased, relative to typical amounts in regular maintenance foods. The study was conducted using a three-period double-crossover design in which each dog served as its own control. Treatment periods 1 and 2 lasted 28 days each and treatment period 3 lasted 42 days. The groups were fed in HP-LP-HP or LP-HP-LP sequence. Proteinuria, as indicated by UPC ratios, was significantly decreased whenever the LP food was fed vs. when the HP food was fed (UPC 1.8 ± 1.1 vs. 4.7 ± 2.2; [p <0.0001]). However, an unexpected result was that the dogs lost body weight when fed the LP food. Unfortunately, the energy content of the LP food was approximately 13 to 14% lower than that of the HP food due to energy digestibility differences between the two foods that were not determined until study completion. Whether or not the body weight loss was due to excessively low amounts of dietary protein or inadequate energy intake could not be determined.

On the basis of current evidence, dogs with protein-losing glomerulonephropathy should be fed reduced-protein foods designed for patients with kidney disease. Patients should be monitored periodically (e.g., every two to four weeks initially) to determine the optimal quantity of dietary protein. The food with reduced levels of dietary protein should continue to be fed if the magnitude of proteinuria declines (as measured by UPC ratios) without substantial evidence of protein malnutrition (i.e., stable or increasing serum albumin and total protein concentrations, stable body weight and body condition score). If evidence of protein malnutrition develops, dietary protein intake should be gradually increased in stepwise fashion while closely monitoring the patient.

Although proteinuria occurs in cats with CKD, glomerular disease is infrequently diagnosed. Feeding a veterinary therapeutic renal food may benefit cats with glomerular disease or proteinuria; however, this has not been studied.

ENDNOTES

a. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Purina Veterinary Diets NF KidNey Function Canine Formula. Néstle Purina PetCare Co., St. Louis, MO. USA.

The Bibliography for **Box 37-2** can be found at www.markmorris.org.

erinary therapeutic renal food with decreased protein, before the onset of azotemia, has beneficial effects in dogs with proteinuria (Valli et al, 1991; Burkholder et al, 2004) (**Box 37-2**).

Effects of decreased dietary protein intake have been studied in dogs with induced CKD (Polzin et al, 1983; Finco et al, 1992a). In a 40-week study, dogs were fed a commercial veterinary therapeutic food[d] containing 8.2% DM protein, a commercial food[e] with 17.2% DM protein or a control food with 44.4% DM protein (Polzin et al, 1983). Feeding the lower protein foods was associated with reduced mortality, serum urea nitrogen concentrations and clinical signs of uremia. Throughout the study, all dogs fed the highest protein food had reduced physical activity and poorer hair quality compared with those parameters in dogs fed the lower protein foods. There were other nutrient differences between foods, which may have contributed to the beneficial effects observed. In another study conducted for two years, reduced dietary protein (16% DM) was not associated with a significant effect on mortality compared with feeding a food containing 32% DM protein (Finco et al, 1992a). Some differences in treatment in addition to nutritional management could have affected study outcome, however (**Box 37-1**).

Two studies evaluated effects of dietary protein on progression of induced CKD for one year in cats (Adams et al, 1993; Finco et al, 1998). In one study, renal function did not progressively decrease, regardless of dietary protein amount and caloric intake (Adams et al, 1993). However, remnant kidneys of cats with induced CKD that were fed a food containing 52% DM protein had significantly more severe glomerular and tubulointerstitial damage than cats with CKD that were fed a food containing 28% DM protein (Adams et al, 1993). Phosphorus amounts were similar between study groups (0.54% DM in the high-protein group and 0.61% DM in the low-protein group); however, cats in the high-protein group consumed significant-

ly more calories. Therefore, changes in renal morphology could have resulted from differences in protein and/or caloric intake. In the other study, no difference in renal function or glomerular lesions were found in cats consuming high-protein foods (52% DM) compared with lower protein foods (28% DM) (Finco et al, 1998). Phosphorus amounts were similar for all study groups (0.87 to 0.96% DM). There were mild and significant increases in cellular infiltrate and tubular lesions in cats that consumed more calories, but no differences were detected based on amount of dietary protein. The authors concluded that protein intake was not a risk factor for progression of renal lesions and that the practice of severe protein restriction was questionable. However, because renal function remained stable throughout both studies, it was not possible to assess the role of limiting dietary protein in decreasing progression of CKD.

Four clinical studies of cats or dogs with naturally occurring CKD compared effects of feeding a commercial veterinary therapeutic renal food with either a control or regular maintenance food that contained more protein (Harte et al, 1994; Elliott et al, 2000; Jacob et al, 2002; Ross et al, 2006). In a six-month study, mean serum creatinine and urea nitrogen concentrations progressively increased in 10 cats receiving more dietary protein (39.4% DM) and declined or remained stable in 25 cats that were fed a lower protein food[f] (25.2% DM) (Harte et al, 1994). In a non-randomized, prospective study, cats receiving a lower protein food[g] (22 to 24% protein) had significantly prolonged median survival time compared with cats that continued eating different maintenance cat foods with higher protein (48% DM) (Elliott et al, 2000). In a two-year study, cats eating a commercial veterinary therapeutic renal food[h] with 28 to 29% DM protein had no uremic episodes or renal-related deaths whereas 26% of cats in the control group consuming a food with higher protein (46 to 48% DM protein) had a uremic crisis and 22% died as a result of CKD (Ross et al, 2006). Finally, dogs receiving a commercial veterinary therapeutic renal food[e] with 14% DM protein had delayed time to onset of uremic crisis, slower decline in renal function and improved survival compared to parameters in dogs receiving a control food that contained 25% DM protein (Jacob et al, 2002). Based on these findings, it is clear that foods with less protein in these studies were associated with significantly improved quality and quantity of life in dogs and cats with naturally occurring CKD. However, because the protein amount was not the only nutrient difference between the veterinary therapeutic renal foods and comparison foods, it is not possible to conclude that limiting dietary protein alone was the sole reason for beneficial effects. **Box 37-3** provides detailed information about long-term studies that evaluated effects of veterinary therapeutic renal foods on survival time of dogs and cats with CKD.

In summary, limiting dietary protein intake is indicated to control clinical signs of uremia in dogs and cats with CKD. Although currently available evidence fails to support a recommendation for or against limiting dietary protein intake alone in non-uremic patients with CKD, there are potential benefits, assuming that patients maintain adequate caloric intake and body condition. Patients may be more likely to accept a change to a new food if it is offered before clinical signs of uremia occur and it may delay onset of uremic signs as CKD progresses (Polzin et al, 2005). On a practical note, it is difficult to achieve the degree of phosphorus restriction desired in veterinary therapeutic renal foods using typical ingredients without limiting the amount of dietary protein (Burkholder, 2000).

In regards to determining how much protein to recommend for dogs and cats with CKD, all patients should be monitored for signs of protein insufficiency and nutritional management adjusted to maintain ideal body condition (**Box 37-4**). For cats with CKD, the minimum dietary protein requirement identified in one study was 20% of calories (Kirk and Hickman, 2001); this translates to approximately 24% DM protein. Similar studies have not been reported for dogs. The minimum recommended allowances for DM dietary protein in foods for healthy adult dogs and cats are 10 and 20%, respectively (NRC, 2006). The minimum DM levels recommended by the Association of American Feed Control Officials are 18% for dog foods and 26% for cat foods (AAFCO, 2007). A report of the mean DM protein content of several popular U.S. grocery brand dog foods was 41.7% for moist foods and 25% for dry foods. For grocery brand cat foods it was 51.5% for moist foods and 35.1% for dry foods (Allen et al, 2000). The recommended range for DM protein levels in foods intended for most patients with CKD is 14 to 20% for dogs and 28 to 35% for cats. Foods with less protein may be needed to control signs of uremia in patients with more advanced CKD; in these patients, it's important to monitor for signs of protein deficiency. In addition to the amount of protein, patients with CKD should receive protein of high biologic value. The concept of ideal protein is useful when considering biologic value (Baker and Czarnecki-Maulden, 1991). Lysine is the limiting amino acid in practical foods for dogs and cats (Baker and Czarnecki-Maulden, 1991). However, experience with typical ingredients used in commercial veterinary therapeutic foods suggests that tryptophan is more frequently limiting. Therefore, based on the concept of ideal protein, foods that meet the requirement for lysine and tryptophan can be assumed to meet the requirement for all indispensable amino acids.

Phosphorus

Decreased dietary phosphorus intake is indicated in dogs and cats with CKD to limit phosphorus retention, hyperphosphatemia, secondary renal hyperparathyroidism (**Figures 37-8** and **37-9**) and progression of kidney disease (Polzin et al, 2005; Rutherford et al, 1977; Barber at al, 1999). The mechanism for the protective effect of limiting phosphorus intake is unknown. Possible factors include reduced nephrocalcinosis, suppression of hyperparathyroidism, reduced cellular energy metabolism and altered renal hemodynamics. It is possible that these mechanisms may synergistically contribute to the beneficial effects of lowering phosphorus intake.

Several studies evaluated effects of limiting dietary phosphorus intake in cats and dogs with induced kidney disease. In cats, high dietary phosphorus intake (1.56% DM phosphorus) for 65 to 343 days was associated with renal mineralization, fibrosis

Box 37-3. Summary of Studies Evaluating Effects of Veterinary Therapeutic Renal Foods on Survival in Dogs and Cats with Naturally Occurring Chronic Kidney Disease.

Numerous studies have evaluated effects of nutritional management of chronic kidney disease (CKD) in dogs and cats. Most were conducted using the remnant kidney model. Although we have learned valuable information from these studies, their findings may not be directly transferable to patients with naturally occurring disease. Three clinical studies evaluated the effects of commercial veterinary therapeutic renal foods on survival and quality of life in cats and dogs with CKD. Those studies are summarized below.

STUDY 1

Fifty cats with naturally occurring stable CKD were evaluated in a prospective study of the effects of feeding a dry or moist veterinary therapeutic renal food[a] compared with a maintenance food. The renal food contained 22 to 24% dry matter (DM) protein and 0.27 to 0.42% DM phosphorus whereas the maintenance food contained 48% DM protein and 1.9% DM phosphorus. Twenty-nine cats accepted the renal food and were assigned to the renal food group, whereas compliance (due to limited intake by the cats or owner resistance to diet change) was not achieved in the remaining 21 cats, which were assigned to the maintenance food group. Cats in the maintenance food group were fed commercial maintenance cat foods with varying amounts of fresh meat or fish. In all cases, the dietary regimens were considered appropriate for maintenance. At diagnosis, both groups of cats were matched in terms of age, body weight, plasma creatinine, phosphate, potassium and parathyroid hormone (PTH) concentrations, packed cell volume and urine specific gravity. Cats in the renal food group received their assigned food for an average of 86.6% of their survival time. Feeding the renal food was associated with a reduction in plasma phosphorus and urea nitrogen concentrations and prevented the increase in plasma PTH concentrations that occurred in the maintenance food group. Median survival time was significantly longer in the renal food group (633 days) compared with the maintenance food group (264 days). *Results of this study provide Grade III evidence for using this commercial veterinary therapeutic renal food to control secondary renal hyperparathyroidism and prolong survival time in cats with naturally occurring CKD.*

STUDY 2

Thirty-eight dogs with stable CKD (serum creatinine values between 2 and 8 mg/dl) were evaluated in a double-blinded, randomized, controlled prospective study to determine effects of feeding a commercial dry veterinary therapeutic renal food[b] compared with a control food formulated to represent the nutrient content of the 10 most popular selling grocery brand maintenance foods. The renal food contained 14% DM protein, 0.28% DM phosphorus and 1.6% DM omega-3 fatty acids, whereas the control food contained 25% DM protein, 1% DM phosphorus and 0.22% DM omega-3 fatty acids. At baseline, clinical and laboratory findings were similar between groups. At the end of the two-year study there were 17 dogs in the control group and 21 dogs in the renal food group. By the end of the study, 33% of dogs in the renal food group had developed uremic crises vs. 65% of dogs in the control group. Time to onset of uremic crises was significantly longer in the renal food group (615 days) compared with the control group (252 days). Feeding the renal food was associated with decreased progression of kidney disease and significantly prolonged median survival time (594 days) vs. the control group (188 days). As described elsewhere, feeding the renal food was associated with significantly improved health-related quality of life. *Results of this study provide Grade I evidence for using this commercial veterinary therapeutic renal food to decrease uremic episodes, delay onset of uremia and progression of kidney disease, increase survival time and improve quality of life in dogs with CKD.*

STUDY 3

Forty-five cats with stable CKD (serum creatinine values of 2.1 to 4.5 mg/dl) were evaluated in a double-blinded, randomized, controlled prospective study to determine effects of feeding a commercial dry and/or moist veterinary therapeutic renal food[c] compared with a control food that was similar to a typical adult maintenance cat food. The renal food contained 28 to 29% DM protein, 0.5% DM phosphorus, and 0.2 to 0.6% DM omega-3 fatty acids, whereas the control food contained 46 to 48% DM protein, 0.9 to 1% DM phosphorus and 0.2% DM omega-3 fatty acids. Cats were fed a combination diet (half renal food, half control food) for six weeks before random assignment to treatment groups; this was done to gradually transition cats to a new food. At the end of the two-year study there were 23 cats in the control group and 22 cats in the renal food group. Dietary compliance (defined as receiving >85% of daily caloric requirement from the assigned food) was excellent throughout the study; 91% of cats continued eating their assigned food. Four cats (two in each group) stopped eating due to nonrenal diseases. A significantly greater percentage of cats in the control group had uremic episodes (26%) compared with the renal food group (0%). There was significant reduction in deaths due to CKD in the renal food group; none of the cats receiving the renal food died during the study whereas 22% of cats in the control group died. *Results of this study provide Grade I evidence for using this commercial veterinary therapeutic renal food to decrease occurrence of uremic episodes and mortality in cats with CKD.*

ENDNOTES

a. Waltham Veterinary Diet, Whiskas Low Phosphorus Low Protein. Masterfoods, Bruck, Austria.
b. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
c. Prescription Diet k/d Feline. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

The Bibliography for **Box 37-3** can be found at www.markmorris.org.

Box 37-4. Dietary Protein Needs in Dogs and Cats with Chronic Kidney Disease and Maintenance of Lean Body Mass.

Minimum protein requirements for patients with chronic kidney disease (CKD) are assumed to be similar to those for healthy dogs and cats; however, this has not been well evaluated. Ten cats with CKD and nine healthy cats were fed foods (free choice) with different amounts of protein (16, 20 or 24% of calories as metabolizable energy [ME]) for four months. Body weight, lean body mass, nitrogen balance and laboratory parameters (hematocrit and serum concentrations of urea nitrogen, albumin and total protein) were measured to assess adequacy of dietary protein intake. Based on study findings, the authors concluded that the protein requirement for cats with CKD and healthy controls appeared to be approximately 20% ME, which is similar to results from previous studies that evaluated protein requirement in healthy cats.

The amount of protein contained in most commercially available veterinary therapeutic renal foods is more than adequate to meet minimum protein requirements of dogs and cats with CKD; however, there is a common perception that these foods are protein deficient. The terminology used to describe therapeutic foods formulated for management of kidney disease may encourage this perception. It may be more appropriate to refer to these foods as "formulated to avoid excessive protein" or "modified protein foods" instead of being "protein restricted", which may incorrectly be interpreted as protein-deficient by pet owners and health care team members.

Loss of lean body mass occurs in patients with kidney disease and may contribute to the perception that veterinary therapeutic renal foods do not contain adequate amounts of protein. Potential mechanisms for decreased lean body mass in dogs and cats with CKD include inadequate dietary protein or caloric intake, altered response to decreased protein intake, increased protein loss (e.g., proteinuria), metabolic acidosis and activation of cytokines by chronic inflammation. Failure to consume an adequate amount of calories may result in catabolism of muscle protein as a source of energy; this is one reason why veterinary therapeutic renal foods have relatively higher amounts of dietary fat. It is important to ensure adequate dietary protein intake; however, protein that is consumed in excess of the patient's needs is metabolized and used for energy, which could worsen clinical signs of uremia. Metabolic acidosis, a common complication of uremia, stimulates the degradation of branched-chain amino acids and proteins and blocks the ability of the patient to respond appropriately to lower protein intake. The specific mechanisms involve increased activity of branched-chain ketoacid dehydrogenase and the ubiquitin-proteasome proteolytic pathway. Besides acidosis, cytokines activate the ubiquitin-proteasome proteolytic pathway and cytokine release occurs with chronic inflammation. These potential mechanisms for loss of muscle mass emphasize the importance of controlling metabolic acidosis, infection and other stressors in patients with CKD.

