Renal Disease in Small Animals: A Review of Conditions and Potential Nutrient and Botanical Interventions

Susan Marie Pollen, DVM, CVA

Abstract
Nutritional and botanical approaches that may benefit small animals diagnosed with renal disease are considered with regard to their effects on renal physiology and ability to ameliorate specific pathologies. Suggestions are made for water- and fat-soluble vitamins, mushrooms, quercetin, and Western and Chinese herbs, based on their activities as free-radical scavengers, immune modulators, antimicrobials, anti-emetics, and erythrocyte production stimulators. Attention is focused on omega-3 fatty acids from fish and flaxseed, in addition to several other nutrients and botanicals. Renal anatomy and physiology is reviewed, as well as the etiology of chronic renal disease in small animals, its symptomatic presentation, and progression.
(*Altern Med Rev* 2001;6 (Suppl):S46-S61)

Introduction

Americans spent $16 billion on functional foods and supplements in 2000,[1] their pocketbooks suggesting they believe, as some veterinarians do, that "nutrition is the foundation of all health."[2] Such a philosophy gives rise to the belief that interventional nutrition should take a central role in the management of renal diseases in veterinary medicine.[3] If this indeed be the case, pet owners may be just as willing to purchase nutritional and botanical supplements for therapeutic use for their pets as they are to purchase these products for themselves, assuming they are correctly informed by their veterinarian how these products will benefit their animals.[4]

Spontaneous renal disease is a common cause of illness and death in dogs[5], and is one of the more frequently diagnosed conditions in cats.[6] Diseases of the kidney, second only to neoplasias in causing death,[7] may be treated effectively with natural methods.[8-11] The decision as to which supplements to prescribe should be based on an animal's individual tolerance and symptomology. For example, for an anorexic animal unable or unwilling to digest foods or oral supplements, injections of vitamins A, E, C, and B complex are recommended. For an animal that will not accept pills, recommendation should be made for whole foods, such as sweet potatoes, fish, or flaxseed. Some nutrients, such as antioxidants and omega-3 fatty acids, benefit the kidneys on multiple levels and may be administered through a variety of routes.

Recommendations regarding supplementation should also take into account species differences. For example, dogs can utilize carotenoids from plants to synthesize retinol, but cats

---

Susan Marie Pollen, DVM, CVA – practices at Coleman Animal Healing Center in Pasco, Washington, treating equine and small animals, including exotics. Prior to becoming a veterinarian she was involved in human medical research.
Correspondence address: 631 W. Clark St., Pasco, WA 99301

require pre-formed vitamin A from animal tissue. Dogs can use either fish or plant sources of omega-3 fatty acids, whereas cats require fish because they lack delta-6 desaturase; i.e., they can synthesize neither eicosapentaenoic acid (EPA) from alpha-linolenic acid (ALA) nor arachidonic acid (AA) from linoleic acid (LA).[12]

Review of Kidney Structure

While chronic renal disease may cause shrunken, swollen, or irregularly shaped kidneys, size and contour do not always correlate with kidney failure. For example, the kidneys of animals with amyloidosis, glomerulonephritis, and acute pyelonephritis may appear radiographically normal.[13] With chronic renal failure, however, there are often palpable or radiographic changes in kidney shape, contour, and texture, reflecting at a macroscopic level changes occurring at the cellular level.

Blood is supplied to the kidneys from the abdominal aorta, via the right and left renal arteries that branch as they form interlobar arteries, arcuate arteries, interlobular arteries, and afferent arterioles. Blood flows from an afferent arteriole through the glomerular capillary and then into the peritubular capillary bed. Vasa recta (straight branches of some peritubular capillaries) supply the medulla with blood and help maintain medullary hypertonicity, which is essential for water conservation.[14,15] Kidney parenchyma, whose oxygen requirement is second only to that of the brain, is particularly susceptible to ischemia because it lacks collateral circulation. The medulla, supplied by vasa recta, receives less blood than the kidney cortex.[16]

Review of Basic Kidney Function

Paired retroperitoneal kidneys receive 25 percent of the cardiac output and provide life-sustaining functions that include: maintenance of fluid volume, composition, and pH; regulation of blood pressure (via renin);

erythrocyte production (via erythropoietin); and conversion of vitamin D into its active form, 1-25-dihydroxycholecalciferol. Kidneys filter an animal's entire blood volume nearly twice an hour and limit urine production to approximately 0.001 percent of the blood filtered. Hence, for every liter of blood flowing through the kidney of a healthy animal, approximately 1-2 milliliters of urine is produced.[14,16]

Urine Generation

Filtration, selective reabsorption, and selective secretion are processes of the kidneys that generate urine. Filtration occurs in the glomeruli as low-molecular weight particles pass through 1-micron capillary pores and into the filtrate. There is a significant blood pressure gradient between the glomerular capillary bed (50 mm Hg) and the peritubular capillary bed (15 mm Hg). This blood pressure gradient, as well as an osmotic pressure gradient, allows net filtration at the glomeruli and net reabsorption at the peritubular capillaries.[14]

To move from the glomeruli into Bowman's capsule, filtered substances pass through two cell layers separated by a negatively charged basement membrane. The negative charge repels plasma proteins, including albumen, so they are not filtered but remain in the blood. Filtrate osmotic concentration in Bowman's capsule is similar to that of plasma; the filtrate contains water, glucose, amino acids, inorganic salts, urea, uric acid, and creatinine. Remaining in the blood and moving on to the peritubular capillary bed are cells and large particles, including erythrocytes, leukocytes, thrombocytes, plasma proteins, and negatively charged amino acids.

The volume of fluid flowing through the glomerular filter is referred to as glomerular filtration rate (GFR). The GFR, relatively insensitive to systemic arterial blood pressure, is influenced by the sympathetic nervous system. If sympathetic impulses constrict afferent arterioles, renal blood flow is reduced, and

Table 1. Functions of the Nephron: Corpuscle and Renal Tubule

LOCATION	ACTION	EFFECT ON
CORPUSCLE		
Glomerulus	**Filters into tubule**	**Water, ions, substances of low molecular weight**
	Maintains	**Large molecules and cellular components: erythrocytes, leukocytes**
Bowman's capsule	**Receives filtrate across a negatively charged basement membrane**	
RENAL TUBULE		
Proximal convoluted	**Reabsorbs into blood**	**60-70% of filtered water** **solutes: glucose, amino acids, creatinine, uric acid** **ions: calcium, phosphate, sulfate, potassium, chloride**
	Secretes into filtrate	**Creatinine and hydrogen ions, organic acids and bases, and most drugs: fatty acids, uric acid, bile salts, prostaglandins, acetylcholine, epinepherine, histamine, dopamine, aspirin, penicillin, morphine, cimetidine**
Loop of Henle descending limb	**Reabsorbs into blood**	**Water**
Loop of Henle ascending limb	**Reabsorbs into blood**	**Chloride and sodium ions**
Distal convoluted	**Reabsorbs into blood**	**Water and sodium ions**
	Secretes into filtrate	**Hydrogen and potassium ions**

glomerular pressure and GFR are decreased. The opposite occurs when sympathetic impulses constrict efferent arterioles.

Once filtration has occurred, nephrons refine filtrate via active secretion and reabsorption so that only very small amounts of physiologically useful substances (glucose, sodium, chloride, phosphate, water) pass into the urine. One of the driving forces for selective reabsorption is the active transport of sodium ions from filtrate to peritubular capillaries. Positively-charged sodium ions within the capillaries attract negatively charged chloride, phosphate, and bicarbonate from the filtrate into the capillaries. As peritubular capillary osmotic pressure increases, water diffuses from tubular filtrate into the peritubular capillaries.

The proximal tubule is the site of most secretion, reabsorption, and active transport. The extracellular environment surrounding the tubule changes from cortex to medulla, and selective absorption across the single layer of tubular epithelial cells is thereby influenced. This influence, along with the specialized receptors along the tubule, allows each tubular section a selective resorptive and secretory function (Table 1).

Filtrate that is osmotically similar to serum at the proximal convoluted tubule has reduced in volume 60-70 percent by the time it reaches the loop of Henle.[16] Virtually all nutrients, most water, fatty acids, prostaglandins, bile salts, acetylcholine, epinephrine, histamine, dopamine, saccharin, most drugs (aspirin, penicillin, morphine, cimetidine, etc.),[16,17] physiologically active ions (sodium, potassium, bicarbonate, calcium, magnesium, phosphate, sulfate), and acids (uric, citric, ascorbic) are regulated in the proximal tubule and moved from the blood into the filtrate. Amino acids, essential for maintenance of serum osmolality, are reabsorbed by three active transport mechanisms such that only a trace remains in the urine. Depending on diet, metabolism, exertion, and illness, renal tubular filtrate contains a number of constituents: urea, sodium chloride, inorganic ions, and traces of most substances circulating in the blood.

The liver, influenced by protein intake and anabolic need, makes urea from deamination of amino acids in the Krebs urea cycle (ornithine-citrulline-arginine cycle). Urea is filtered into Bowman's capsule, of which half is passively reabsorbed in the tubule. Urea is used by the body to maintain high renal medullary osmolar concentrations, and in the presence of ADH (antidiuretic hormone) diffuses from the collecting tubules into the medulla. Muscle phosphocreatine, an energy storage molecule, is formed in a series of steps involving the pancreas, kidneys, small intestines, and the liver.[16] In the muscle, phosphocreatine is steadily converted to creatinine at a rate of one to two percent a day. Animals with more muscle mass, consuming more meat proteins, or with a negative nitrogen balance, produce more total creatinine. Uric acid, formed from nucleic acids, is reabsorbed from filtrate by active transport, and a small portion is actively secreted into the urine.

Carnivores with high-protein diets have more acidic blood than herbivores because sulfur and phosphorus from meat proteins are oxidized to sulfuric and phosphoric acids.[7] Surplus hydrogen ions are buffered and excreted. If the filtrate contains a large amount of acid, kidney tubules form ammonium salts; i.e., ammonia is not extracted from the blood, but is manufactured in the kidney from circulating amino acids, particularly glutamine, to buffer acidic filtrate via formation of ammonium sulfate or ammonium phosphate. These salts, along with other inorganic salts (calcium chloride, potassium chloride), dissociate in solution; thus, the filtrate may contain ammonium sulfate, sodium chloride, ammonium chloride, or sodium sulfate.

After passing through the tubule, filtrate from the distal convoluted tubule joins filtrate from other distal convoluted tubules in the collecting tubule where further refinement occurs. Filtrate, at this point identical to urine, passes through the renal pelvis and into the ureter to the bladder where it is excreted.[14]

Regulation of Blood Pressure

GFR is regulated by cells of the juxtaglomerular apparatus on the distal convoluted tubule in contact with both afferent and efferent arterioles. If GFR decreases, the filtrate ion concentration decreases; juxtaglomerular cells then dilate the afferent arteriole and renin is released. Renin, an enzyme, breaks down an alpha-2 globulin plasma protein to form inactive angiotensin I, which is rapidly converted into angiotensin II. Angiotensin II stimulates aldosterone release, and aldosterone stimulates distal tubule sodium reabsorption. In this manner, kidneys provide long-term regulation of blood pressure via regulation of extracellular volume.[14,15]

Maintenance of pH, Potassium Ion Regulation, and Erythrocyte Production

Acid:base balance is controlled by renal regulation of bicarbonate and hydrogen ions and by pulmonary excretion of carbon dioxide. Normal catabolic processes produce sulfuric, phosphoric, and organic acids that are buffered by bicarbonate ions in the blood, forming carbon dioxide. This buffering consumes a bicarbonate ion, which the kidneys replenish to maintain a homeostatic pH. Thus, for every hydrogen ion produced by metabolism, healthy kidneys reabsorb one bicarbonate molecule. This system involves an exchange of bicarbonate ions for hydrogen ions, with the hydrogen excreted in the urine. If, however, pulmonary excretion of carbon dioxide is excessive, the kidneys excrete bicarbonate ions. The proximal convoluted tubule is specialized to control pH by actively secreting hydrogen ions.