Although some patients with CKD lose lean body mass, evidence supports that these patients can maintain body condition and weight while eating a veterinary therapeutic renal food. In a study of cats with induced CKD, those that consumed adequate calories of a low-protein food (28% dry matter protein; 20% protein as calories) maintained stable or increasing body weights, hematocrit values and serum albumin concentrations and had no clinical signs of protein-calorie malnutrition. In the absence of metabolic acidosis, dietary protein requirements did not appear to be different between cats with CKD and control cats with normal renal function. In another study of cats with naturally occurring CKD, mean body weight of the control group that received the higher protein food continued to decline, with most of the cats experiencing weight loss, compared with a mean weight gain in the group receiving a commercial veterinary therapeutic renal food with less protein. Although clinical condition (halitosis, gingivitis, appetite and body condition) deteriorated in both groups of cats, it was less apparent in the lower protein group based on observations by pet owners and veterinary clinical evaluations. The methods for assessing these observations were not indicated. In addition, packed cell volume, serum albumin and total protein increased in the lower protein group and decreased in the higher protein group. In another clinical study of cats with CKD that received either a veterinary therapeutic renal food or a typical maintenance food, no significant differences in body weights or hematocrit values were noted between groups at the midpoint of the study. In a randomized, double-blinded clinical study of cats with CKD managed by feeding either a veterinary therapeutic renal food or a control food (with higher protein), there were no significant differences in body weights or body condition scores at the midpoint and end of the two-year study.

In a double-blinded clinical study of dogs with naturally occurring CKD that received either a veterinary therapeutic renal food or a control food (with higher protein), health-related quality of life was determined using a content-validated questionnaire to obtain owner assessments. Nutritional status was assessed by periodic physical examinations and measurement of laboratory parameters. The renal food was superior to the control food for maintaining health-related quality of life and nutritional status; the renal food group remained stable based on body weights, body condition scores, hematocrit values and serum albumin concentrations.

It is highly likely that beneficial effects of feeding a veterinary therapeutic renal food are due to a combination of key nutritional factors (in addition to limited dietary protein). However, results of studies described above demonstrate that nutritional status can be maintained and quality of life improved in dogs and cats with CKD when fed a commercial veterinary therapeutic renal food containing less protein than typical adult maintenance pet foods. Regardless, all patients with CKD should be monitored for signs of protein-calorie malnutrition so that treatment can be adjusted to maintain body condition and improved quality of life.

The Bibliography for **Box 37-4** can be found at www.markmorris.org.

and mononuclear cell infiltration whereas lower phosphorus intake (0.42% DM phosphorus) was not (Ross et al, 1982) (**Figure 37-10**). Progressive changes in GFR were not detected; however, in either the high- or low-phosphorus group. Effects of dietary phosphorus restriction were studied in dogs that were fed either a low-phosphorus (0.44% DM) food or a high-phosphorus (1.44% DM) food for 24 months (Brown et al, 1991). Both foods provided reduced amounts of protein (17% DM).

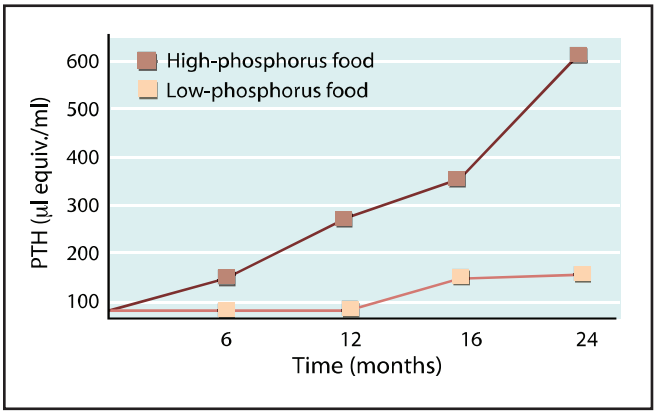


Figure 37-8. The effect of dietary phosphorus on serum parathyroid hormone (PTH) concentrations in dogs with experimentally induced kidney disease. Note that consumption of higher levels of phosphorus resulted in excessive PTH secretion. High phosphorus means dogs ingested 60 to 80 mg phosphorus/kg body weight/day, Low phosphorus means dogs ingested 15 to 40 mg phosphorus/kg body weight/day. (Adapted from Rutherford WE, Bordier P, Marie P, et al. Phosphate control and 25-hydroxycholecalciferol administration in preventing experimental renal osteodystrophy in the dog. Journal of Clinical Investigation 1977; 60: 332-341.)

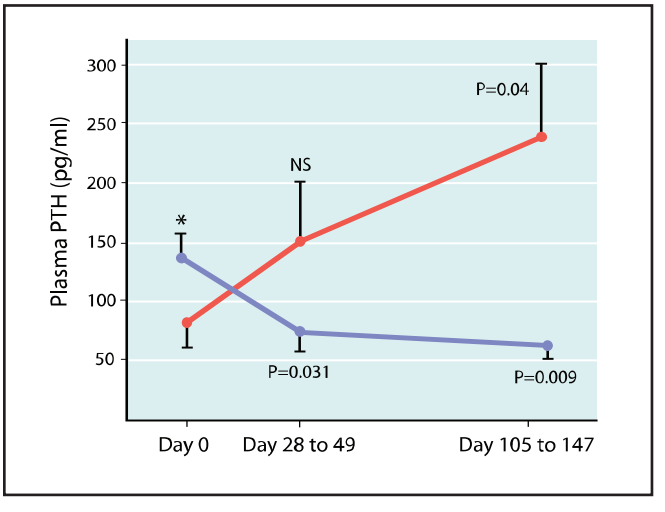


Figure 37-9. Plasma parathyroid hormone (PTH) concentrations in cats with chronic kidney disease that were fed either a veterinary therapeutic renal food with decreased phosphorus (blue line) (n=14) or a maintenance food with higher phosphorus (red line) (n=8). Results expressed as mean ± SEM. NS = not significant.
P values represent statistical significance of each value compared with pre-treatment value (Day 0).
*No significant difference between groups at baseline (Day 0).
(Adapted from Barber PJ, Rawlings JM, Markwell PJ, et al. Effect of dietary phosphate restriction on renal secondary hyperparathyroidism in the cat. Journal of Small Animal Practice 1999; 40: 62-70.)

Survival rate was significantly higher in the low-phosphorus group (75%) compared with the high-phosphorus group (33%) (**Figure 37-11**). Kidney function also deteriorated at a more rapid rate in the high-phosphorus group. Decrements of renal function were more closely related to nephrocalcinosis and tubulointerstitial lesions than to glomerular abnormalities (Brown et al, 1991). Specifically, in this study, progression and death were associated with interstitial fibrosis, tubular atrophy and dilatation and mineralization of cortical basement membranes, tubular epithelia and vascular and tubular lumina. The association of progression with tubulointerstitial lesions and nephrocalcinosis, however, does not necessarily establish a causal role for nephrocalcinosis. A similar study was conducted by investigators in the same laboratory to evaluate effects of dietary phosphorus restriction (0.48 vs. 1.46% DM) when a higher protein food (32% DM) was fed (Finco et al, 1992). In contrast to the previous study, improved survival was not observed in the group fed low-phosphorus food. An additional study compared the effects of feeding four foods of varying phosphorus and protein content (low phosphorus/low protein; high phosphorus/low protein; low phosphorus/high protein; high phosphorus/high protein) to four groups of dogs with CKD (remnant kidney model). In this study, survival was significantly increased by feeding either of the low-phosphorus foods (0.44 to 0.49% DM phosphorus) and was not affected by the amount of dietary protein (16.7 to 32% DM) (Finco et al, 1992a).

Beneficial effects of limiting dietary phosphorus intake, by feeding a veterinary therapeutic renal food, have also been demonstrated in cats and dogs with naturally occurring CKD (Elliott et al, 2000; Barber et al, 1999; Jacob et al, 2002; Ross et al, 2006). In one study, feeding a dry or moist veterinary therapeutic renal food[e] with low phosphorus (0.29 or 0.41% DM) was associated with significantly decreased plasma phosphorus and PTH concentrations compared with results from cats fed a typical maintenance food with higher phosphorus (1.9% DM) (Barber et al, 1999). In three additional studies, dogs and cats managed by feeding a veterinary therapeutic renal food with decreased phosphorus had significantly prolonged survival times compared with patients that were fed a higher phosphorus maintenance food (Elliott et al, 2000; Jacob et al, 2002; Ross et al, 2006) (**Box 37-3**).

The minimum recommended allowance for dietary phosphorus is 0.3% DM in foods for healthy adult dogs and 0.26% DM for healthy adult cats (NRC, 2006). The mean DM phosphorus contents of several grocery brand dog and cat foods were 1.39 and 1.54%, respectively (Allen et al, 2000). To achieve beneficial effects, the recommended phosphorus levels for foods used to manage CKD are 0.2 to 0.5% DM for dogs and 0.3 to 0.6% DM for cats.

Sodium and Chloride

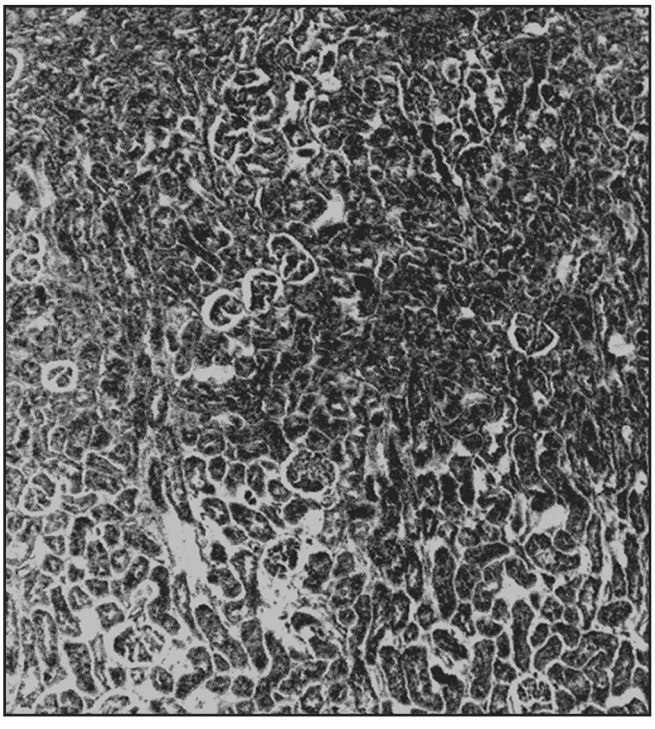
As renal function deteriorates, fractional sodium excretion increases to maintain sodium balance and preserve extracellular fluid volume. The fractional excretion of sodium must change markedly to maintain sodium balance when dietary sodium intake changes (Klahr and Slatopolsky, 1973). Patients with decreased renal function can only vary sodium excretion over a limited range, which narrows progressively as GFR declines. Thus, patients with CKD may not tolerate excessively high or low dietary sodium levels. If excessive sodium is ingested, sodium retention with expansion of extracellular fluid volume can occur and produce or worsen preexisting hypertension, fluid

overload and edema. If sodium intake is inadequate, negative sodium balance develops with resultant declines in extracellular fluid volume, plasma volume and GFR. Also, excessive dietary sodium intake may increase the absorptive workload on surviving nephrons, increasing oxygen consumption and contributing to hypoxia and increased production of damaging ROS. (See Antioxidants below.)

Limiting dietary sodium intake has been recommended for patients with CKD because of its potential to help manage concomitant hypertension; however, this has not been critically evaluated in dogs and cats with CKD. Systemic hypertension has been reported in 9 to 93% of dogs and 19 to 65% of cats with CKD (Elliott et al, 2001; Syme et al, 2002; Brown et al, 2007). The mechanism for hypertension in renal parenchymal disease is not well understood. It has been postulated that reduced intrarenal blood flow activates the renin-angiotensin-aldosterone system, which leads to chronic expansion of the extracellular fluid and elevations in blood pressure. Other possible mechanisms include secondary renal hyperparathyroidism and reduced levels of renal vasodilators such as prostaglandins.

Kidney disease may cause hypertension, and the kidneys may suffer the consequences of uncontrolled hypertension. The mechanism by which hypertension damages the kidney is not completely understood (Klahr, 1989). Canine CKD patients with major reduction of functional renal mass have impaired renal autoregulation as evidenced by increased renal arterial pressure. Dysfunctional autoregulation may result in further renal damage during hypertensive episodes, which contribute to a progressive decline in kidney function (Brown et al, 1995). Dogs with surgically induced CKD with more pronounced hypertension had significantly lower GFR values, higher UPC ratios and increased renal lesions (Finco, 2004). Hypertension has been associated with increased risk of uremic crisis and death in dogs with naturally occurring CKD (Jacob et al, 2003). In cats with CKD, however, hypertension has not been associated with decreased survival (Elliott et al, 2001; Syme et al, 2006; Jepson et al, 2007). Based on other studies, increased dietary sodium intake has not been associated with increased blood pressure in healthy cats, dogs, cats with induced kidney disease, or cats with naturally occurring CKD (Buranakarl et al, 2004; Greco et al, 1994; Luckschander et al, 2004; Kirk et al, 2006).

Currently, the role of sodium intake in progression of CKD is a topic of considerable interest in human medicine and has been mentioned in dogs and cats with CKD (Polzin, 2007; Chandler, 2008). Sodium may be directly nephrotoxic and restricting sodium intake may be beneficial in CKD, independent of its effect on blood pressure (Cianciaruso et al, 1998; Ritz et al, 2006; Jones-Burton et al, 2006; Sanders, 2004; Weir and Fink, 2005; Verhave et al, 2004). Potential mechanisms for the negative effects of salt in patients with CKD include: 1) increased TGF-β expression in renal endothelial cells, which may lead to renal fibrosis, 2) increased oxidative stress and 3) increased proteinuria. Angiotensin II or increased dietary salt intake may independently increase production of TGF-β (Sanders, 2004). Increased production of TGF-β, in turn, results in increased renal oxidative stress by production of ROS



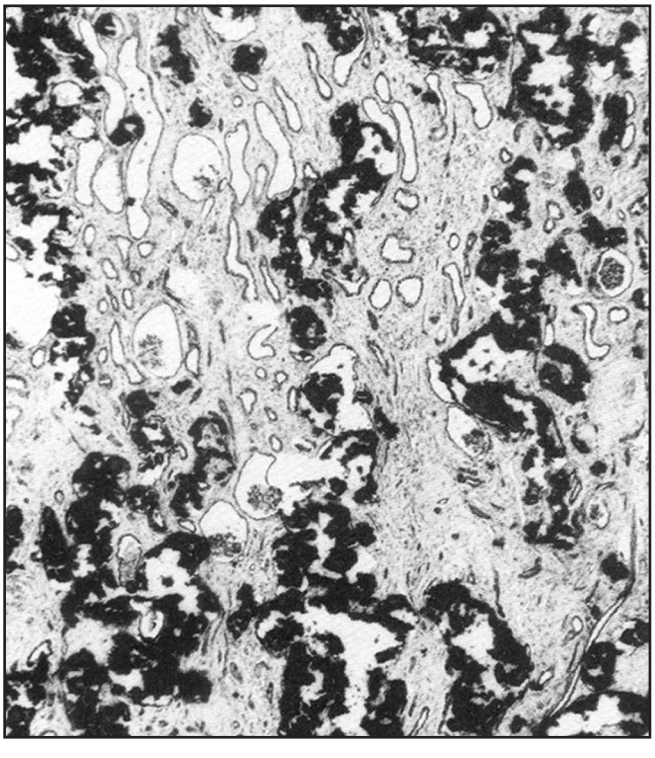


Figure 37-10. Photomicrographs of the renal cortex from cats with experimentally induced chronic kidney disease. (Above) Renal tissue from a cat fed a low-phosphorus food (0.42% DM phosphorus). Mineralized foci are not seen in this kidney (hematoxylin-eosin stain). (Below) Renal tissue from a cat fed a food with normal phosphorus levels (1.56% DM phosphorus). Mineralization (black foci), fibrosis and mononuclear cell infiltrates are extensive compared with that seen on a renal photomicrograph from a cat eating the lower phosphorus food (von Kossa's stain). (Reprinted with permission from Ross LA, Finco DR, Crowell WA. Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass. American Journal of Veterinary Research 1982; 43: 1023-1026.)

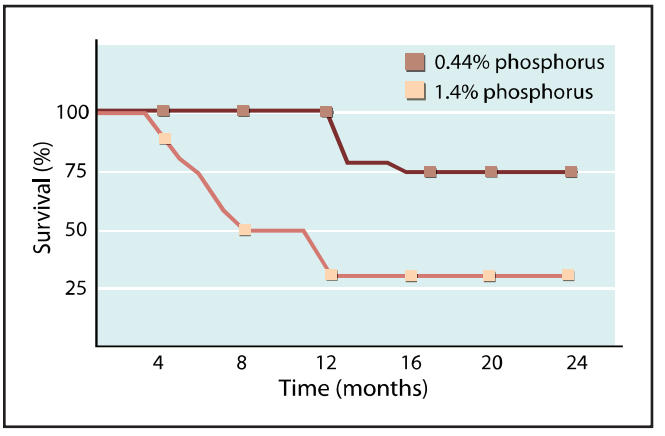


Figure 37-11. Survival of dogs with experimentally induced chronic kidney disease fed low-protein foods with different levels of phosphorus. Note that survival was much improved in dogs consuming the low-phosphorus food. (Adapted from Brown SA, Crowell WA, Barsanti JA, et al. Beneficial effects of dietary mineral restriction in dogs with marked reduction of functional renal mass. Journal of the American Society of Nephrology 1991; 1: 1169-1179.)

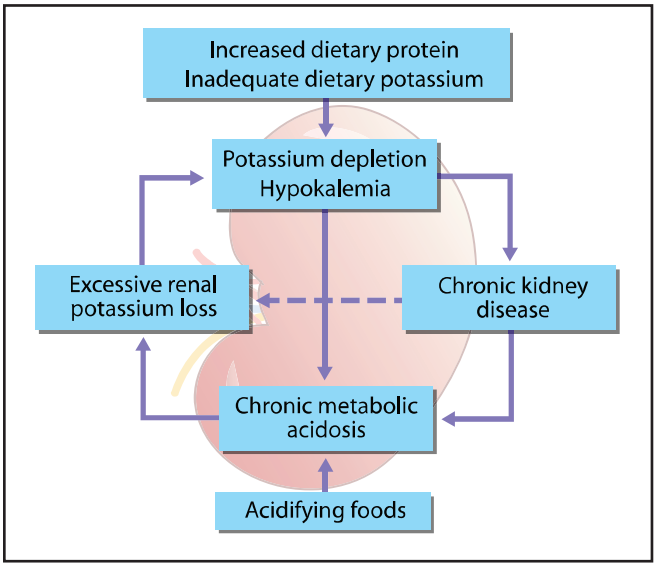


Figure 37-12. Proposed relationship between dietary potassium intake, excessively acidifying foods and feline chronic kidney disease.

(**Figure 37-7**). In human patients with CKD, the anti-proteinuric effect of angiotensin-converting enzyme (ACE) inhibition was strongly dependent on dietary sodium restriction; increased sodium intake virtually abolished the anti-proteinuric effect of the ACE inhibitor lisinopril (Heeg et al, 1989). Administration of ACE inhibitors has been associated with decreased proteinuria in dogs and cats (Grauer et al, 2000; King et al, 2006; Mizutani et al, 2006). The role of dietary sodium on beneficial effects of ACE inhibition has not been evaluated in dogs and cats; however, most patients in these studies were also fed veterinary therapeutic renal foods, which likely contained decreased amounts of sodium. Additional clinical studies are needed to evaluate the role of salt in progression of CKD; however, until results of such studies are available, it has been recommended that modest dietary avoidance of salt be encouraged in human patients with CKD, especially if they have hypertension and/or proteinuria (Jones-Burton et al, 2006).

The long-term effects of altering dietary sodium intake alone in cats and dogs with naturally occurring CKD have not been reported. Feeding veterinary therapeutic renal foods with decreased sodium (0.18 to 0.3% DM sodium in cats and 0.17% DM sodium in dogs) has been associated with increased survival time compared with feeding maintenance foods that contain more sodium (0.4 to 1.1% DM sodium in cats and 0.4% DM sodium in dogs) (Ross et al, 2006; Jacob et al, 2002; Elliott et al, 2000). Several reports describe short-term effects (seven days to six months) of feeding differing amounts of sodium on renal function in dogs and cats (Buranakarl et al, 2004; Greco et al, 1994; Luckschander et al, 2004; Kirk et al, 2006; Xu et al, 2009). In healthy adult cats (mean age = seven years), feeding foods containing 1.11% DM sodium was not associated with increased serum concentrations of urea nitrogen, creatinine or phosphorus, compared with feeding foods containing 0.55% DM sodium for six months (Xu et al, 2009). In this study, data from nine cats with serum creatinine values >1.5 mg/dl were evaluated; there were no significant differences between groups based on dietary sodium intake. Urine concentrating ability for these nine cats was not reported; however, mean urine specific gravity for all cats at the beginning of the study ranged from 1.049 to 1.053. In a study in cats with induced kidney disease, three different amounts of sodium (0.34, 0.68 and 1.35% DM) were fed for seven days (Buranakarl et al, 2004). Feeding the lowest amount of sodium was associated with increased urinary potassium loss and reduced GFR (Buranakarl et al, 2004). The effects of high salt intake (1.19% DM sodium) for three months were evaluated in six cats with naturally occurring CKD (azotemia with urine specific gravity <1.035) (Kirk et al, 2006). The CKD cats fed the high-salt food had significant and progressive increases in blood urea nitrogen, serum creatinine and serum phosphorus compared with results from cats consuming food with 0.37% DM sodium (Kirk et al, 2006). Two of the cats were removed from the study after beginning the high-sodium food due to decreased food intake; this did not affect results of statistical analysis or study conclusions.

A number of studies examined the interaction of dietary sodium with other ions, including chloride. The full expression of sodium chloride-sensitive hypertension in people depends on the concomitant administration of both sodium and chloride (Kurtz et al, 1987; Boegehold and Kotchen, 1989; Luft et al, 1990). In experimental models using rodents with sodium chloride-sensitive hypertension and in clinical studies with small numbers of hypertensive people, blood pressure and volume were not increased by a high dietary sodium intake provided with anions other than chloride. Furthermore, high chloride intake without sodium has less effect on blood pressure than does sodium chloride intake (Kurtz et al, 1987; Boegehold and Kotchen, 1989; Kotchen et al, 1981). The failure of non-chloride sodium salts to produce hypertension or hypervolemia may be related to their failure to expand plasma volume because the

renal tubular signal for renin release is responsive to renal tubular chloride (Boegehold and Kotchen, 1989; Luft et al, 1990; Kotchen et al, 1981, 1987). Chloride may also act as a direct renal vasoconstrictor (Boegehold and Kotchen, 1989). These findings suggest that both sodium and chloride are nutrients of concern in patients with hypertension and CKD.

Based on current information, dietary DM sodium intakes for patients with CKD are 0.3% or less for dogs and no more than 0.4% for cats. For comparison, the minimum recommended DM allowances for sodium in foods for healthy adult dogs and cats are 0.08 and 0.096%, respectively (NRC, 2006). The mean sodium levels in several moist grocery brand dog foods were 0.87% DM and 0.9% DM in moist cat foods, although some moist foods contain more sodium. In contrast, dry foods contained approximately half those amounts (Allen et al, 2000). The minimum recommended allowances for chloride for foods for healthy adult dogs and cats are 1.5 times the recommended sodium levels (NRC, 2006). That same factor is suggested for chloride content of foods for canine and feline CKD patients. Some patients may have obligatory urinary sodium losses and abruptly changing these patients to a low-sodium food may result in dangerous contraction of the extracellular fluid volume. Therefore, it is recommended that dogs and cats with CKD be gradually transitioned to foods with reduced amounts of sodium.

Potassium

Cats with CKD appear to be particularly predisposed to disorders in potassium homeostasis (**Figure 37-12** and **Case 37-3**). Decreased dietary potassium intake due to inappetence or vomiting and increased urinary losses due to polyuria can contribute to hypokalemia in CKD. Hypokalemia (potassium values <3.5 mEq/l) has been reported to occur in 19 to 20% of cats with CKD and was moderate to severe (potassium <3.1 mEq/l) in more than half of the cases in one study (DiBartola et al, 1987; Elliott and Barber, 1998). Conversely, hyperkalemia was observed in 9 to 13% of these cats. Hyperkalemia was observed in oliguric and polyuric kidney disease and was most common (22%) in cats with endstage CKD.

Potassium depletion leads to functional and morphologic changes in the kidneys of dogs and cats. Functional changes include reduced GFR and urine concentrating ability. Chronic potassium depletion stimulates renal ammonia synthesis. In hypokalemic rats, increased renal ammoniagenesis contributed to chronic lymphoplasmacytic tubulointerstitial nephritis (Nath et al, 1985). Studies in cats demonstrated that potassium depletion may result from feeding acidifying foods that are high in protein and low in potassium. CKD was observed in three of nine adult cats fed a food high in protein (40% DM) and low in potassium (0.32% DM) content for two years. Lymphoplasmacytic interstitial nephritis and interstitial fibrosis were detected in these cats and in two other cats without laboratory abnormalities (DiBartola et al, 1993).

The minimum recommended allowances for foods for healthy adult dogs and cats are 0.4% DM, and 0.52% DM, respectively (NRC, 2006). The potassium requirement for cats is proportional to the protein content of the food. Using purified foods, 0.3% potassium was required for growth in kittens fed a 33% protein food; however, 0.5% potassium was required with a 68% protein food (Hills et al, 1982). Acidifying foods and chronic metabolic acidosis may contribute to hypokalemia (**Figure 37-12**) (Dow et al, 1990).

The recommended range for potassium for foods for dogs with CKD is 0.4 to 0.8% DM and for cats 0.7 to 1.2% DM. For cats with hypokalemia, oral supplementation with potassium gluconate should be considered if diet alone does not maintain serum potassium concentration above 4.0 mEq/l (Polzin, 2007). Oral administration is safest and is the preferred route unless a critical emergency exists or if oral administration is impossible or contraindicated. Oral potassium gluconate appears to be tolerated well; the initial recommended dose is 2 to 6 mEq potassium gluconate/cat/day, depending on the size of the cat and severity of clinical signs. The potassium gluconate dose should be adjusted based on clinical response and serial analyses of serum potassium concentration. During initial treatment, serum potassium concentration should be checked every two to four days. Later, serum potassium should be checked every two to four weeks. Additional studies are needed to determine whether routine potassium supplementation is indicated in all cats with CKD, regardless of serum potassium concentration (Polzin et al, 2000).

Omega-3 Fatty Acids

The specific dietary fatty acid content of a food can influence progression of CKD by affecting: 1) renal hemodynamics, 2) platelet aggregation, 3) lipid peroxidation, 4) systemic blood pressure, 5) proliferation of glomerular mesangial cells and 6) plasma lipid concentration. Appropriate levels of omega-3 (n-3) fatty acids (e.g., eicosapentaenoic acid [EPA] and docosahexaenoic acid) in foods compete with arachidonic acid in several ways to alter eicosanoid production. These alterations are considered to be renoprotective (Brown et al, 1998).

Specific ingredients (e.g., menhaden fish oil) contain increased levels of omega-3 fatty acids; therefore, animals fed menhaden fish oil have decreased levels of 2-series eicosanoids, which are normally derived from arachidonic acid, and increased levels of 3-series eicosanoids, derived from omega-3 fatty acids. The 3-series eicosanoids are less potent at inducing vasoconstriction and platelet aggregation than the 2-series eicosanoids. Saturated fatty acids found in animal fat do not serve as precursors for eicosanoid production.

In dogs with a remnant kidney model of CKD, dietary omega-3 fatty acid supplementation reduced proteinuria, prevented glomerular hypertension and decreased production of proinflammatory eicosanoids (Brown et al, 1998, 2000). Dietary fat composition altered the rate of CKD progression in dogs following 15/16 nephrectomy (**Figure 37-13**). A low-fat food (<1% DM fat) was supplemented with one of three different fat sources (menhaden fish oil, beef tallow or safflower oil) to achieve a total DM fat concentration in the food of 15%. Dogs were assigned to dietary treatment two months following nephrectomies and followed for 20 months. Compared with

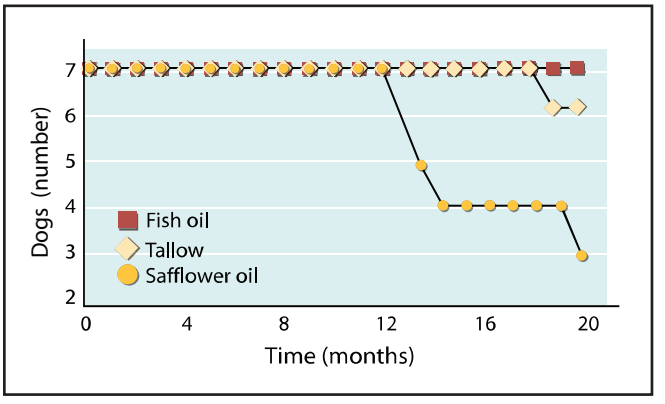


Figure 37-13. Survival of dogs with experimentally induced chronic kidney disease fed foods with three different fat sources (fish oil, tallow, safflower oil). Note that survival was increased in those dogs consuming foods with either tallow or fish oil compared to safflower oil. Dietary fatty acid composition appears to affect hemodynamic adaptations to renal disease in dogs. (Adapted from Brown SA, Brown CA, Crowell WA, et al. Dietary lipid composition alters chronic course of canine renal disease (abstract). Journal of Veterinary Internal Medicine 1996; 10: 168.)

the other two groups, the group receiving the food supplemented with safflower oil had greater glomerular enlargement and mean glomerular capillary pressure. Dietary fatty acid composition appeared to alter hemodynamic responses to renal insufficiency. Final mean exogenous creatinine clearance was 1.3 ml/min./kg body weight for the menhaden fish oil group, 0.9 ml/min./kg body weight for the beef tallow group and 0.5 ml/min./kg body weight for the safflower oil group. Mean UPC ratios were 0.6 in the menhaden fish oil group, 1.5 in the beef tallow group and 2.1 in the safflower oil group. Survival was similar in groups receiving menhaden oil and beef tallow; however, four of seven dogs in the safflower oil group were euthanized. In other studies in dogs with a remnant kidney model of CKD, dietary supplementation with either omega-3 fatty acids or antioxidants was renoprotective and their effects were additive when used together (Brown, 2008).

However, in normal and CKD dogs fed foods supplemented with safflower and menhaden fish oil, the oil supplement had no significant effect on the ratio of urinary eicosanoids (Crocker et al, 1996). The ratio of the urinary eicosanoids thromboxane B_2 (a stable urinary metabolite of thromboxane A_2) and prostaglandin E_2 has been used as an index of renal vascular tone in normal and CKD dogs. Failure to demonstrate a change in the ratio may be related to the length of the washout period (three weeks) and uncertain stability of lipid supplements in this study.

A retrospective CKD study was conducted to evaluate survival times in 146 cats fed one of seven commercial veterinary therapeutic renal foods, compared with survival times in 175 cats fed regular maintenance foods (Plantinga et al, 2005). The median survival time for cats fed maintenance foods was seven months whereas the median survival time for cats fed veterinary therapeutic renal foods was 16 months. The group with the longest median survival time (23 months) was fed the food with the highest reported content of EPA. However, because of study design and differences between groups (e.g., age of cats, plasma creatinine concentrations) and foods (e.g., potassium, phosphorus) used, it is not possible to conclude that differences in survival times were due to increased amounts of EPA. In addition, EPA content was not determined for all foods used in the study.

Although the recommended amount of omega-3 fatty acids for foods for CKD patients has not been definitively determined, the amounts in the aforementioned studies in dogs (Brown et al, 1998, 2000; Brown, 2008) ranged from 0.41 to 4.37% DM. With a 5:1 omega-6:omega-3 fatty acid ratio, the lower end of the range (0.41%) was effective in reducing the magnitude of glomerular hypertension and renal generation of inflammatory eicosanoids (Brown, 2008). The omega-6:omega-3 ratio was not reported in the earlier studies (Brown et al, 1998, 2000). To date, studies like these have not been done in cats but it seems likely that similar levels would be effective. Based on results of canine studies described above, the recommended range for total omega-3 fatty acid content in foods for canine and feline CKD patients is 0.4 to 2.5% DM. Until there is definitive work, a somewhat broad range for the omega-6:omega-3 fatty acid ratio is recommended (1:1 to 7:1). These recommendations are similar to omega-3 fatty acid content and omega-6:omega-3 ratios recommended for dogs and cats with cancer, osteoarthritis and inflammatory skin diseases.