Renal adjustment of pH is also influenced by ammonia. Serum ammonia diffuses into the tubule lumen, binds hydrogen ions and becomes polar, positively charged ammonium ions (NH_4^+). Ammonium is unable to diffuse through lipid cell membranes, thus stays in the filtrate and is excreted, ridding the body of excess hydrogen ions.

Kidneys also regulate potassium ion concentrations, significant because extracellular potassium influences membrane depolarization. While the majority of potassium regulation occurs in the proximal tubule and loop of Henle, in acidosis, distal tubular and collecting duct cell regulation becomes increasingly important.

Kidneys also produce erythropoietin, a hormone that stimulates red blood cell (RBC) production in the bone marrow. Normal RBC concentration per cubic millimeter of blood is $4.95-7.87 \times 10^6$, canine, and $5-10 \times 10^6$, feline.[18] Erythropoietin production in a healthy kidney is stimulated by lower RBC concentration; however, there is insufficient kidney tissue to produce the necessary erythropoietin in renal disease. Therefore, anemia is a part of severe kidney disease.

Diagnostic Measures for Renal Disease

Specific Gravity

Solute particle size, weight, and number give urine its osmotic concentration. The measure of osmotic concentration, or specific gravity (SpGr), ranges from 1.001-1.065, with SpGr increasing as urine becomes more concentrated. Normal canine SpGr is 1.030 or higher; normal feline, 1.035 or higher. With renal failure and inability to concentrate urine typical of chronic renal failure, SpGr becomes fixed in the isosthenuric range, 1.008-1.012.[18]

Creatinine Clearance Tests

Among the laboratory tests measuring for renal disease are those measuring azotemia, the amount of nitrogenous wastes in the blood. An estimated 15-20 percent of older cats and dogs have some degree of azotemia.[7] Normal canine and feline creatinine concentrations are between 0.6-1.2 mg/dL.[17] States of azotemia can be determined from creatinine levels above those of normal. Because creatinine is steadily produced and freely filtered, and not reabsorbed as is urea, creatinine is a better measure of renal function than blood urea nitrogen (BUN).

Creatinine clearance tests are used to assess the rate of nephron filtration, the GFR. Normal GFR is 120 mL/min, and obvious symptoms of renal disease appear when GFR falls below 30 mL/min. As GFR decreases, water and electrolyte balances are maintained by diet. When GFR is below 3 mL/min, dietary intervention is insufficient and dialysis or transplant may become necessary. Nutritional support has the greatest potential for benefiting animals with renal disease when GFR ranges from 30-120 mL/min.

Table 2. Signs of Renal Disease

Fever
Cachexia
Anorexia
Halitosis
Oral Ulceration
Nausea and Vomiting
Diarrhea or Constipation
Edema
Nocturia
Oliguria
Anuria
Polyuria and Polydipsia
Flank Pain
Hypertension
Abdominal Distention
Acute Respiratory Distress
Acute Blindness Secondary to Hypertension

Renal Disease in Small Animals: Pathophysiology and Potential Nutrient Interventions

Renal diseases, whether immune-mediated, neoplastic, degenerative, or due to infection, cause death and debility, with signs ranging from anorexia to anuria (Table 2).[17] Renal disease accounts for as much as five percent of all deaths in dogs.[7] Renal disease is one of the most frequently observed conditions in cats examined in veterinary clinics in the United States.[6] Studies by the Mark Morris Institute in 1995 and 1998 cite renal disease as the cause of one-quarter of cat deaths, and renal disease to be present in 2.4 percent of cats over 10 years examined by veterinarians.

Renal failure is commonly distinguished as either acute renal failure (ARF) or chronic renal failure (CRF) based on four criteria: history, physical exam, laboratory tests, and prognosis (Table 3).[16,17,19] In cases of ARF, animals are often anuric, producing less than 0.1 mL/kg/hr of urine. With CRF, animals often progress through oliguria, with urine production of at least 0.25 mL/kg/hr, to polyuria. Because ARF is sudden, severe, and frequently has a poor prognosis, there may be insufficient time for nutritional therapy to be of benefit. CRF, on the other hand, persists for an extended period during which alternative methods should be considered.[10,20,21]

When the kidneys fail, allopathic medications used to treat animals may include famotidine for nausea, potassium gluconate for hypokalemia, phosphate binders (aluminum carbonate), calcitriol for renal secondary hyperparathyroidism, erythropoietin to stimulate RBC production, angiotensin-converting enzyme inhibitors to control blood pressure, and oxazepam to stimulate appetite.[17]

Several nutritional and botanical options exist for the treatment of renal disease,[22] including antioxidants, immune modulators, antimicrobials, anti-emetics, and appetite stimulants.

Many products are formulated with the understanding that, "nutritional therapy may be generally more successful when a combination of products is used to boost and enhance various metabolic pathways of the body."[9] In Chinese medicine, herbs are combined mindful of the six effects of mixed ingredients: potentiation, enhancement, counterdrive, suppression, antagonism, and incompatibility.[23] For example, a standard Chinese herbal kidney tonic, Rehmannia 6, contains six herbs. Other kidney tonics based on Rehmannia 6 add more ingredients, such as cinnamon bark and aconite, to warm the kidneys.[8,24]

The benefit of a combination product is that it targets many of the aspects of a disease. Rehmannia 6 is a traditional Chinese herbal: Rehmannia for hypertension, hypokalemia, hypercholesterolemia; Cornus for hypertension, low back pain, and infection; Dioscorea for energizing the kidney, spleen,

Table 3. Criteria that Distinguish Acute and Chronic Renal Failure

	ACUTE	CHRONIC
History	Exposure to nephrotoxin, ischemia, infection; sudden onset	Slowly progressing
Physical exam	Good body condition, normal kidneys	Debility
Laboratory tests	Metabolic acidosis, hyperkalemia, progressive azotemia; active urine sediment	Nonregenerative anemia, mild acidosis, normal or hypokalemia, stable azotemia, inactive urine sediment
Prognosis	Less favorable	Better

and lungs; Moutan for inflammation and hypertension; Hoelen for diuresis, improving GI function, and providing potassium; and Alisma for hypertension, hypokalemia, and to increase urea excretion. Chinese herbal kidney preparations are often combined with liver-benefiting herbs; these may be combined with allopathic medications to treat renal disease.[8]

Several common pathologies of renal disease are discussed below, with recommendations regarding the appropriate treatment for each. When possible, references are provided for research on treatment in small animals with renal disease. However, in many instances, clinical studies on substances have not yet been undertaken. In these cases, experiments that elucidate a mechanism of action are referenced, and inferences are made as to their possible application in the treatment of renal disease in dogs and cats.

Glomerular Pathology

Glomerular pathology is multi-causal and can include neoplastic and immune-mediated mechanisms (where antibodies are directed either at glomerular tissue or toward non-renal tissue, depositing in glomerular tissue as antigen-antibody complexes).[16] If the inflammatory or immune-mediated processes producing these antibodies can be stopped, renal disease may be slowed or prevented. Substances of benefit include those that are anti-inflammatory, antimicrobial, or immune-stimulating. Anti-inflammatory agents include omega-3 fatty acids,[5,25-32] *Aloe vera*, curcumin, and Boswellia.[33,34] Antimicrobials and immune-stimulators include: Artemisia,[2] Coptis,[35] Uva ursi,[36] maitake and shiitake mushrooms,[37] Siberian ginseng, Echinacea, vitamin C, and Astragalus.[2,38] Anti-neoplastic foods include the maitake, shiitake,[39] chanterelle, reishi, and ganoderma mushrooms.[37]

Altered GFR

Capillary pressure coming into the kidney parenchyma is significant because if GFR is too high, tubules do not have time to reabsorb filtered substances; and if too low, substances collect in the blood. In addition to hydrostatic pressure, GFR is influenced by glomerular plasma osmotic pressure. As filtration occurs, osmotic pressure within the capillary rises, opposing filtration. Obstruction distal to Bowman's capsule (enlarged prostate, urinary calculi) increases hydrostatic pressure in the capsule and opposes glomerular filtration. Any condition significantly altering blood pressure (hyper- or hypoadrenocorticism, steroid

medication, hypovolemia, cardiac insufficiency) may affect GFR and damage renal parenchyma. Alterations to plasma osmotic pressure, from protein-losing enteropathy to proteinuria, may also alter GFR.

Supplements that address these problems include saw palmetto for enlarged prostate,[40] and deglycyrrhizinated licorice,[2,22,41] L-glutamine, and transfer factors for protein-losing enteropathy and GI epithelial instability.[42] Botanicals that assist in lowering blood pressure include garlic,[43] grindelia, and hawthorne.[22]

Excessive Renin Production

Failing kidneys often self-regulate by releasing more renin in an attempt to increase GFR, resulting in hypertension. Here again, garlic, grindelia, and hawthorne may be of benefit.[22]

If extracellular volume is depleted, as it can be with vomiting, diarrhea, or sweating, GFR decreases and additional renin is released. If extracellular fluid volume or pressure in the afferent arteriole increases, renin secretion is inhibited. In the case of renal failure, this renin-mediated control of blood pressure can malfunction and renin production continues when it is not beneficial. For example, renal failure can induce vomiting, which lowers fluid volume and induces renin production; hypertension follows, which further damages the kidney.[7] An animal with renal failure that is vomiting may benefit from herbs that calm the digestive tract and function as anti-emetics, such as peppermint,[44] chamomile, ginger, and wild bergamot.[41]

GFR is also negatively affected by deposition of immune-complexes or by immune cells directly attacking the glomeruli or Bowman's capsule. When glomerulonephritis is the result of an inflammatory condition, immune-modulating nutrients, such as plant sterols,[45] colostrum,[42] or mushrooms,[37] may provide protective benefit. Plant sterol:sterolin combinations impact the immune system by

increasing the T-helper 1 activity and down-regulating T-helper 2 cells. Because T-helper 2 cells enhance antibody production, dampening an overactive T-helper 2 subset results in a decrease in autoimmune antibody production.[45] Fish oil supplements are useful when the nephropathy is IgA immunoglobulin mediated.[20] Studies have found significant decreases in proteinuria and increases in survival rate in humans supplemented with omega-3 fish oils at a dose of 12 g daily. End-stage renal disease was 40 percent in the placebo group and only 10 percent in the fish oil group after two years.

Inflammation and Mineralization of Kidney Tissue

In chronic renal insufficiency with decreased GFR, serum phosphorus and phosphate concentrations increase. Elevated serum phosphate stimulates parathyroid hormone (PTH) release. PTH decreases phosphate reabsorption in the proximal convoluted tubule and stimulates mineral release from bone. These minerals may inflame and mineralize renal tissue, causing further kidney damage. Dietary phosphate restrictions and phosphate binders can increase longevity in dogs and cats with renal disease.[7] Supplementation with iron may be beneficial as it binds phosphorus in the intestines and lowers absorption.

PTH also interacts with calcium and vitamin D, increasing serum calcium by mobilization and vitamin D by enhancing renal production of 1-25 dihydroxycholecalciferol (active vitamin D). Normally, increased serum calcium and vitamin D provide inhibitory feedback that decreases PTH secretion. However, PTH is not effectively suppressed in animals with kidney disease, perhaps because there is insufficient functioning renal tissue. Thus, animals with renal disease may benefit from vitamin D supplementation.[7]

Ineffective Selective Resorption

Because sodium ions are essential in selective resorption, regulating them becomes crucial in renal disease; i.e., intake must be sufficient to cover losses but not be excessive. Historically, renal disease has been treated with sodium restriction, but current research suggests the best diet for renal patients should include moderate amounts of salt.[7] Canned and moist packaged pet foods often have high sodium concentrations. Therefore, caution is advised when feeding canned and moist packaged foods. Sodium intake for dogs with CRF should be 0.1-0.25-percent dry matter weight and for cats 0.2-0.35-percent dry matter weight or 10-40 mg/kg body wt per 24 hours.