Dietary omega-3 fatty acid supplementation in combination with antioxidants (See Antioxidants below.) can further reduce renal oxidant injury. In a study in dogs with the remnant model of CKD, dietary supplementation with omega-3 fatty acids and antioxidants (vitamin E, carotenoids and lutein), both were independently renoprotective; when combined, their effects were additive (Brown, 2008). In this model, addition of antioxidants reduced proteinuria, glomerulosclerosis and interstitial fibrosis independent of the ratio of dietary omega-6 to omega-3 fatty acids (Brown, 2008).

Antioxidants: Vitamins E and C

Oxidative damage is a component in the progression of renal injury in several types of kidney disease (**Figure 37-7**) (Diamond et al, 1986; Agarwal, 2003; Vasavada and Agarwal, 2005). Unquenched ROS may damage proteins, lipids, DNA and carbohydrates, resulting in structural and functional abnormalities and progressive renal injury. Renal oxidative stress occurs when production of ROS exceeds quenching capacity of antioxidant defense mechanisms (Brown, 2008). As previously discussed (See Etiopathogenesis above.), increased renal oxidative stress has been linked to proteinuria as a potential mediator of tubulointerstitial damage and to progression of CKD (Brown, 2008; Agarwal, 2003; Agarwal et al, 2004; Vasavada and Agarwal, 2005). Specifically, overloading tubular mechanisms for resorption of filtered albumin by proximal tubular cells can stimulate production of proinflammatory and profibrotic cytokines by activation of the redox-sensitive gene nuclear factor-κB thereby contributing to tubulointerstitial damage (Agarwal, 2003; Rossert and Froissart, 2006).

Numerous antioxidant defense mechanisms are designed to

minimize damage by ROS including several nutritional antioxidants: vitamins E and C and carotenoids (Brown, 2008). Supplementation of foods with these antioxidants has been evaluated in dogs and cats with naturally occurring CKD. In a canine study, 10 patients with CKD (IRIS stage 2 to 3) and 10 healthy dogs were evaluated to determine effects of supplementation of vitamins E (1,200 IU/kg DM) and C (150 mg/kg DM), and β-carotene (1.6 mg/kg DM) in a dry veterinary therapeutic renal food (Yu et al, 2006). Levels of vitamins E and C and β-carotene in the control food were not reported. The antioxidant supplementation reduced oxidative stress as measured by significantly reduced plasma malondialdehyde concentration. The antioxidant-supplemented renal food significantly reduced serum creatinine concentration and resulted in increased body weight and activity (eight of 10 dogs) in the CKD dogs compared with dogs receiving the unsupplemented commercial maintenance-type food (Yu et al, 2006).

Similarly, effects of antioxidants on renal oxidative stress were studied in 10 cats with CKD compared with healthy cats (Yu and Paetau-Robinson, 2006). Supplementation of vitamins E (742 mg/kg DM) and C (84 mg/kg DM) and β-carotene (2.1 mg/kg DM), compared with the control food containing 166 mg/kg DM vitamin E, less than 5 mg/kg DM vitamin C and 1.4 mg/kg DM β-carotene, resulted in reduced markers of oxidative injury. Antioxidant supplementation significantly reduced DNA damage in cats with CKD as evidenced by reduced serum 8-hydroxy-2'-deoxyguanosine (8-OHdG) and comet assay parameters (Yu and Paetau-Robinson, 2006). Based on these studies, supplementation with vitamins E and C and β-carotene as antioxidants may benefit dogs and cats with CKD.

Dietary supplementation with antioxidants in combination with increased omega-3 fatty acids (discussed above) reduces renal oxidant injury. Supplementation with vitamin E suppressed renal oxidative stress in rats with 5/6 nephrectomy (Tain et al, 2007). Also, as mentioned above in dogs with a remnant kidney model of CKD, dietary omega-3 fatty acid supplementation reduced proteinuria, prevented glomerular hypertension and decreased production of proinflammatory eicosanoids (Brown et al, 1998, 2000). In other studies in dogs with a remnant kidney model of CKD, dietary supplementation with omega-3 fatty acids and antioxidants (vitamin E, carotenoids and lutein) both independently were renoprotective and their effects were additive when used together (Brown, 2008). In this model, addition of antioxidants reduced proteinuria, glomerulosclerosis and interstitial fibrosis independent of the ratio of dietary omega-6 polyunsaturated fatty acids to omega-3 polyunsaturated fatty acids (Brown, 2008).

The DM requirement of vitamin E in foods for adult dogs is 30 IU/kg (NRC, 2006). An upper limit of 1,000 to 2,000 IU/kg food DM has been suggested for dogs (AAFCO, 2007). One antioxidant biomarker study in dogs indicated that for improved antioxidant performance, foods should contain at least 500 IU vitamin E/kg DM (Jewell et al, 2000). Besides helping to prevent chronic diseases associated with oxidative stress, increasing dietary intake of vitamin E, up to 2,010 mg/kg food DM in older dogs improved immune function (Hayes et al, 1969; Hall et al, 2003; Meydani et al, 1998). Based on the above studies, foods for canine CKD patients should contain at least 400 IU vitamin E/kg DM and higher levels are probably better. In one report, dietary supplementation of food for dogs with induced CKD, 5 IU/kg body weight was effective; this amount translates to approximately 450 IU/kg food DM (Brown, 2008).

The minimum recommended allowance of vitamin E in foods for healthy adult cats is 38 IU/kg DM (NRC, 2006). No safe upper limit has been established for cats. One antioxidant biomarker study suggested that cat foods should contain 600 IU/kg DM for improved antioxidant function (Jewell et al, 2000). A study in aged cats showed that increasing dietary intake of vitamin E to 272 and 552 IU/kg of food DM improved immune function (Hayes et al, 1969; Hall et al, 2003). Based on these data and studies in cats with CKD discussed above, foods for cats with CKD should contain at least 500 IU/kg DM and, as with dogs, higher levels are probably better. Foods high in polyunsaturated fatty acids (e.g., those containing fish oils), may require increased amounts of vitamin E (four or more times levels in typical foods) to prevent steatitis (NRC, 2006).

Healthy dogs can synthesize required amounts of vitamin C for normal maintenance conditions (Innes, 1931; Naismith, 1958; Chatterjee et al, 1975) and they can rapidly absorb supplemental vitamin C (Wang et al, 2001). However, in vitro studies indicate that dogs and cats have from one-quarter to one-tenth the ability to synthesize vitamin C as other mammals (Chatterjee et al, 1975). Foods for canine and feline CKD patients should contain at least 100 and 100 to 200 mg vitamin C/kg DM, respectively. This recommendation is based on the aforementioned vitamin E levels in foods for dogs and cats with CKD and data indicating that vitamin C regenerates vitamin E at about a 1:1 molar ratio (Barclay et al, 1985). This range is not a risk factor for urinary oxalate production in cats (Yu and Gross, 2005).

Other Nutritional Factors

β-carotene

β-carotene is a carotenoid like lutein and lycopene. As mentioned above, the carotenoids have antioxidant properties. β-carotene can be absorbed by dogs and cats. β-carotene is also a precursor for vitamin A. Dogs, but not cats, are able to convert β-carotene to vitamin A. β-carotene can be pro-oxidant at high levels in people and laboratory animals (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994). β-carotene values in foods typically are difficult to obtain from manufacturers. For these reasons, at this time, β-carotene is not considered a key nutritional factor for foods for dogs or cats with CKD.

Acidifiers and Buffers

Metabolic acidosis is a common finding in patients with CKD. Decreased venous blood pH and plasma bicarbonate or total CO_2 concentrations are common, particularly in cats

with uremic signs or endstage disease (Lulich et al, 1992; Elliott and Barber, 1998; Elliott et al, 2003, 2003a). The kidneys play an important role in regenerating bicarbonate and excreting dietary acids, which may be derived from several sources. Sulfuric acid is formed when sulfur-containing amino acids (i.e., methionine and cysteine) are oxidized to sulfate. In general, animal-source proteins are higher in sulfur-containing amino acids than are plant-source proteins. Exogenous- and endogenous-source proteins are equally important. Insufficient energy intake results in protein catabolism and increased hydrogen ion production. Urinary urea production and total urinary hydrogen ion excretion are directly proportional. Organic acids are produced from partial oxidation of carbohydrates, fats, proteins and nucleic acids. Phosphoric acid can be ingested in the food or it can be produced endogenously. Phosphoric acid is used in some cat foods as a palatability enhancer, either separately or as a component of topically applied animal digests. Phosphoric acid can be derived from hydrolysis of phosphate esters in proteins and nucleic acids, if they are not neutralized by mineral cations (e.g., sodium, potassium and magnesium). The contribution of dietary phosphate to acid production depends on the type of protein ingested. Some proteins generate phosphoric acid, whereas others generate only neutral phosphate salts. Hydrochloric acid is generated when positively charged cationic amino acids (e.g., lysine and arginine) are broken down into neutral products.

Some commercial veterinary therapeutic renal foods are formulated with combinations of ingredients that will alkalinize the urine and blood, which minimizes dietary acid load (Burkholder et al, 2000). These foods are limited in protein ingredients, particularly those that are high in sulfur-containing amino acids. For patients with CKD, the serum total CO_2 should be maintained within the reference range for healthy patients. Ideally, blood gas analysis should be done to more accurately confirm the presence of metabolic acidosis. As CKD progresses and acidosis becomes more severe, alkali therapy (e.g., sodium bicarbonate, potassium citrate) should be considered in addition to nutritional management. Although urinary pH may be used as an indirect assessment of acid/base status, monitoring venous blood gases is a more sensitive method to evaluate effectiveness of alkalinization therapy.

Vitamin D

Calcitriol (1,25-dihydroxyvitamin D) plays an important role in the pathogenesis of secondary renal hyperparathyroidism. Patients with severe CKD have decreased circulating levels of 1,25-dihydroxyvitamin D because of decreased synthesis by the kidney. Hyperphosphatemia and the progressive loss of renal epithelial cells inhibit conversion of 25-hydroxyvitamin D to calcitriol by renal 1-α-hydroxylase. At earlier stages of CKD, circulating levels of 1,25-dihydroxyvitamin D may be normal due to the compensatory effect of increased concentrations of PTH on renal 1-α-hydroxylase activity and tubular synthesis of 1,25-dihydroxyvitamin D.

Calcitriol is an important regulator of parathyroid chief-cell function. Calcitriol acts by decreasing PTH messenger RNA expression, increasing expression of vitamin D receptors and controlling the "set point" of chief cells, which determines responsiveness to negative feedback by ionized serum calcium concentrations. Decreased circulating calcitriol levels in CKD lead to chief-cell hyperplasia and increased secretion of PTH. Increased PTH levels have been suggested to play a role in the severity of clinical signs and progression of CKD (Nagode and Chew, 1992).

Avoiding excessive dietary phosphorus and using phosphate binders reduce the inhibitory effects of hyperphosphatemia on renal 1-α-hydroxylase activity, thereby increasing calcitriol production by tubular cells. Oral administration of low doses of calcitriol is associated with decreased serum PTH concentrations. Strong evidence supports the use of calcitriol therapy for slowing progression of CKD in dogs but not in cats (Polzin et al, 2005a; Polzin, 2007). The effect of varying vitamin D levels in foods has not been studied; therefore, it is not included as a key nutritional factor.

B Vitamins

Limited information exists concerning vitamin nutrition in dogs and cats with CKD; however, these patients are at risk for B-vitamin deficiency because of decreased appetite, vomiting, diarrhea and polyuria. Human patients with CKD apparently are especially prone to pyridoxine and folate deficiency (Gilmour et al, 1993). Thiamin and niacin deficiency may contribute to anorexia associated with renal failure. Empirical administration of vitamins seems appropriate in anorectic patients with CKD. However, care must be taken to avoid excessive amounts of fat-soluble vitamins. Patients eating adequate amounts of commercial veterinary therapeutic renal foods are unlikely to need B-vitamin supplementation.

Trace Minerals

Presumably, CKD alters metabolism of trace minerals. For example, nutrients such as copper and zinc that are highly bound to protein may be lost with severe proteinuria. Aluminum may accumulate in human patients with CKD who are treated with aluminum-containing phosphate binders. Aluminum toxicity can cause metabolic bone disease, encephalopathy and anemia. However, exact data are not available to support making a routine recommendation for dietary trace mineral modification for dogs and cats with CKD. There are no reports of trace mineral problems in dogs and cats with CKD that eat commercial veterinary therapeutic renal foods.

Soluble Fiber

It is well established that soluble fiber causes bacterial proliferation in the colon. Bacterial growth requires a source of nitrogen. Although dietary protein provides some nitrogen, blood urea is the largest and most available source of nitrogen for bacterial protein synthesis in the colon (Younes et al, 1995). Urea is the major end product of protein catabolism in mammals. When blood urea diffuses into the large bowel it is broken

down by bacterial ureases and used for bacterial protein synthesis. These bacterial proteins are excreted in the feces. The net effect is increased fecal urea excretion, reduced serum urea nitrogen concentration and reduced urinary urea excretion in rats and people (Younes et al, 1995, 1996; Bliss et al, 1996). Whether soluble fiber is effective in foods for dogs and cats with CKD has not been studied.

FEEDING PLAN

Based on current evidence, nutritional management with an appropriately formulated commercial veterinary therapeutic renal food should begin when serum creatinine exceeds 2 mg/dl in dogs and cats with CKD (stage 2 CKD and higher). Although not evaluated in controlled studies, recommending a veterinary therapeutic renal food seems logical when earlier stages of CKD are documented (e.g., persistent renal proteinuria, loss of urine concentrating ability or mild azotemia). Nutritional management is the cornerstone of treatment for dogs and cats with CKD; however, inappetence, vomiting and diarrhea may be prominent in patients with moderate to severe CKD and evidence of systemic illness (uremia). These patients should receive aggressive fluid and electrolyte therapy in an attempt to ameliorate azotemia, uremia, electrolyte abnormalities and acidosis before initiating a traditional feeding plan.

Assess and Select the Food

Foods for dogs and cats with CKD should be evaluated for all the key nutritional factors previously discussed (**Table 37-9**). **Tables 37-11** and **37-12** list commercial veterinary therapeutic foods designed for CKD patients (dogs and cats, respectively), including comparisons to recommended levels of key nutritional factors. These comparisons will help determine the best food to consider for initial feeding. Although commercial veterinary therapeutic renal foods share some features in common, they are not the same. It is important to consider the evidence supporting effectiveness of individual foods when making nutritional recommendations for patients with CKD (**Table 37-10** and **Box 37-3**). In addition, it may be necessary to consider nutrients that may affect concomitant diseases (e.g., dogs with CKD and pancreatitis or cats with CKD and diabetes mellitus) (**Case 37-4**).

All possible sources of nutrients that patients with CKD will receive should be evaluated and discussed with pet owners. It may be easy to simply recommend that owners not give any treats; however, the reality is that most owners give their pet treats. When asked how they showed affection to their pets, 71% of 1,212 dog owners and 44% of 820 cat owners said they give their pets treats and 42 and 25% of dog and cat owners, respectively, said they give their pets people food (Habits and Practices Study, 2002). Therefore, when communicating feeding plan recommendations for dogs and cats with CKD, it's important to discuss treats with pet owners. One option is to recommend that the owner keep kibbles of dry veterinary therapeutic renal food in a separate container located in a different area from where the pet is normally fed and use these as treats. Small amounts of moist veterinary therapeutic renal food formed into balls could also be offered. If an owner insists on feeding other treats, the amount of treats and snacks fed should be less than 5% of the volume or weight of the total food intake. Many commercial pet treats and processed human foods contain excess sodium, chloride and phosphorus and should be avoided in CKD patients. However, some commercial treats contain moderate amounts of these nutrients. High-phosphorus human foods (e.g., milk, milk products, cheese, fish, beef liver, chocolate, nuts and legumes) should be avoided. In addition to treats, it's important to discuss with owners what forms of food they prefer to feed and to offer them the same forms (dry and moist) of the veterinary therapeutic renal food. In a survey of more than 800 cat owners, 66% preferred to feed both moist and dry food to their cats (Habits and Practices Study, 2002). In this situation, if the owners purchased a dry veterinary therapeutic renal food from their veterinarian for a cat with CKD, it is highly likely they would buy a moist food elsewhere and use it with the dry food. Feeding a typical over-the-counter moist cat food that contains increased amounts of sodium, chloride and phosphorus could decrease or negate effectiveness of the veterinary therapeutic renal food.