When the basement membrane of the glomerulus is disrupted and negative charge lost, as with nephritis, albumen and proteins pass into the filtrate, producing proteinuria. Loss of albumen and proteins, either from uncontrolled glomerular filtration, or from ineffective reabsorption, prevents establishment of normal capillary osmotic pressure. Because capillary osmotic pressure maintains extracellular fluid volume, loss of osmotic pressure encourages interstitial edema. Botanicals that promote diuresis and decrease edema include dandelion,[2,22,40] gravelroot,[22] and Astragalus.[36,46]

Polyuria

When selective reabsorption and active transport are overwhelmed by solute concentrations that exceed transport thresholds, these solutes remain in the filtrate and are passed into the urine. High solute concentrations prevent water reabsorption from the filtrate and high volumes of water are lost in the urine. This condition of polyuria can cause polydipsia. The long-term sequelae are impaired electrolyte conservation, loss of water-soluble vitamins and micronutrients, and eventual destruction of renal parenchyma. Renal failure patients benefit from replacement of water-soluble C and B vitamins,[41,47,48] especially folate and pyridoxine.[11]

Nephrotoxicity

If the kidney is malfunctioning, drugs normally cleared through the kidney accumulate in the blood. Thus, drug selection and dosing intervals become serious considerations when treating animals with kidney disease.[49,50] Potentially nephrotoxic drugs which should be avoided include: amphotericin B, cephalosporins, cisplatin, cyclosporin, sulfonamides, tetracyclines, thiacetarsemides, and vancomycin.[17,49,50] Omega-3 fatty acids have been found to reduce the nephrotoxicity of cyclosporin.[51]

It is preferable to treat animals with renal disease using drugs that are neither directly nephrotoxic nor cleared through the kidney, or by using botanicals with similar mechanisms. For example, garlic,[52] goldenseal,[53] and Echinacea are antimicrobial or immune-stimulating;[40] maitake,[54] ganoderma, and shiitake mushrooms are anti-neoplastic;[37] and omega-3 fatty acids are anti-inflammatory.[5,25-32,38,55]

Renal Hypoxia

Because poorly perfused tissues, such as kidney parenchyma, are at higher risk for hypoxia and free-radical generation, antioxidants may help limit renal damage. Among important antioxidants are carotenoids, including alpha-carotene, beta-carotene, lutein, and lycopene; proanthocyanidins, such as grape seed extract[56] and maritime pine tree bark;[2] superoxide dismutase;[57] and vitamins A, C,[2,38] and E.[10,20,47,48] Animals with ischemic conditions caused by cardiac insufficiency, liver failure, prolonged anesthesia, pancreatitis, sepsis, trauma, and vasculitis, may be especially predisposed to renal hypoxia,[16] and may have the greatest potential of benefiting from free-radical scavenging supplements.

Metabolic Acidosis

As nephrons fail and tubular structures cannot make adjustments, hydrogen ions are retained, and kidney disease is accompanied by metabolic acidosis.[14] Because enzyme and

cellular activity are pH-dependent, acidosis precludes normal renal function. To limit metabolic acidosis, renal diets may include a greater ratio of plant-to-meat protein because meat is catabolized to acidic by-products.[7] Introducing fermentable fiber to the diet, such as gums, pectins, and mucilages from apples and flax, may mediate acidosis by providing a hydrogen ion trap in the colon. There is a common agreement that the diet of renal patients should not contain excessive protein or calories, but should contain sufficient amounts to replace that lost in urine, preventing protein catabolism cachexia.

In animals with chronic acidosis, the kidneys synthesize ammonia, creating more filtrate buffering capacity. However, as the kidneys fail, this ammonia remains in the blood.[7] Hydrogen ion resorption in the gut by flax and fermentable fibers can help neutralize the acidic concentration.

Potassium Depletion

If ion regulation fails in the proximal tubule and loop of Henle, causing elevated potassium levels, cellular membranes become excitable and cardiac fibrillation is possible; if decreased, flaccid paralysis is possible.[17] Renal diseases will often cause an increase in serum potassium, but deplete total body potassium. There have also been recent clinical observations showing potassium deficiency may be a contributing factor in the development of chronic renal disease in cats.[58] Chinese herbal preparations address hypokalemia with the use of Alisma, Hoelen, and Rehmannia, which are all high in potassium.[8]

Renal Calculi

Although dogs and cats can be subject to urinary tract calculi, it is generally not in conjunction with chronic renal failure, since animals with CRF generally exhibit dilute urine coupled with polyuria.

When calcium and magnesium ions in the filtrate combine with phosphate radicals, either soluble or insoluble salts will form. If urine is acidic, soluble calcium and magnesium phosphates will form. However, if urine is not quickly eliminated and bacteria converts urea to ammonia, urine will become alkaline, resulting in precipitation of calcium and magnesium ammonium phosphate crystals. When insoluble salts, or calculi, lodge in ureters, bladder, or urethra, infection and hydrostatic problems occur.

Calculi management is based on the stone's composition. The most common, calcium oxalate stones, can be prevented with magnesium and citrate supplementation, both known to prevent precipitation of calcium.[59,60] Adding cranberries, prunes, and starchy foods may also help by producing an acid ash which decreases calcium stone precipitation.[61] Vitamin B6 reduces endogenous production and urinary excretion of oxalates, and thus may be another important addition to a prevention protocol.[62] Fiber may also be of benefit as it can bind dietary oxalates in the gut and prevent absorption.

In the case of uric acid stones, folic acid may reduce uric acid secretion. Renal epithelia irritated by any form of calculi may benefit from mucilaginous-producing herbs, such as marshmallow and slippery elm.[22,36] In the case of bacterial infections associated with stones, such as stones containing ammonia, controlling the infection with antimicrobials (either antibiotics or herbal antibiotics such as goldenseal and uva ursi) is a prime objective of treatment. Cranberry may be beneficial in these cases as it prevents bacterial adherence to bladder epithelia.[36]

Azotemia

In an animal with a functioning liver and nonfunctioning kidney, urea levels are elevated; whereas, in an animal with a nonfunctioning liver and functioning kidney, urea levels are low because urea is not being

produced. With low GFR, whether prerenal (shock, dehydration), renal (amyloidosis), or postrenal (calculi), more urea is reabsorbed, so BUN rises. Normal canine BUN is 8-23 mg/dL; feline,19-34 mg/dL. Even with renal damage, BUN increases are often initially slow and then rapid later on in severe failure. In the case of GFR decreases of 75 percent or greater, BUN will increase; but generally BUN will not be affected by GFR decreases of less than 75 percent.[16,18] Nutritional therapy for azotemia includes fermentable fibers that act as intestinal nitrogen traps.[7]

Additional Filtrate Abnormalities

If plasma levels of uric acid become abnormally high, uric acid precipitates in the joints. Drugs or genetic factors inhibiting uric acid tubular reabsorption increase the urine's uric acid concentration. The herb plantain is thought to stimulate renal secretion of uric acid.[36]

Kidney-associated Anemia

Kidney-associated anemia is characteristically normocytic, normochromic, and nonregenerative.[18] Anemia may cause tachycardia, lassitude, and cold and exercise intolerance.[17] Erythropoietin must be given. In addition, nutrients that benefit RBC production, including water-soluble vitamins B12 and folic acid, are especially important when vitamins are lost in isosthenuric urine. Also useful are eggs, raw beef liver, liquid chlorophyll, kelp,[63] and supplements containing vitamin C for optimal iron absorption, vitamin E for antioxidant protection of RBCs, vitamin A, and iron and copper for hemoglobin synthesis. Supplementing branched-chain amino acids (valine, leucine, and isoleucine) and glutamine is also useful if nephrogenic anemia is accompanied by amino acid deficiency.[61]

Omega-3 Fatty Acids in Renal Disease

As the kidneys fail, many physiological processes are affected. Supplementation with omega-3 fatty acids may be the most universally beneficial nutritional recommendation because they benefit the kidney on multiple levels. Sources of omega-3 oils include fish, (especially salmon, mackerel, tuna, halibut, and blue fin) and flaxseed.[61,64] Essential fatty acids include LA, an omega-6 fatty acid and precursor to gamma-linolenic acid (GLA), and ALA, an omega-3 fatty acid and precursor to EPA and docosahexanoic acid (DHA).[12] In cats, arachidonic acid (an omega-6 fat) is also essential. While omega-3 and -6 fatty acids do not interconvert, they do not compete with each other.[12]

Fatty acids are incorporated in cell membranes where they are stored, oxidized as fuel, or converted to molecules such as hormones and eicosanoids (prostaglandins, thromboxanes, and leukotrienes).[12,65] The eicosanoids, especially the prostaglandins (PGs), are of the most interest when discussing renal disease. There are three classes of PGs, each derived from different fatty acids. The PG-1 series are anti-inflammatory and are derived from GLA, while the PG-2 series are derived from arachidonic acid and are pro-inflammatory. Like the PG-1 series, the PG-3 series is anti-inflammatory and can be derived from omega-3 fatty acids. This involves conversion of ALA to EPA and DHA. While dogs are capable of this conversion, cats lack the necessary desaturase enzymes so must ingest EPA directly (salmon, tuna, mackerel, herring). Cats are also unable to convert LA to GLA so supplementation with pre-formed GLA (borage, black currant, or evening primrose oils) is necessary.

While all three classes of PGs are essential for health, decreasing the ratio of omega-6 to omega-3 decreases pro-inflammatory mediators. Research indicates fish, fish

oils, flaxseed, and flaxseed oil benefit animals with renal disease, in part because these foods promote anti-inflammatory mediators. Several mouse studies illustrate this point. A palatable flaxseed lignan precursor was observed to delay onset of proteinuria and preserve GFR in the mouse lupus model.[66] Flax was found to be renoprotective in a mouse model for lupus nephritis; and EPA and DHA improved renal disease.[67] A 10-percent rat flaxseed diet was shown to ameliorate renal pathology in Han:SPRD-cy rats predisposed to polycystic kidney disease.[31] Protein restriction and fish oil supplementation preserved renal structure and function in the mouse.[68] Fish oil supplements in the preservation of glomerular filtration were reviewed, implying fish may possess an anti-inflammatory action in progressive kidney injury.[69] Increased longevity was seen in lupus-prone mice when their diet was supplemented with fish oil.[70]

Research in dogs has also shown the renoprotective benefits of omega-3 fatty acids. The benefit of menhaden fish oil supplementation for dogs with experimentally-induced kidney disease has been demonstrated. The benefits included lower serum cholesterol and lower glomerular capillary pressure than were found in dogs supplemented with omega-6 fatty acids.[28]

The mechanism of action of fish and flaxseed oils for protection of kidney function has been investigated. The benefits are thought to be due to their anti-inflammatory effects.[70] The rapid incorporation of omega-3 oils in cell membranes has been observed. This incorporation promotes changes in membrane fluidity, and in ligand- and receptor-binding.[65] Increased EPA in the organs, muscles, and plasma of pigs fed whole flaxseed was measured, and demonstrated the whole body benefit of fatty acid supplementation.[71] Positive changes in blood pressure, urine proteins, glomerular filtration rate, plasma lipids, and saturated and unsaturated fatty acid levels were also observed.[32]

Because fatty acids, especially fish oils, oxidize readily, recommendations may be made to couple fat-soluble antioxidant supplements, such as vitamin E, with fish or flaxseed supplements. Recommendations may also be made with regard to using wild rather than farmed fish, and wild rather than cultivated crops when available, because modern agricultural and aquacultural techniques have lowered omega-3 fatty acid levels in both foods and farmed fish.[27]

Quercetin in Renal Disease

Quercetin, a polyphenolic bioflavonoid widely distributed in fruits and vegetables, has received attention due to its strong antioxidant and renoprotective properties.[72,73] The cranberry is among the many fruits, vegetables, and other plants containing quercetin.[74] When its activity was compared to the free-radical scavenging ability of other antioxidants, quercetin possessed 10 times the antioxidant capacity of vitamin C.[75] Quercetin has shown a marked ability to inhibit mitosis and apoptosis in glomerular cells, both *in vivo* and *in vitro*.[76] In rats, serum creatinine levels were decreased, and inflammatory sequelae and ischemia-reperfusion injury reduced when the animals underwent pretreatment with quercetin prior to induced, nonimmune renal injury.[77] Quercetin and other bioflavonoids, such as curcumin,[34,77] may hold promise for use in treatment of renal disease in small animals.