Assess and Determine the Feeding Method

Changing the feeding method in the management of CKD may not be necessary, especially in patients with early or uncomplicated CKD. It is important, however, to verify that an appropriate feeding method is being used. Items to consider include access to water, amount fed, how food is offered, access to other foods and who feeds the pet. Patients with uremia and other signs of systemic disease may be partially or completely anorectic and require alternate feeding methods (Chapters 25 and 26).

How the previous food was offered (e.g., free-choice feeding or multiple offerings per day of a prescribed amount) can be continued if the form of the food is unchanged.

The amount to feed is based on the patient's energy requirement. The energy needs of patients with kidney disease are presumed to be similar to those of normal pets having the same level of activity. In general, energy intake tends to decrease as renal function declines because of progressive anorexia. In addition, numerous factors (e.g., gender, changes in environment and activity) influence the energy requirement for an individual patient. The starting point for estimating daily energy requirement (DER) for an individual patient is to calculate the resting energy requirement (RER) and multiply this number by a factor that varies based on the severity of chronic metabolic disease. The formula for calculating RER in kcal/day is $70(BW_{kg})^{0.75}$. Table 5-2 also provides RER estimates for dogs and cats. The recommended DER range for most canine patients with CKD is 1.1 to 1.6 x RER. The DER range for most feline patients with CKD is 1.1 to 1.4 x RER. After the DER is estimated, it is divided by the energy density of the food on an as fed basis to determine the amount to feed. Feeding recommendations from the manufacturer of the select-

Table 37-11. Key nutritional factors in selected commercial veterinary therapeutic foods for dogs with chronic kidney disease compared to recommended levels.*

Moist foods	Energy density (kcal/can)**	Protein (%)	P (%)	Na (%)	K (%)	Omega-3 fatty acids (%)	Omega-6: omega-3	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**14-20**	**0.2-0.5**	**≤0.3**	**0.4-0.8**	**0.4-2.5**	**1:1-7:1**	**≥400**	**≥100**
Hill's Prescription Diet g/d Canine	377 kcal/13 oz.	18.1	0.41	0.22	0.78	0.67	3.7:1	719	107
Hill's Prescription Diet k/d Canine	458 kcal/13 oz.	14.8	0.22	0.19	0.37	1.93	2.3:1	844	130
Hill's Prescription Diet u/d Canine	489 kcal/13 oz.	13.3	0.17	0.28	0.45	0.38	13.5:1	643	na
Medi-Cal Reduced Protein	525 kcal/396 g	16.5	0.5	0.2	0.5	na	na	na	na
Medi-Cal Renal LP	643 kcal/385 g	16.8	0.2	0.1	1.0	na	na	na	na
Medi-Cal Renal MP	532 kcal/380 g	28.2	0.4	0.2	1.5	na	na	na	na
Medi-Cal Weight Control/Mature	370 kcal/396 g	21.5	0.6	0.3	0.6	na	na	na	na
Purina Veterinary Diets NF KidNey Function Canine Formula	498 kcal/12.5 oz.	16.5	0.30	0.24	0.72	0.59	6.9:1	na	na
Royal Canin Veterinary Diet Renal LP	785 kcal/13.6 oz.	16.1	0.24	0.08	0.84	na	na	1,034	na
Royal Canin Veterinary Diet Renal MP	670 kcal/13.4 oz.	26.2	0.42	0.19	1.17	na	na	552	na
Dry foods	**Energy density (kcal/cup)****	**Protein (%)**	**P (%)**	**Na (%)**	**K (%)**	**Omega-3 fatty acids (%)**	**Omega-6: omega-3**	**Vit. E (IU/kg)**	**Vit. C (mg/kg)**
Recommended levels	**–**	**14-20**	**0.2-0.5**	**≤0.3**	**0.4-0.8**	**0.4-2.5**	**1:1-7:1**	**≥400**	**≥100**
Hill's Prescription Diet g/d Canine	358	18.7	0.41	0.21	0.61	0.78	3.5:1	263	na
Hill's Prescription Diet k/d Canine	396	14.7	0.24	0.23	0.67	1.54	1.9:1	679	344
Hill's Prescription Diet u/d Canine	396	11.2	0.15	0.23	0.54	0.74	4.4:1	856	na
Iams Veterinary Formula Renal Early Stage	245	21.0	0.46	0.41	0.63	na	5:1	na	na
Medi-Cal Reduced Protein	360	13.7	0.4	0.2	0.7	na	na	na	na
Medi-Cal Renal LP	283	14.7	0.3	0.1	0.7	na	na	na	na
Medi-Cal Renal MP	336	18.4	0.4	0.1	0.7	na	na	na	na
Medi-Cal Weight Control/ Mature	320	19.5	0.8	0.2	0.8	na	na	na	na
Purina Veterinary Diets NF KidNey Function Canine Formula	459	15.9	0.29	0.22	0.86	0.30	9.3:1	na	na
Royal Canin Veterinary Diet Renal LP 11	275	14.7	0.30	0.08	0.66	na	na	302	na
Royal Canin Veterinary Diet Renal MP 14	327	18.4	0.40	0.10	0.66	na	na	302	na

Key: P = phosphorus, Na = sodium, K = potassium, omega-6:omega-3 = omega-6 to omega-3 fatty acid ratio, Vit. E = vitamin E, Vit. C = vitamin C, na = information not available from manufacturer, g = grams.
*All values are reported on a dry matter basis unless otherwise indicated. Moist foods are best. All values were obtained from manufacturers' published information.
**Energy density as fed (per can or cup) is useful for determining the amount to feed; cup = 8-oz. measuring cup; to convert kcal to kJ, multiply kcal by 4.184.

ed food can also be used as a starting point. Also, feeding a similar amount to the amount of maintenance food that was previously fed is another starting point. The initial food dose should be adjusted from these starting points to maintain optimal body weight and condition. Gradual transition to a new food improves acceptance and also decreases the likelihood of problems in those patients that cannot rapidly adjust urinary sodium levels because of their renal dysfunction. Dogs with CKD usually tolerate a dietary change over seven to 10 days, whereas, cats may need three to four weeks or longer to make a successful transition. This requires patience and persistence by the pet owner and veterinary health care team. However, the end result is worth it because feeding a commercial veterinary therapeutic renal food is the only treatment that has been shown to prolong survival time in dogs and cats with CKD. Unfortunately, the "cold turkey" approach to feeding (i.e., own-

Table 37-12. Key nutritional factors in selected commercial veterinary therapeutic foods for cats with chronic kidney disease compared to recommended levels.*

Moist foods	Energy density (kcal/can)**	Protein (%)	P (%)	Na (%)	K (%)	Omega-3 fatty acids (%)	Omega-6: omega-3	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**28-35**	**0.3-0.6**	**≤0.4**	**0.7-1.2**	**0.4-2.5**	**1:1-7:1**	**≥500**	**100-200**
Hill's Prescription Diet g/d Feline	165 kcal/5.5 oz.	34.3	0.52	0.32	0.72	0.64	6.1:1	817	104
Hill's Prescription Diet k/d with Chicken Feline	183 kcal/5.5 oz.	28.9	0.38	0.30	1.18	0.72	6.1:1	814	103
Iams Veterinary Formula Multi Stage Renal	199 kcal/6 oz.	33.6	0.60	0.40	1.03	na	5:1	na	na
Medi-Cal Reduced Protein	265 kcal/170 g	33.9	0.5	0.2	0.7	na	na	na	na
Medi-Cal Renal LP	125 kcal/85-g pouch	29.3	0.5	0.6	1.1	na	na	na	na
Purina Veterinary Diets NF KidNey Function	234 kcal/5.5 oz.	31.1	0.52	0.16	0.96	0.85	3.7:1	na	na
Royal Canin Veterinary Diet Modified Formula	256 kcal/6 oz.	34.7	0.65	0.28	0.81	na	na	178	na
Royal Canin Veterinary Diet Renal LP	126 kcal/3-oz. pouch	34.1	0.55	0.47	1.10	na	na	437	na
Dry foods	**Energy density (kcal/cup)****	**Protein (%)**	**P (%)**	**Na (%)**	**K (%)**	**Omega-3 fatty acids (%)**	**Omega-6: omega-3**	**Vit. E (IU/kg)**	**Vit. C (mg/kg)**
Recommended levels	**–**	**28-35**	**0.3-0.6**	**≤0.4**	**0.7-1.2**	**0.4-2.5**	**1:1-7:1**	**≥500**	**100-200**
Hill's Prescription Diet g/d Feline	297	33.5	0.54	0.32	0.77	0.19	15.5:1	232	na
Hill's Prescription Diet k/d Feline	477	28.8	0.46	0.24	0.75	0.25	15.1:1	952	229
Iams Veterinary Formula Multi Stage Renal	514	32.1	0.42	0.39	0.65	na	5:1	na	na
Medi-Cal Reduced Protein	440	28.1	0.6	0.3	0.8	na	na	na	na
Medi-Cal Renal LP	409	24.7	0.5	0.2	1.0	na	na	na	na
Purina Veterinary Diets NF KidNey Function	398	30.8	0.41	0.20	0.88	0.31	6.4:1	na	na
Royal Canin Veterinary Diet Modified Formula	432	27.1	0.49	0.23	1.07	na	na	380	na
Royal Canin Veterinary Diet Renal LP 21	395	24.7	0.49	0.16	1.02	na	na	355	na

Key: P = phosphorus, Na = sodium, K = potassium, omega-6:omega-3 = omega-6 to omega-3 fatty acid ratio, Vit. E = vitamin E, Vit. C = vitamin C, na = information not available from manufacturer, g = grams.
*All values are reported on a dry matter basis unless otherwise indicated. Moist foods are best. All values were obtained from manufacturers' published information.
**Energy density as fed (per can or cup) is useful for determining the amount to feed; cup = 8-oz. measuring cup; to convert kcal to kJ, multiply kcal by 4.184.

ers returns home with their pet and immediately switch to the new food), rather than transitioning to the new food over several days to weeks is common. In this scenario, the outcome often results in failure to implement the nutritional recommendation. Changing the eating habits of most dogs and cats is relatively easy, but changing the feeding habits of some pet owners and veterinarians is often more difficult. Some veterinarians are still unaware that commercial veterinary therapeutic renal foods are as palatable, or more so, than regular maintenance foods. The feeding plan is more likely to be successful if the owner is told that the veterinary therapeutic renal foods are highly palatable (positive bias). **Box 37-5** provides additional tips to aid in increasing acceptance of veterinary therapeutic renal foods by dogs and cats with CKD.

When switching to a veterinary therapeutic food, it may help to use a familiar form of food initially (e.g., moist or dry or a combination). However, some patients may switch their preferences after CKD develops and prefer different forms of foods. Moist veterinary therapeutic renal foods can be made more palatable by warming (not above body temperature). Palatability of dry foods can often be increased by adding water or flavoring agents such as tuna juice, clam juice, chicken broth, low-sodium soups, garlic, brewer's yeast or sweeteners (dogs only) such as honey or syrup. Uneaten moistened foods should not be allowed to remain at room temperature for more than a few hours (Chapter 11). Some of the aforementioned supple-

Box 37-5. Tips for Encouraging Acceptance of Veterinary Therapeutic Renal Foods in Patients with Chronic Kidney Disease.

Educate pet owners about the effectiveness of nutritional management for prolonging survival time and improving quality of life in patients with kidney disease. For treatment to succeed, owners must commit their time and money, which is more likely to occur if they understand the benefits of their efforts.

Begin nutritional management sooner rather than later. Current evidence supports feeding a veterinary therapeutic renal food when serum creatinine is ≥2 mg/dl. Waiting until later (e.g., when there are signs of uremia) is not advised because patients with more advanced disease may be less likely to accept a change in treatment and therefore will not receive optimal benefits of a renal therapeutic food.

Probably the single most important thing you can do to increase patient acceptance of a veterinary therapeutic renal food is gradually transition to the new food. The transition period should be a minimum of seven days; however, some patients (especially cats) need a transition of three to four weeks or longer. It is critical to discuss the need for this transition with pet owners, otherwise, they are likely to buy a new food, go home and switch from the old food to the new food at the next meal. In this scenario, many patients will refuse to eat the new food, which results in an unhappy owner and a patient that will likely not receive the benefits of nutritional management.

One option for transitioning to a renal food is to mix the old and new food, gradually adding more of the new food over time. Another approach is to provide both foods (old and new) in side-by-side food dishes. This technique assists with gradual transition and also allows cats to express their preferences. For more information, visit www.vet.osu.edu/indoorcat for The Indoor Cat Initiative.

If transitioning cats from dry to moist food, use a flat food dish (e.g., saucer) instead of a bowl. This avoids rubbing the cat's whiskers on the food dish, which could affect acceptance of new food.

Avoid offering veterinary therapeutic renal foods in stressful environments (e.g., sick and/or hospitalization, during force-feeding); a food aversion may develop causing decreased acceptance of the food when the patient is feeling better. Stated another way, while patients are hospitalized, do not feed them (especially cats) the food you want them to eat for the rest of their lives. In this situation, one option would be to feed a maintenance food that avoids excessive protein, phosphorus and sodium until the patient is feeling better and then gradually transition to a therapeutic renal food.

Use fresh food at room temperature. Some patients may eat refrigerated food that is warmed, but others will only eat food from a newly opened container. Some patients may eat food that has been refrigerated and stored in a plastic container vs. food stored in the original can.

Offer foods with different textures (e.g., minced formulas) or form (dry vs. moist). Some pets may prefer dry or moist food all their lives and when they develop kidney disease, their preferences may switch (e.g., a cat that has eaten dry food all its life may eat moist food after kidney disease occurs and vice versa).

Add flavor enhancers (low-sodium chicken broth or tuna juice) or a small amount of maintenance food to encourage the patient to eat all the veterinary therapeutic food. Excessive use of other foods will likely decrease the beneficial effects of the veterinary therapeutic renal food; therefore, the smallest amount possible should be used.

If you have followed the steps above and there is still reluctance to eat a veterinary therapeutic renal food, switch to a different brand. Although commercially available renal foods have general features in common, they are not the same. In addition, individual pets may express a preference for one brand over another. Avoid giving the owner samples of several different brands of foods at once; this could result in a food aversion to all veterinary therapeutic renal foods, especially if owners offer each sample at successive meals or on consecutive days. **Tables 37-11** and **37-12** can be used to select foods with the best key nutritional factor profiles for dogs and cats, respectively.

ments are high in sodium content (e.g., clam and tuna juice); however, and should not be used long-term due to excessive sodium intake above the amount in the veterinary therapeutic food. Environmental factors should also receive consideration when transitioning pets to a veterinary therapeutic renal food. Owner compliance and pet acceptance of the food must be adequate for nutritional management to be effective. Knowing who feeds the patient is important for compliance, and limiting the patient's access to other foods improves acceptability (e.g., a dog having access to cat food or a cat living in a multi-cat household). Feeding location and presentation are important. Timid animals should be fed in a quiet place. Cats should be fed away from loud, persistent barking or other distracting noises. Food bowls should not be kept in close proximity to litter boxes and noisy areas. Food for cats should be offered in wide bowls or on a plate to avoid stimulation of tactile whiskers. Placing small quantities of palatable food in a patient's mouth or on its paws (moist food) to stimulate licking or swallowing (i.e., hand feeding) may facilitate eating. Patients' appetite can be influenced by the person feeding the patient (server). The likelihood of eating increases in direct proportion to the time the patient has spent with the server in a nonstressful situation (Delaney, 2006). For hospitalized pets, the ideal server is likely the pet owner followed by either a technician or kennel assistant who has not restrained or otherwise antagonized the patient.

Food aversion is possible if a nauseated pet is force-fed or if a painful or unpleasant experience is associated with feeding. Unpalatable medications (e.g., some phosphate binders) should not be mixed with veterinary therapeutic foods. Managing underlying abnormalities in fluid, electrolyte and acid-base balance will help minimize nausea and vomiting. Pharmacologic agents (e.g., ranitidine, famotidine, metoclopramide and sucralfate) can be used to limit uremic gastritis, nausea and vomiting. Veterinary therapeutic foods intended for long-term management of patients with CKD should not be offered during periods of nausea and vomiting to prevent possible food aversions. Consider using an appropriate, alternative food temporarily

during hospitalization for dogs and cats with uremic signs.