Botanicals For Prevention of Acute Renal Failure

A study was conducted on the two Chinese botanicals, *Astragalus membranaceus* and *Salvia miltiorrhiza*, for the prevention of experimentally-induced acute renal failure in rabbits. One group received Astragalus, the second received Salvia, and the third a combination of the two herbs, while the fourth group served as a control, receiving saline. Both the Astragalus and the Astragalus/Salvia groups

experienced less damaged and more prompt return of kidney function than either the Salvia-alone or control groups.[78]

Additional Dietary Considerations

While chronic renal failure is common in dogs and cats of all stages of life, this disease becomes more prevalent as animals age.[79] Older dogs showing signs of renal insufficiency may benefit from a moderate-protein, low-phosphorus diet. Clinical studies of such a diet (20-31% protein, 0.4% phosphorus) have elicited beneficial responses, such as less proteinuria, less renal impairment, and lower mortality.[80,81] Elevated plasma renin activity has also been found in obese dogs under experimental conditions (2.3-fold greater than lean animals); a high-fat diet (of primarily beef fat) caused increased arterial pressure, glomerular hyperfiltration, and structural changes in the kidney, indicating that severe glomerular injury may be associated with prolonged obesity.[82]

Conclusion

Research supports the use of a variety of nutrient and botanical treatments and dietary modifications for small animals diagnosed with chronic renal failure. Several compounds have been shown to act as antioxidants, immune modulators, antimicrobials, anti-emetics, and appetite stimulants, and may benefit small animals diagnosed with renal failure. While omega-3 fatty acids may be among the best understood in relation to their renoprotective activities, many other supplements may be equally beneficial and should also be considered as part of a treatment protocol for renal pathology. Use of nutrients and botanicals does not exclude the use of allopathic methods for treating renal disease when indicated.

References

1. Spake A. Natural hazards. *US News & World Report* 2001;130:42-49.

2. McCluggage D. Introduction to clinical nutrition: healing with nutrition. *Proceedings of the 1998 American Holistic Veterinary Medical Association Annual Conference*: 18-29.

3. Brown SA, Finco DR, Bartges JW, et al. Interventional nutrition for renal disease. *Clin Tech Small Anim Pract* 1998;13:217-223.

4. American Veterinary Medical Association. Guidelines for alternative and complementary veterinary medicine. *AVMA Directory and Resource Manual*, 48th ed. Schaumbrg, IL: American Veterinary Medical Association; 1999.

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

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

7. Burkholder WJ. Dietary considerations for dogs and cats with renal disease. *J Am Vet Med Assoc* 2000;216:1730-1734.

8. Schwartz C. Chinese herbal medicine in small animal practice. In: Schoen AM, Wynn SG, eds. *Complementary and Alternative Veterinary Medicine, Principles and Practice*. St. Louis, MO: Mosby; 1998:437-450.

9. Kendall R. Therapeutic nutrition. In: Schoen AM, Wynn SG, eds. *Complementary and Alternative Veterinary Medicine, Principles and Practice*. St. Louis, MO: Mosby; 1998:53-72.

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

11. Makoff R. Vitamin replacement therapy in renal failure patients. *Miner Electrolyte Metab* 1999;25:349-351.

12. Hall JA. Potential adverse effects of long-term consumption of (n-3) fatty acids. *Compend Contin Educ Practicing Vet* 1996;18:879-895.

13. Feeney DA, Johnston GR. The kidneys and ureters. In: Thrall Donald, ed. *Textbook of Veterinary Diagnostic Radiology*, 2nd Ed. Philadelphia, PA: WB Saunders; 1994:442-258.

14. Hole JW. *Essentials of Human Anatomy & Physiology,* 4th Ed. Dubuque, IA. WC Brown Publishers; 1992:448-467.

15. Thibodeau GA. *Anatomy and Physiology*. St. Louis, MO. Mosby; 1999:822-846.

16. Neel JA, Grindem CB. Understanding and evaluating renal function. *Vet Med* 2000;July:555-566.

17. Tilley L. *The 5-minute Veterinary Consult: Canine and Feline*, 2nd ed. Philadelphia, PA: Lippincott, Williams & Watkins; 2000.

18. Duncan JL, Prasse KW, Mahaffey EA. *Veterinary Laboratory Medicine, Clinical Pathology*, 3rd ed. Ames, IA: Iowa State University Press; 1994.

19. Noninfectious diseases of the urinary system of small animals: 835-848; Basic concepts in pharmacotherapeutics, renal disease: 1466-1467; Renal secondary hyperparathyroidism: 473-474. In: Fraser CM, ed. *Merck Veterinary Manual*, 6th ed. Rahway, NJ: Merck & Co; 1986.

20. Donadio JV Jr, Grande JP, Bergstralh EJ, et al. The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. *J Am Soc Nephrol* 1999;10:1772-1777.

21. Otani H, Mune M, Yukawa S, et al. Vitamin E treatment of experimental glomerular disease in rats. *Kidney Int Suppl* 1999;71:S66-S69.

22. Wulff-Tilford ML, Tilford GL. *All You Ever Wanted to Know About Herbs for Pets*. Irvine, CA: Bowtie Press; 1999.

23. Xie H. Veterinary herbal therapy. In: Schoen AM, Wynn SG, eds. *Complementary and Alternative Veterinary Medicine, Principles and Practice*. St. Louis, MO: Mosby; 1998:405-435.

24. Harada M, Hirayama Y, Yamazaki R. Pharmacological studies on Chinese cinnamon. V. Catecholamine releasing effect on cinnamaldehyde in dogs. *J Pharmacobiodyn* 1982;5:539-546.

25. Murthy R, Murthy M. Omega-3 fatty acids as anti-inflammatory agents: a classical group of nutraceuticals. *J Nutraceuticals Funct Med Foods* 1999:2:53-72.

26. Bauer JE, Dunbar BL, Bigley KE. Dietary flaxseed in dogs results in differential transport and metabolism of (n-3) polyunsaturated fatty acids. *J Nutr* 1998;128:2641S-2644S.

27. Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr* 1999;70:560S-569S.

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

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

30. Wander RC, Hall JA, Gradin JL, et al. The ratio of dietary (n-6) to (n-3) fatty acids influences immune system function, eicosanoid metabolism, lipid peroxidation and vitamin E status in aged dogs. *J Nutr* 1997;127:1198-1205.