Finally, a common approach that is used for "picky" eaters is to offer samples of several different foods and then recommend the food they will eat. This may be effective in some patients but there is a major disadvantage of using this approach in patients with CKD. The "cafeteria" approach should not be used in patients with diseases that commonly have a learned food aversion or that have limited commercial veterinary therapeutic food options (Delaney, 2006). Offering samples of all the commercially available veterinary therapeutic renal foods to a CKD patient that is not eating well or has uremic signs should be avoided to minimize the likelihood of a learned food aversion to all the foods the patient may need to be fed long-term (Delaney, 2006).

REASSESSMENT

Frequency of reassessment depends on the stage of CKD and presence of concurrent conditions. Patients with azotemia should be rechecked every two to three months and uremic patients should be rechecked as often as every two to four weeks. Duration between evaluations may be longer in patients with stable disease. Parameters included in the reassessment are listed in **Table 37-13**. Serial evaluation of appropriate laboratory tests, including UPC ratios, is a good means of reassessment. Because of daily variation in UPC ratios, minor changes in UPC ratio may or may not be clinically important. It is important to monitor trends on multiple UPC ratios over time rather than rely on individual measurements. Increasing UPC ratios over time can indicate worsening glomerular disease, whereas serial declining UPC ratios are consistent with clinical improvement. Decreases in urine protein concentrations, however, may not always be associated with improved glomerular function. If accompanied by increases in serum creatinine concentrations, declining UPC ratios may reflect progressive glomerular sclerosis and obsolescence. As glomeruli become obsolescent, they no longer lose protein; however, these same glomeruli also lose their functional ability, potentially resulting in azotemia.

After nutritional management has been implemented for patients with CKD, it is very important to monitor for signs of malnutrition (e.g., accurate body weights over time, body condition score, hematocrit, serum albumin) so that food offerings can be adjusted as needed. Unfortunately, it is common to see gradual weight loss over time and increasing the amount of food offered does not help if the patient has anorexia. A common mistake is to insist that an owner feed only a veterinary therapeutic renal food, even if caloric intake is inadequate. Although avoiding excess dietary protein and minerals is important in patients with CKD, offering only such a food should not be imposed to the detriment of overall nutrient intake. Changing to a different commercial food or homemade food may be a more beneficial solution for some patients. Appetite may be cyclical in patients with advanced CKD, both in respect to overall appetite and food preferences. A dedicated owner is often required and a trial-and-error approach must be used with different foods, food forms (dry vs. moist) and feeding methods (**Box 37-5**).

If caloric intake is insufficient to maintain body weight, clinical recommendations often include a stepwise approach designed to facilitate adequate food intake (Polzin et al, 2005; Polzin, 2007). The first step is to ensure that metabolic and other medical causes of decreased appetite have been corrected including dehydration, gastrointestinal hemorrhage, metabolic acidosis, hypokalemia, anemia, urinary tract infection, dental disease and drug-associated anorexia. Recombinant human erythropoietin[i] has been used successfully to improve clinical well-being of dogs and cats with CKD; improved appetite may precede improvement in hematocrit values in some CKD patients managed with erythropoietin (Cowgill et al, 1998). Significantly improved appetite also has been noted in cats with proteinuria (UPC ≥1), when managed with the ACE inhibitor benazepril[j] (King et al, 2006). When metabolic and other medical causes of anorexia have been excluded or corrected, therapy for uremic gastroenteritis should be initiated with an H_2-antagonist such as ranitidine or famotidine. If inappetence still persists, appetite stimulants such as cyproheptadine or mirtazapine[k] can be attempted; however, results are unpredictable, intermittent and tend to be short-lived (Delaney, 2006). Regardless of the effects of the above treatments on appetite, it is important to confirm that any apparent response to such therapy sufficiently enhances food intake to meet nutritional goals.

If food intake remains inadequate to meet caloric needs for more than three to five days with no trend toward improving, assisted feeding is indicated (Delaney, 2006). Long-term use of percutaneous gastrostomy or esophagostomy tubes has been successful for delivering food, extra water and medications to patients with CKD (Elliott et al, 2000a; Elliott, 2009) (Chapter 25). Anecdotal reports suggest that tube feeding can reverse the progressive weight loss associated with CKD and patients can have extended periods of improved quality of life (Polzin et al, 2005; Polzin, 2007).

SUMMARY

CKD is commonly diagnosed in dogs and cats and increases in frequency with age. A variety of compensatory and adaptive responses are likely involved in the pathogenesis and progression of naturally occurring CKD. The goals of managing patients with CKD are to improve quality and quantity of life. Nutritional management plays a key role in both of these goals. Although there are many available treatments, veterinary therapeutic renal food is the only one that has been shown to prolong survival time and improve quality of life for dogs and cats with CKD. Therefore, nutritional intervention is a critical component of managing patients with CKD. When designing a therapeutic regimen for dogs and cats with CKD, it is helpful to consider key nutritional factors (water, protein, phosphorus, omega-3 fatty acids, antioxidants, sodium, chloride and potas-

Table 37-13. Reassessment of patients with chronic kidney disease.

Physical examination
Abdominal palpation (size and contour of kidneys, presence of ascites)
Blood pressure measurement
Body condition/muscle mass
Body weight
Fundic examination (retinal hemorrhage, detached retina)
Hair and coat quality
Hydration status
Oral examination (uremic odor, ulcers, mucous membrane color)
Laboratory evaluation
Serum biochemistries (urea nitrogen, creatinine, albumin, phosphorus)
Serum electrolytes (calcium, potassium, chloride, sodium, magnesium)
Total serum carbon dioxide or venous blood gases (blood pH, bicarbonate, base excess) to evaluate acid-base status
Urinalysis
Microscopic sediment exam (pyuria or bacteriuria may indicate urinary tract infection)
Urine specific gravity (crude index of tubulointerstitial function)
pH (very crude index of acid-base status)
Urine protein-creatinine ratio (assess proteinuria and response to treatment)
Diagnostic imaging
Abdominal radiographs (assess kidney shape and size, reference L_2 vertebra on ventrodorsal view)
Excretory urogram (assess obstruction due to nephroliths)
Ultrasound (assess kidney and prostate gland, presence of hydronephrosis, hydroureter, uroliths)

sium). In addition to key nutritional factors, it is important to consider available evidence supporting effectiveness of specific veterinary therapeutic renal foods as well as other treatments for CKD. Individual patient needs and responses and owner preferences must also be considered to design an optimal therapeutic regimen. Transitioning to a therapeutic renal food often requires a team approach and effective communication involving the owner and health care team. There are many strategies that can be used to increase therapeutic success and thus improve the lifespan and quality of life for dogs and cats with CKD.

ACKNOWLEDGMENT

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ENDNOTES

a. Sulfosalicylic acid (5%). Ricca Chemical Company, Arlington, TX, USA.
b. E.R.D.-HealthScreen. Heska Corporation, Loveland, CO, USA.
c. VetTest Urine P:C ratio. IDEXX Laboratories, Inc., Westbrook, ME, USA.
d. Prescription Diet u/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
e. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
f. Whiskas Feline Low Protein Diet. Waltham, Effem, Austria.
g. Whiskas Feline Low Phosphorus, Low Protein. Waltham Veterinary Diet, Masterfoods, Bruck, Austria.
h. Prescription Diet k/d Feline. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
i. Epogen. Amgen Inc., Thousand Oaks, CA, USA.
j. Fortekor. Norvartis Animal Health, Basel, Switzerland.
k. Remeron. Organon, West Orange, NJ, USA.

REFERENCES

The references for **Chapter 37** can be found at www.markmorrisinstitute.org.

CASE 37-1

Hematemesis in a Shih Tzu

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Patient Assessment

The referring veterinarian initially evaluated a four-year-old intact male Shih Tzu for hematuria, anorexia and vomiting. The dog had been diagnosed with chronic kidney disease (CKD) and a possible urinary tract infection. The suspected urinary tract infection had been treated with a combination of trimethoprim and sulfamethoxazole. The dog had also developed thrombocytopenia (platelet count 11 x 10^3/µl [reference range 300 to 900 x 10^3/µl]) and progressive anemia in the month before referral. The trimethoprim-sulfamethoxazole combination was discontinued and the dog was treated with prednisone for thrombocytopenia and suspected immune-mediated hemolytic anemia. The current history included vomiting, hematemesis, hematochezia and decreased

appetite. The dog also had a lifelong history of polydipsia and polyuria.

Physical examination revealed 5% dehydration, thin body condition (body condition score 2/5, body weight 5.9 kg), pale mucous membranes, poor coat quality, blood dripping from the penis and a small, irregular left kidney. Rectal examination revealed symmetric, nonpainful prostatomegaly and hematochezia.

Clinicopathologic abnormalities included nonregenerative anemia (hematocrit 15% [reference range 37 to 55%]), azotemia (urea nitrogen 139 mg/dl [reference range 7 to 32 mg/dl], creatinine 3.3 mg/dl [reference range 0.5 to 1.5 mg/dl]) and hyperphosphatemia (8.3 mg/dl [reference range 2.2 to 7.9 mg/dl]). Examination of the blood smear revealed acanthocytosis (1+), poikilocytosis (1+) and occasional schistocytes; spherocytes were not present. The platelet count was within normal limits (341 x 10^3/µl). Urinalysis revealed isosthenuria (specific gravity 1.012) and hematuria (too numerous to count red blood cells per high-power field).

Problems identified included CKD, nonregenerative anemia, prostatomegaly, hematemesis and hematochezia. Additional diagnostic procedures performed included fecal flotation, urine culture, bone marrow aspiration, indirect blood pressure measurement, fundic examination, abdominal radiographs and ultrasound and ultrasound-guided fine-needle aspiration of the prostate gland. Fecal flotation was negative for intestinal parasites. Aerobic urine culture yielded no bacterial growth. Cytologic examination of the bone marrow aspirate revealed erythroid hypoplasia with adequate iron stores. Abdominal radiographs revealed prostatomegaly and small irregular renal margins. Abdominal ultrasonography revealed that the kidneys were bilaterally hyperechoic with very thin renal cortices (3 cm width). Considering the dog's age and breed, these findings were consistent with congenital renal dysplasia. Ultrasonography of the prostate gland revealed diffuse prostatomegaly with multiple small intraprostatic cysts. Cytologic examination of the prostatic aspirates revealed normal prostatic epithelial cells, numerous RBCs and small numbers of neutrophils and macrophages. The ultrasonographic and cytologic findings were consistent with benign prostatic hyperplasia with intraprostatic cyst formation. Aerobic culture of the prostatic aspirate yielded no bacterial growth. Results of indirect measurements of systemic blood pressure were within normal limits. The fundic examination was normal.

Assess the Food and Feeding Method

Originally the dog had been fed a commercial dry dog food; after the diagnosis of CKD was made, a commercial veterinary therapeutic renal food[a] with controlled levels of protein, phosphorus and sodium was recommended. The dog continued to vomit and refused to eat the food, however. The owner had switched to a moist commercial grocery brand dog food supplemented with commercial treats. The moist food was fed twice daily and treats were given multiple times throughout the day to encourage the dog to eat. The dog only ate small amounts of the moist food and some treats during the week before admission.

Questions

1. What are the most likely reasons for this dog's anemia?
2. Why was the magnitude of increase in serum creatinine and urea nitrogen concentrations markedly different?
3. What nutritional recommendations should be made to optimize management of this dog's problems?
4. What other therapies might improve nutritional management of this patient?

Answers and Discussion

1. There were multiple reasons for this dog's anemia. Although the anemia was initially presumed to be an immune-mediated hemolytic anemia, this diagnosis was unlikely at this time. The referring veterinarian submitted a sample to a commercial laboratory for a Coombs test, and results were negative. Red blood cell morphologic examination revealed evidence of fragmentation (which occurs with uremia) and no spherocytes. Likewise, the serum bilirubin concentration remained normal and bilirubinuria was not present. The presumption of an immune-mediated process was based on the concurrent thrombocytopenia and progressive anemia following trimethoprim-sulfamethoxazole therapy. The thrombocytopenia quickly resolved with discontinuation of trimethoprim-sulfamethoxazole therapy and treatment with prednisone. However, anemia worsened progressively. Thrombocytopenia was likely immune-mediated secondary to trimethoprim-sulfamethoxazole therapy; however, there was no evidence of immune-mediated hemolytic anemia.

   Results of bone marrow examination were interpreted to be consistent with a hypoproliferative anemia secondary to relative erythropoietin deficiency. Dogs with moderate to severe CKD consistently have low erythropoietin concentrations relative to the degree of anemia. Therefore, based on the bone marrow findings and concurrent diagnosis of CKD, it was likely that erythropoietin deficiency secondary to CKD was responsible for a major component of the anemia.

   Another contributing factor to the anemia was gastrointestinal (GI) blood loss from uremic gastritis and concurrent prednisone therapy. The dog had a history of hematemesis (fresh blood and vomitus that appeared like "coffee grounds") and hematochezia. Additionally, during hospitalization the dog had marked melena. Uremic gastritis may contribute to GI bleeding, vomiting and anorexia as seen in this dog. Prednisone therapy probably contributed to some of the GI ulceration presumed to be present.
2. There are multiple reasons for the discrepancy in the magnitude of serum creatinine and urea nitrogen concentrations in this dog. Creatinine enters the blood as a result of the nonenzymatic breakdown of phosphocreatine in skeletal muscle. Therefore, the rate of entry of creatinine into the blood depends on muscle mass. Serum creatinine concentration will be lower than would be expected from the glomerular filtration rate (GFR) in a dog with decreased muscle mass. Therefore, the serum creatinine concentra-

tion was probably low in this dog relative to serum urea nitrogen concentration, thereby overestimating relative GFR and underestimating the severity of renal dysfunction.

The urea nitrogen concentration was probably higher relative to the GFR in this dog. The rate of urea production depends on dietary protein intake, rate of production by the liver and catabolism of endogenous body protein stores. This dog was currently being fed relatively high levels of dietary protein, which would contribute to greater production of nitrogenous waste products such as urea. GI hemorrhage mimics a high-protein meal resulting in an increased rate of urea synthesis by the liver. Also, administration of corticosteroids results in catabolism of body proteins, which releases nitrogen-containing amino acids. Urea is produced when these amino acids are catabolized for energy. Therefore, the rate of urea production in this dog was probably increased from GI bleeding and catabolism induced by prednisone therapy. The net result is that the urea nitrogen concentration was increased relative to the serum creatinine concentration and actual GFR. Increased production of potentially toxic nitrogenous breakdown products (represented by urea) probably worsened uremic signs in this dog.

3. This dog was classified as having CKD, most likely stage 3; however, final staging should be based on a stable serum creatinine concentration obtained after correction of dehydration. Feeding a veterinary therapeutic renal food[a] to dogs with stage 2 to 3 CKD has been associated with prolonged survival time, decreased uremic episodes and improved quality of life compared with feeding a maintenance food that contains higher amounts of protein, phosphorus and sodium. Avoiding excessive protein intake is important in advanced stages of CKD to control clinical signs of uremia. However, attempting to immediately feed any food to a patient with anorexia and vomiting from severe uremic gastritis is likely to fail. Therefore, our recommendation was to treat the uremic crisis first, and then reintroduce an appropriate food after the GI signs were controlled. To avoid food aversion associated with hospitalization or nausea in some patients (especially cats and small dogs), it may be more appropriate to feed a food for mature adult dogs during hospitalization and then have the owner gradually transition to the therapeutic renal food at home.
4. Other therapies to treat the consequences of the uremic syndrome are indicated when a dog has moderate to advanced CKD (late stage 3 and stage 4). Therapy should be aimed at controlling uremic gastritis, secondary renal hyperparathyroidism, anemia and hypertension (if present). Uremic gastritis is thought to occur secondary to hypergastrinemia in dogs with advanced stages of CKD. Therapy designed to minimize uremic gastritis and gastric and duodenal ulceration includes H_2-receptor antagonists (i.e., cimetidine, famotidine, etc.), misoprostol, omeprazole and sucralfate. Therapy designed to minimize secondary renal hyperparathyroidism includes avoiding excessive phosphorus intake, intestinal phosphate-binding agents and potentially low-dose calcitriol therapy after correction of hyperphosphatemia. The most effective method of treating the anemia of CKD is to administer recombinant human erythropoietin (r-HuEPO). Therapy with r-HuEPO is reserved for patients with moderately severe anemia (i.e., hematocrit values <20 to 25% in dogs).

Therapy Including Feeding Plan

The dog was initially treated with intravenous fluid therapy, intravenous cimetidine[b] and oral misoprostol[c] and sucralfate.[d] Food was withheld for 48 hours until the vomiting ceased. The dog was then offered a food for mature adults with controlled levels of protein, phosphorus and sodium, divided into four small meals per day. The amount of food was initially calculated to meet the resting energy requirement for an ideal body weight of 7.5 kg.

Progress Notes

The vomiting, hematemesis, hematochezia and melena resolved. Azotemia improved with intravenous fluid therapy; serum urea nitrogen concentration decreased to 58 mg/dl and serum creatinine decreased to 2.1 mg/dl. However, hematocrit decreased to 11%. These findings are consistent with stage 3 CKD. The dog was discharged after five days of hospitalization while the owners considered castration. Nutritional recommendations were to gradually transition to a veterinary therapeutic renal food[a] or a homemade food that avoided excessive levels of protein and phosphorus. Therapy was continued at home including oral famotidine, oral aluminum hydroxide and subcutaneous injections of r-HuEPO[e] three times per week.

Reevaluation nine days after discharge from the hospital revealed the dog's attitude and appetite had improved. The dog had been chewing its tail for two days; however, and the distal 4 cm of the tail were dark blue to black, had several scabs and lacked pain sensation. The tail lesions were thought to be due to ischemic necrosis related to uremic vasculitis. Serum creatinine concentration was 3.1 mg/dl and urea nitrogen concentration was 111 mg/dl. Hematocrit had improved to 19%. The dog was given intravenous fluid therapy in preparation for surgical amputation of the distal tail. Castration was also recommended to treat the benign prostatic hyperplasia with intraprostatic cysts. The serum urea nitrogen and creatinine concentrations decreased with fluid therapy and surgery was performed for tail amputation and castration (**Figure 1**). The dog was discharged with similar treatment recommendations to those listed above. In addition, a combination of amoxicillin and clavulanic acid[f] was administered for two weeks as a prophylactic antibiotic for the tail amputation, and low-dose calcitriol[g] therapy was initiated. Calcitriol was administered to decrease serum parathyroid hormone concentration associated with renal secondary hyperparathyroidism.

The dog's condition remained stable with this combination of nutritional and medical therapy for several months. The dog continued to eat the veterinary therapeutic renal food well and gained weight (body weight 7.5 kg). The coat returned to normal quality (**Figure 2**). The anemia resolved and the r-HuEPO was decreased to a maintenance dose twice weekly. The magnitude of

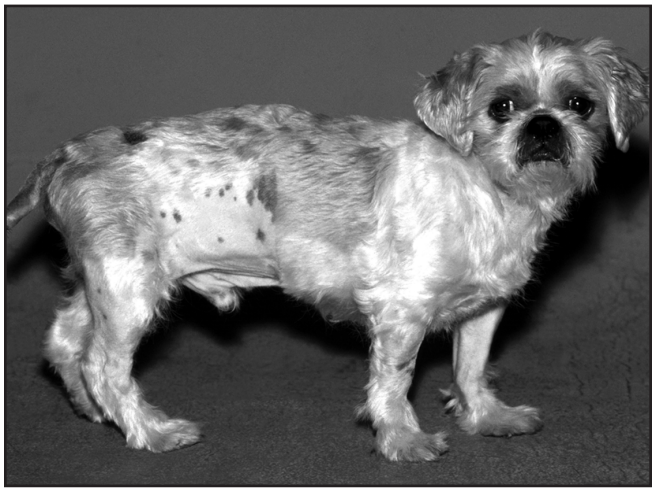

Figure 1. Postoperative picture of a four-year-old male Shih Tzu with CKD and probable uremic vasculitis involving the tail. The tail was amputated and a castration was performed to manage concurrent prostatic disease.

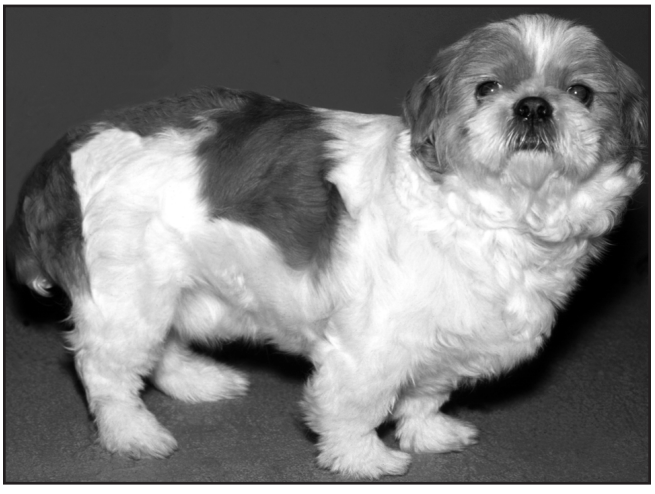

Figure 2. A four-year-old castrated male Shih Tzu two months after therapy was instituted for CKD. The dog's coat quality had returned to normal and overall clinical condition was improved.

azotemia progressively increased over the next six months. Subcutaneous fluid therapy (100 ml every other day) was added when serum creatinine concentration exceeded 5 mg/dl. The dog died of progressive CKD 11 months after initial evaluation.

Endnotes

a. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Tagamet. SmithKline Beecham Pharmaceuticals, Philadelphia, PA, USA.
c. Cytotec. GD Searle & Co, Chicago, IL, USA.
d. Carafate. Marion Merrell Dow, Kansas City, MO, USA.
e. Epogen. Amgen Inc., Thousand Oaks, CA, USA.
f. Clavamox. Pfizer Animal Health, Exton, PA, USA.
g. Rocaltrol. Roche Laboratories, Nutley, NJ, USA.

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CASE 37-2

Weight Loss in a Cat

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Patient Assessment

A 13-year-old spayed female domestic shorthair cat was examined for weight loss of several months' duration. The owners had also noticed increased water intake and urine volume, decreased appetite and a few episodes of vomiting in the last month. The cat also seemed weak. Characteristics of the feces were unknown because the family dog often consumed any fecal material deposited in the litter box. The cat usually remained indoors but did spend some time outdoors during the summer.

Physical examination revealed a very thin cat, with a body weight of 2.4 kg and a body condition score of 1/5. According to the medical record, the cat weighed 5 kg four years earlier. Moderate accumulation of dental calculus was noted. Abdominal palpation revealed excess accumulation of gas in the intestines and a small left kidney; the right kidney could not be palpated.

Results of a complete blood count revealed anemia (i.e., decreased total erythrocyte count, hemoglobin and hematocrit). Significant serum biochemistry profile findings included azotemia, hyperphosphatemia, low normal serum potassium concentration and metabolic acidosis (**Table 1**). Serum thyroxine (T_4) concentration was normal. Urinalysis was normal except for a urine specific gravity of 1.009. The tentative diagnosis was stage 4 chronic kidney disease (CKD).

Assess the Food and Feeding Method

The cat was normally fed a mixture of two different commercial specialty brand dry foods; one was a "light" food and the other was a food formulated for older cats (mature adult food). The combination of dry foods was offered free choice. The owners noted that the cat was still eating but overall appetite had decreased.

Questions

1. What are the key nutritional factors to consider in cats with CKD?
2. Prepare a treatment and feeding plan for this cat.
3. What parameters should be monitored if this patient goes home with conservative management?

Answers and Discussion

1. Key nutritional factors to consider in cats with CKD include water, protein, phosphorus, sodium, chloride, potassium, omega-3 fatty acids and antioxidants. Adequate water intake is important to maintain hydration, blood volume and renal perfusion in a patient with polyuria. Parenteral fluids are indicated if vomiting, diarrhea, dehydration, blood volume contraction and renal hypoperfusion are clinically important. Avoiding excess dietary phosphorus and protein will help reduce clinical signs of uremia and may slow progression of kidney disease. Compared with feeding a maintenance food, feeding a therapeutic renal food[a] has been associated with prolonged survival time and decreased occurrence of uremic episodes in cats with CKD. Increased intake of omega-3 fatty acids and antioxidants has beneficial effects in CKD. Avoiding excess dietary sodium and chloride may help control systemic hypertension, which is a common sequela to CKD in cats. Potassium is also an important nutrient because hypokalemia is common in cats with CKD and may lead directly to clinical signs in some cats. Adequate energy intake in the form of non-protein calories is important in this cat to promote weight gain and minimize further catabolism of lean body mass.
2. Parenteral fluid therapy is indicated to promote excretion of nitrogenous wastes and improve overall hydration status. Water should be available free choice at all times. The food offered to this cat should avoid excessive phosphorus, protein, sodium and chloride while providing adequate amounts of potassium and increased omega-3 fatty acids and antioxidants. A commercial veterinary therapeutic food or homemade food designed for cats with CKD should meet these nutritional goals. Because of nausea associated with uremia, the food should be offered in small, frequent meals. The daily energy requirement (DER) should be calculated to promote weight gain (i.e., 1.2 x resting energy requirement [RER] for an ideal body weight of 4.5 kg) after a normal appetite has returned. Enteral or parenteral nutritional support may be necessary if the cat is eating less than its calculated RER per day. Adjunctive medical therapy including antiemetics and H_2-receptor antagonists for uremic gastropathy and erythropoietin for anemia is indicated to improve the overall well being of the patient.
3. Clinical and biochemical parameters should be monitored two to four weeks after implementing nutritional recommendations. A good response to conservative management includes decreased vomiting, increased appetite and activity level, weight gain, decreased serum urea nitrogen and phosphorus concentrations and increased plasma bicarbonate concentration (or total CO_2). Plasma bicarbonate concentration should be maintained within the laboratory reference range. Alkalinization therapy should be

considered if the plasma bicarbonate or total CO_2 concentration remains below the recommended range. Phosphorus binders should be considered if hyperphosphatemia persists despite avoiding excessive dietary phosphorus. Retinal examinations are important to evaluate for end-organ changes associated with systemic hypertension. The owner should be encouraged to closely monitor the cat's daily food intake to ensure that adequate energy is being consumed.

Table 1. Selected serum biochemistry values from a cat with vomiting and weight loss.

Parameters	Day 1	Day 57	Day 160	Reference values
Urea nitrogen (mg/dl)	104	78	66	10-32
Creatinine (mg/dl)	7.4	5.4	5.0	0.1-2.1
Phosphorus (mg/dl)	8.2	5.4	5.2	2.4-6.1
Potassium (mg/dl)	3.4	4.7	4.8	3.2-6.2
Total CO_2 (mmol/l)	12.8	20.0	18.5	18-21

Progress Notes

The cat was stabilized with parenteral fluid therapy and was discharged from the hospital. The owner was instructed to gradually transition to a commercially available veterinary therapeutic renal food.[a] The DER was calculated at 1.2 x RER for an ideal body weight of 4.5 kg to promote weight gain. This was approximately 250 kcal (1,046 kJ) or one-half cup of dry food daily. Subcutaneous fluids (120 ml/24 hours) and oral famotidine were administered at home.

Two months later (Day 57), the cat was examined and found to have gained weight (body weight 3.1 kg). Serum urea nitrogen, creatinine and phosphorus concentrations were decreased and serum potassium and total CO_2 concentrations were increased (**Table 1**). These serum biochemistry changes persisted when the cat was reevaluated on Day 160; however, body weight was not recorded at that time. The owners reported that the cat was active, maintained a good appetite and had no evidence of vomiting when the combination of dietary therapy and subcutaneous fluids was used.

The owners did not return with the cat again until one year later. The cat was experiencing an acute uremic crisis and was euthanized at the owners' request without further diagnostic or postmortem evaluation.

Endnote

a. Prescription Diet k/d Feline. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

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CASE 37-3

Generalized Weakness in a Cat

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Patient Assessment

A 13.5-year-old spayed female domestic shorthair cat was examined for lethargy, weakness and anorexia of two days' duration. The owner reported that the cat was so weak that it could not lift its head. Physical examination revealed a thin cat (body condition score [BCS] 1/5) weighing 2.2 kg. The coat was dull and unkempt. Generalized weakness, cervical ventriflexion and ataxia were noted. Small, irregular kidneys were evident during abdominal palpation. Dehydration was suspected on the basis of dry mucous membranes.

The cat was hospitalized and a blood sample obtained for a complete blood count and serum biochemistry profile. Urine was obtained by cystocentesis for urinalysis. The complete blood count was normal except for a low hematocrit. Serum biochemistry profile abnormalities included azotemia, hypernatremia, hyperchloremia, hypokalemia, decreased total CO_2 and increased total protein concentration (**Table 1**). Urinalysis results included a urine specific gravity of 1.013, 2+ protein on the dipstick and normal sediment examination.

On the basis of renal azotemia (i.e., increased urea nitrogen and creatinine values with low urine specific gravity and small, irregular kidneys) with associated dehydration and evidence of blood volume contraction (i.e., tacky mucous membranes and increased

total protein, sodium and chloride concentrations), anemia (i.e., low hematocrit with dehydration), metabolic acidosis (i.e., decreased TCO_2) and hypokalemia, the cat was diagnosed with chronic kidney disease (CKD).

Assess the Food and Feeding Method

The cat was fed a mixture of commercial semi-moist and dry foods. These foods and water were always available.

Questions

1. What is the cause of this cat's generalized weakness and cervical ventriflexion?
2. What is the likely cause of the hypokalemia?
3. Outline a treatment and feeding plan for this cat.
4. What parameters should be monitored to assess response to treatment?
5. How would you classify the stage of CKD in this cat using the International Renal Interest Society staging scheme (**Table 37-1**)?

Answers and Discussion

1. Potassium depletion results in morphologic and functional changes in muscle and kidney, alterations in carbohydrate metabolism and protein synthesis and disturbances in acid-base balance. Muscle weakness develops when the serum potassium concentration falls below 3.0 mEq (mmol)/l and frank rhabdomyolysis or life-threatening respiratory muscle paralysis may occur when the serum potassium concentration is less than 2.0 mEq/l.

   Clinical signs of hypokalemic polymyopathy include appendicular muscle weakness, reluctance to walk or a stiff stilted gait with forelimb hypermetria and a broad-based hind-limb stance and apparent pain on palpation of muscles. The most dramatic myopathic finding is a characteristic cervical ventriflexion due to weakness of the extensor muscles of the neck. Similar ventriflexion has been observed in cats with thiamin deficiency and myasthenia gravis. Other neuromuscular signs may be observed in some cats, including bilateral mydriasis, disorientation, staggering and falling.
2. In retrospective studies, hypokalemia was found in approximately 20% of cats with CKD and CKD was the most common associated disorder in cats with hypokalemia. The hypokalemia observed in cats with CKD presumably is caused by a combination of inappetence, weight loss with muscle wasting and polyuria. A clinically distinct syndrome of polymyopathy and nephropathy characterized by hypokalemia, azotemia, impaired renal concentrating ability and lymphoplasmacytic tubulointerstitial nephritis has been documented to occur in cats fed a food low in potassium and high in acid content; however, the role of hypokalemia as a cause of CKD is uncertain.
3. The initial management of cats with clinically apparent potassium-depletion requires diligent potassium supplementation by oral and intravenous routes. Potassium chloride usually is added to parenteral fluids for intravenous administration. Infusion of potassium-containing fluids initially may be associated with a further decrease in serum potassium concentration as a result of dilution, increased distal renal tubular flow and cellular uptake of potassium, especially if the fluid contains glucose. Selecting a fluid that does not contain glucose, administering fluids at an appropriate rate and beginning oral potassium supplementation as soon as possible can minimize this complication.

   Potassium gluconate is recommended for oral supplementation of hypokalemic cats because potassium chloride and potassium bicarbonate are often unpalatable. The recommended initial oral dosage of potassium gluconate is 2 to 6 mEq potassium gluconate/day divided into two or three doses; the dose should be adjusted based on clinical response and serial analyses of serum potassium concentration. Clinical improvement is usually seen after one to three days of treatment. Feeding a commercial veterinary therapeutic renal food, which contains increased amounts of potassium, may be all that is need to maintain normokalemia. However, oral supplementation with potassium gluconate should be considered if food alone does not maintain serum potassium concentration above 4.0 mEq/l. Additional studies are needed to determine whether routine potassium supplementation is indicated in all cats with CKD, regardless of serum potassium concentration.
4. It is difficult to estimate the amount of potassium required to reestablish normal potassium balance in a given patient. Thus, the amount of potassium required must be determined by judicious supplementation and serial measurement of serum potassium concentrations during treatment and recovery. Treatment usually results in resolution of muscle weakness within one to two weeks, weight gain and an improved coat. During recovery, renal function (i.e., urea nitrogen and creatinine concentrations) and anemia (i.e., hematocrit values and red blood cell count) may stabilize and improve in some cats. Persistent CKD is managed using conservative medical and nutritional management.
5. Staging of CKD should be performed on the basis of stable serum creatinine concentrations (at least two measurements approximately two weeks apart) obtained while the patient is well hydrated. Because the initial serum biochemistry profile was obtained while the cat was clinically dehydrated, the serum creatinine may be higher because of an additional prerenal component of the azotemia. Therefore staging should be determined after rehydration and measurement of stable serum creatinine concentrations. The cat was eventually classified as having stage 2 CKD (**Table 1**).

Progress Notes

An intravenous catheter was inserted in the cat's jugular vein and 20 ml of lactated Ringer's solution was administered per hour during the first eight hours. After eight hours, the rate was reduced to 12 ml/hour. Sixteen mEq of potassium chloride were added to each liter of lactated Ringer's solution to produce a final potassium concentration of 20 mEq/l. During the first day of hospitalization, 4 mEq of potassium gluconate gel (Tumil-K[a]) were administered per os every 12 hours. Water was offered free choice. Body weight was measured daily using the same pediatric scale, and urine output was estimated by weighing the litter box before and after voiding.

Table 1. Selected serum biochemistry values from a cat with generalized weakness.

Parameters	Day 1	Day 2	Day 3	Day 4	Day 6	Day 25	Reference values
Hematocrit (%)	31	20.3	ND	ND	ND	ND	30-45
Hemoglobin (g/dl)	9.9	6.7	ND	ND	ND	ND	8-15
Total protein (g/dl)	7.9	7.1	6.1	6.3	6.5	ND	6.1-7.7
Urea nitrogen (mg/dl)	53	58	47	48	51	36	15-25
Creatinine (mg/dl)	3.0	3.1	2.0	1.9	2.1	2.3	0.8-1.8
Sodium (mmol/l)	165	167	160	158	153	152	140-157
Potassium (mmol/l)	3.0	3.4	4.2	5.5	4.6	5.2	3.8-5.3
Chloride (mmol/l)	137	134	124	122	116	118	115-128
Total CO_2 (mmol/l)	11	17	23	29	28	23	18-23

Key: ND = not done.

The cat's weakness was noticeably improved by Day 2. The cat's resting energy requirement (RER) was calculated at its estimated ideal body weight of 3.5 kg (RER at 3.5 kg = 175 kcal [732 kJ]). The cat was offered small quantities of dry and moist forms of a commercial food for mature adult cats with controlled amounts of protein and phosphorus, every three to four hours. The cat was consuming sufficient food to meet its RER by Day 4.

The azotemia, hypokalemia, acidosis and muscle strength progressively improved over the next three days (**Table 1**). Six days after initial hospitalization, the patient was discharged to the owner's care with instructions to gradually transition to feeding a dry veterinary therapeutic renal food[b] and to administer 4 mEq potassium gluconate gel every 12 hours. The quantity of food was increased to a daily energy requirement of 1.4 x RER.

The owner reported that the cat was bright, alert, active and eating well with normal muscle strength 25 days after initial examination. Physical examination was normal except the patient was still underweight (body weight 2.8 kg, BCS 2/5) and the kidneys were still palpably small and irregular. Results of a serum biochemistry profile included mild azotemia, normal serum electrolyte concentrations and normal acid-base status (**Table 1**). Oral potassium gluconate was discontinued and the dry veterinary therapeutic renal food was continued. The owners asked about purchasing moist food from the grocery store to add to the dry veterinary therapeutic renal food. Because most grocery brand foods contain excessive phosphorus and protein compared with therapeutic renal foods, this was not recommended. Instead, several cans of the veterinary therapeutic renal food were dispensed so the owners could determine if the cat preferred moist food in addition to the dry food.

Endnotes

a. Daniels Pharmaceuticals Inc., St. Petersburg, FL, USA.
b. Prescription Diet k/d Feline. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

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CASE 37-4

Chronic Kidney Disease in a Miniature Schnauzer with Multiple Problems

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Patient Assessment

A 12-year-old spayed female miniature schnauzer was presented for evaluation of vulvar discharge, possible polydipsia and occasional vomiting that began within the past month. Laboratory evaluation performed by the referring veterinarian revealed mild azotemia. The dog was currently receiving a low dose of enrofloxacin[a] once daily. The dog's appetite was normal. However, the owner thought it was losing weight. Physical examination abnormalities included a grade III/VI holosystolic murmur (left side), purulent vulvar discharge and vulvar erythema, malodorous breath and markedly decreased body condition (body condition score = 1.5/5); body weight was 5.5 kg (**Figure 1**).

Initial diagnostic evaluation included a CBC, serum biochemistry profile, urinalysis and diagnostic imaging (**Table 1**). Significant abnormal laboratory findings included leukocytosis characterized by mature neutrophilia, azotemia, low-normal serum albumin, inappropriately concentrated urine (specific gravity = 1.028), proteinuria (3+ dipstick) and hematuria (60 to 70 RBCs/hpf). Thoracic radiographs revealed no significant abnormal findings. Abdominal ultrasound revealed a mildly enlarged left renal pelvis. Additional diagnostic tests were performed to further evaluate initial abnormal findings. Urine culture revealed growth of *Escherichia coli* (800 colony forming units/ml of urine) and the urine protein-creatinine (UPC) ratio was 4.3. Systolic blood pressure measured indirectly by Doppler technique was 180 mm Hg. Results of an assay for canine pancreatic lipase immunoreactivity were normal.

On the basis of all findings, CKD, hypertension and urinary tract infection (UTI) were diagnosed. Mitral valvular disease was also considered likely. CKD was determined to be stage 2, P, Hnc (P = proteinuric, Hnc = high risk for target organ damage due to hypertension but no current evidence of complications [**Table 37-1**]). Pyelonephritis was suspected because of renal ultrasound findings and presence of leukocytosis. There was no evidence of cardiac decompensation on thoracic radiographs. Active pancreatitis was considered unlikely.

Assess the Food and Feeding Method

Because of several episodes of apparent pancreatitis in the past, the patient was eating a commercial dry, low-fat veterinary therapeutic weight-reduction food.[b] Water was available free choice at all times.

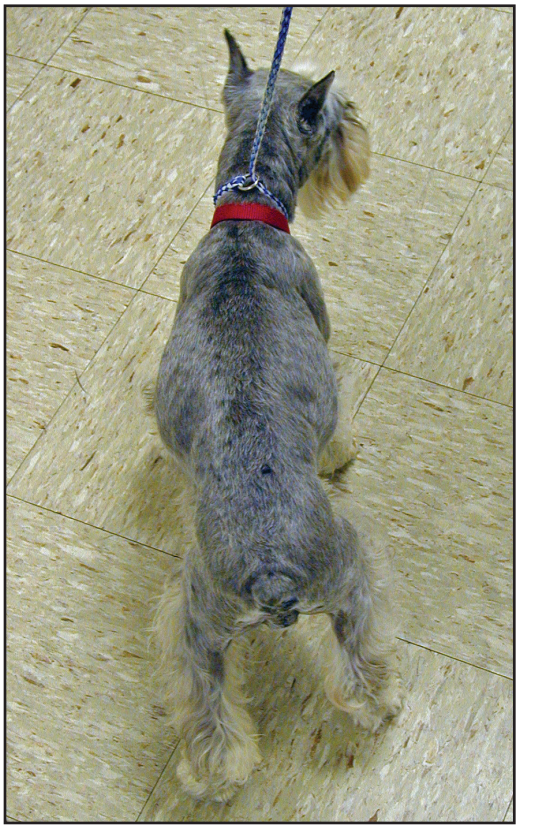

Figure 1. A 12-year-old miniature schnauzer that presented for evaluation of multiple problems.

Questions

1. What treatment is indicated for UTI and hypertension in this dog?
2. What treatment recommendations are appropriate for managing CKD in this patient?
3. What key nutritional factors should be considered in a dog with a history of pancreatitis?
4. What are some guidelines for managing patients with concurrent disorders such as CKD and pancreatitis?

Answers and Discussion

1. Because this dog has CKD, UTI and a dilated left renal pelvis, treatment for pyelonephritis is indicated. An extended course of treatment is needed; therefore, an appropriate antimicrobial should be selected based on susceptibility testing. In addition, urine cultures should be done periodically during and after treatment to confirm therapeutic success.

   Controlling hypertension is indicated because this patient is at severe risk for target organ damage because systolic blood pressure is ≥180 mm Hg. Hypertension may worsen progression of CKD in dogs and has been associated with increased risk of uremic crisis and death in dogs with naturally occurring CKD. Treatment of hypertension also is indicated to avoid worsening of mitral valve disease. Excessive dietary intake of sodium should be avoided; however, selection of an appropriate food should be based on

other patient factors such as presence of CKD in this case. In dogs, administration of an angiotensin-converting enzyme (ACE) inhibitor usually is the initial treatment of choice for hypertension. Because ACE inhibitors preferentially dilate the efferent arteriole, they have the potential to decrease glomerular filtration rate and worsen azotemia. Therefore starting at a lower dose and gradually increasing it over time while monitoring renal function may be helpful.

2. It is difficult to definitively localize the proteinuria as of renal origin from CKD vs. postrenal from the UTI. UTIs add plasma proteins to the urine after glomerular filtration, thus postrenal proteinuria is recognized by the presence of proteinuria with hematuria and pyuria. The urine sediment examination only revealed hematuria without pyuria, most likely because of current antibiotic administration. Therefore, postrenal proteinuria was less likely. The proteinuria was confirmed to be of renal origin by follow-up urinalyses that showed persistence of proteinuria despite resolution of the UTI.

Table 1. Results of initial laboratory evaluation including CBC, serum biochemistries and urinalysis.

Parameters	Day 1	Reference ranges
Hematocrit (%)	46	37-62
Total white blood cell count (x 1,000/µl)	21.5	5.4-16.6
Segmented neutrophils (x 1,000/µl)	18.92	3.24-10.7
Bands (x 1,000/µl)	0.215	0.0-0.25
Lymphocytes (x 1,000/µl)	1.29	0.75-5.65
Monocytes (x 1,000/µl)	1.075	0.1-1.19
Glucose (mg/dl)	119	89-135
Urea nitrogen (mg/dl)	67	8-27
Creatinine (mg/dl)	1.6	0.6-1.4
Phosphorus (mg/dl)	5.2	2.6-6.0
Calcium (mg/dl)	10.1	9.5-11.6
Total protein (g/dl)	6.5	5.4-7.2
Albumin (g/dl)	2.8	2.7-3.8
Total CO_2 (mmol/l)	19	18-24
Potassium (mg/dl)	4.6	3.5-5.5
Amylase (IU/l)	985	338-1,007
Lipase (IU/l)	1,245	268-1,796

Proteinuria occurs as a result of CKD; however, it may also play a role in the pathogenesis of progressive CKD. In one study, an initial UPC ≥1 in dogs with CKD was associated with greater risk of having a uremic crisis or dying compared with dogs that had a UPC <1. Dogs with proteinuria should be fed a reduced-protein food designed for patients with CKD, whether azotemia exists or not (**Box 37-2**). Patients should be monitored periodically (e.g., every two to four weeks initially) to determine the optimal quantity of dietary protein that maintains lean body mass and decreases magnitude of proteinuria, as measured by UPC ratios. Patients should receive enough calories to achieve and maintain ideal body weight and condition. Administration of an ACE inhibitor also is indicated for dogs with proteinuria due to glomerular disease. In a study of dogs with naturally occurring idiopathic glomerulonephritis, treatment with enalapril was associated with significant improvement compared with dogs that received a placebo. Both groups also received low-dose aspirin and a veterinary therapeutic renal food.[c] Resorption of excessive amounts of protein from the tubular filtrate in dogs with CKD and proteinuria may damage the tubules resulting in progressive tubulointerstitial injury. (See Renal Oxidative Stress in the Etiopathogenesis section.)

3. This dog does not have active pancreatitis. However, long-term management should include feeding foods with relatively less fat that avoid excessive protein because both are stimuli for pancreatic secretion. Feeding a moderate-fat food (≤15% dry matter [DM]) has been recommended for patients recovering from pancreatitis, whereas a low-fat food (≤10% DM) may be more appropriate for those with concurrent obesity or hypertriglyceridemia. Clinical studies have not evaluated effects of feeding different amounts of fat on recurrence of pancreatitis. One approach is to feed less fat than the patient was eating when the most recent episode of pancreatitis occurred.
4. Patients with multiple disorders can be challenging to manage, especially when treatment for one condition may not be ideal for a concurrent disease. Feeding a veterinary therapeutic renal food is indicated for this patient. These foods often contain increased amounts of fat, which would not be ideal for a patient at risk for pancreatitis. One approach for this patient would be to recommend a renal food with the lowest fat content. In general, dry foods contain less fat; therefore, feeding a dry food may be preferable as long as the dog is able to maintain hydration. If the patient does not respond well to a commercially available food, an alternative would be to formulate a homemade food. In these cases, it is recommended to seek input from a board-certified clinical nutritionist who can help design a nutritionally balanced maintenance food tailored for that patients' particular needs.

Progress Notes

Enrofloxacin (5 to 7 mg/kg per os twice daily for six to eight weeks) was recommended to treat possible pyelonephritis. This antimicrobial was selected because the organism was susceptible based on urine culture and sensitivity results. A low number of organisms most likely grew on the initial urine culture because the dog was receiving a low dose of antimicrobial at the time urine was collected. A follow-up urine culture was recommended one week after beginning treatment, one week after completing antimicrobial treatment and once monthly for three months thereafter to ensure eradication of infection.

Additional treatment included administration of an ACE inhibitor, H_2-receptor antagonist and a veterinary therapeutic renal food. Benazepril[d] (0.25 to 0.5 mg/kg orally once or twice daily) was begun to manage hypertension and proteinuria. To avoid potential for worsening azotemia, it was recommended to begin at the lowest dose once daily and gradually increase while monitoring serum creatinine and urea nitrogen concentrations. Cimetidine[e] (5 to 10 mg/kg orally, twice daily) was prescribed to help manage possible uremic gastritis. All dry versions of commercially available veterinary therapeutic renal foods from major companies con-

tain <20% DM fat, which would be appropriate for a dog with a history of pancreatitis (**Table 2**). The dog's current food contained approximately 9% DM fat; therefore, it was recommended to initially transition to a veterinary therapeutic renal food[f] formulated for early kidney disease that contained a similar amount of fat.

Table 2. Fat content of canine therapeutic renal foods.

Foods	Form	Fat (%)*
Hill's Prescription Diet g/d Canine	Can	10.8
Hill's Prescription Diet g/d Canine	Dry	11.0
Hill's Prescription Diet k/d Canine	Dry	19.4
Hill's Prescription Diet k/d Canine	Can	26.7
Iams Eukanuba Veterinary Formula Renal Early Stage	Dry	13.7
Purina Veterinary Diets NF KidNey Function Canine Formula	Dry	15.7
Purina Veterinary Diets NF KidNey Function Canine Formula	Can	27.4
Royal Canin Veterinary Diet Renal LP	Can	29.9
Royal Canin Veterinary Diet Renal LP 11	Dry	14.0
Royal Canin Veterinary Diet Renal MP 14	Dry	16.5

*Dry matter basis.

The amount of new food to feed was based on an estimate of the patient's resting energy requirement (RER) at its ideal weight (7.3 kg) and multiplying it by a factor of 1.2 (assumes a small amount of physical activity) to determine the daily energy requirement (DER). RER at 7.3 kg = 311 kcal (1,300 kJ); DER = RER x 1.2 = 373 kcal (1,561 kJ). The as fed energy density of the food was 358 kcal/8-oz. measuring cup. The daily amount to feed is estimated by dividing the DER (373 kcal) by the as fed energy density (358 kcal/cup), which equals slightly more than one cup of food daily. The patient was offered small quantities of the food every three to four hours.

The owners were instructed to return the dog to their primary care veterinarian seven to 10 days after discharge for physical examination, urine culture, blood pressure evaluation and measurement of serum biochemistries and UPC ratio. Long-term monitoring was recommended every one to four months indefinitely to assess effectiveness of treatment and make adjustments as needed. The dog's condition continued to decline over the next six months and the patient was euthanized after it began having seizures; a postmortem examination was not done.

Endnotes

a. Baytril. Bayer HealthCare, Shawnee Mission, KS, USA.
b. Prescription Diet r/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
c. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
d. Fortekor. Norvartis Animal Health, Basel, Switzerland.
e. Tagamet. SmithKline Beecham Pharmaceuticals, Philadelphia, PA, USA.
f. Prescription Diet g/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

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