31. Ogborn MR, Nitschmann E, Weiler H, et al. Flaxseed ameliorates interstitial nephritis in rat polycystic kidney disease. *Kidney Int* 1999;55:417-423.

32. Ingram AJ, Parbtani A, Clark WF, et al. Effects of flaxseed and flax oil diets in a rat-5/6 renal ablation model. *Am J Kidney Dis* 1995;25:320-329.

33. Ammon HP, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol* 1993;38:113-119.

34. No authors listed. Monograph: Boswellia serrata. *Altern Med Rev* 1998;3:306-307.

35. Liu F, Ng TB. Antioxidative and free radical scavenging activities of selected medicinal herbs. *Life Sci* 2000;66:725-735.

36. Duke JA, duCellier J, Beckstrom-Sternberg S. Western herbal medicine: traditional materia medica. In: Schoen AM, Wynn SG, eds. *Complementary and Alternative Veterinary Medicine, Principles and Practice*. St. Louis, MO: Mosby; 1998:299-336.

37. Hobbs C. *Medicinal Mushrooms, An Exploration of Tradition, Healing & Culture*, 2nd ed. Santa Cruz, CA: Botanica Press; 1995.

38. Reinhard T. *Vitamin Sourcebook*. Los Angeles, CA: Lowell House; 1998.

39. Chang R. Functional properties of edible mushrooms. *Nutr Rev* 1996;54:S91-S93.

40. deGuzman E. Western herbal medicine: clinical applications. In: Schoen AM, Wynn SG, eds. *Complementary and Alternative Veterinary Medicine, Principles and Practice*. St. Louis, MO: Mosby; 1998:337-378.

41. Schwartz C. *Four Paws Five Directions, A Guide to Chinese Medicine for Cats and Dogs*. Berkeley, CA: Celestial Arts; 1996:290-319.

42. Taillon C, Andreason A.Veterinary nutraceutical medicine. *Can Vet J* 2000;41:231-234.

43. Martin N, Bardisa L, Pantoja C, et al. Experimental cardiovascular depressant effects of garlic (*Allium sativum*) dialysate. *J Ethnopharmacol* 1992;37:145-149.

44. Tilford GL. Western herbs in clinical veterinary practice. In: Proceedings of the 1998 American Holistic Veterinary Medical Association Annual Conference: 13-35.

45. Bouic PJ, Lamprecht JH. Plant sterols and sterolins: a review of their immune-modulating properties. *Altern Med Rev* 1999;4:170-177.

46. Pierce A. *American Pharmaceutical Association Practical Guide to Natural Medicine*. New York, NY: William Morrow and Co.; 1999.

47. Durak I, Karabacak HI, Buyukkocak S, et al. Impaired antioxidant defense system in the kidney tissues from rabbits treated with cyclosporine. Protective effects of vitamins E and C. *Nephron* 1998;78:207-211.

48. Kavutcu M, Canbolat O, Ozturk S, et al. Reduced enzymatic antioxidant defense mechanism in kidney tissues from gentamicin-treated guinea pigs: effects of vitamins E and C. *Nephron* 1996;72:269-274.

49. Randall SR, Adams LG, White MR, DeNicola DB. Nephrotoxicity of amphotericin B administered to dogs in a fat emulsion versus five percent dextrose solution. *Am J Vet Res* 1996;57:1054-1058.

50. Benet LZ. Pharmacokinetics: absorption, distribution & elimination. In: Katzung BG, ed. *Basic & Clinical Pharmacology*, 5th ed. Norwalk, CT: Appleton & Lange; 1992:35-48.

51. Donadio JV Jr. Omega-3 polyunsaturated fatty acids: a potential new treatment of immune renal disease. *Mayo Clin Proc* 1991;66:1018-1028.

52. Pedraza-Chaverri J, Maldonado PD, Medina-Campos ON, et al. Garlic ameliorates gentamicin nephrotoxicity: relation to antioxidant enzymes. *Free Radic Biol Med* 2000;29:602-611.

53. No authors listed. Berberine. *Altern Med Rev* 2000;5:175-177.

54. Mayell M. Maitake extracts and their therapeutic potential. *Altern Med Rev* 2001;6:48-60.

55. Erasmus U. *Fats That Heal, Fats That Kill*, 2nd ed. Burnaby, BC: Alive Publishing; 1993.

56. Bagchi D, Bagchi M, Stohs SJ, et al. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. *Toxicology* 2000;148:187-197.

57. Thamilselvan S, Byer KJ, Hackett RL, Khan SR. Free radical scavengers, catalase and super oxide dismutase provide protection from oxalate-associated injury to LLC-PK1 and MDCK cells. *J Urol* 2000;164:224-229.

58. DiBartola SP, Buffington CA, Chew DJ, et al. Development of chronic renal disease in cats fed a commercial diet. *J Am Vet Med Assoc* 1993;202:744-751.

59. Wunderlich W. Aspects of the influence of magnesium ions on the formation of calcium oxalate. *Urol Res* 1981;9:157-161.

60. Pak CY, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med* 1986;104:33-37.

61. Garrison R, Somer E. *The Nutrition Desk Reference*. New Canaan, CT: Keats Publishing; 1995.

62. Murthy MS, Farooqui S, Talwar HS, et al. Effect of pyridoxine supplementation on recurrent stone formers. *Int J Clin Pharmacol Ther Toxicol* 1982;20:434-437.

63. Goldstein M. *The Nature of Animal Healing*. New York, NY: Alfred A. Knopf; 1999.

64. Simopoulos AP, Kifer RR, Martin RE, eds. *Health Effects of Polyunsaturated Fatty Acids in Seafoods*. Orlando, FL: Academic Press; 1986.

65. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. *Nutrition* 1998;14:627-633.

66. Clark WF, Muir AD, Westcott ND, Parbtani A. A novel treatment for lupus nephritis: lignan precursor derived from flax. *Lupus* 2000;9:429-436.

67. Robinson DR, Xu LL, Tateno S, et al. Suppression of autoimmune disease by dietary n-3 fatty acids. *J Lipid Res* 1993;34:1435-1444.

68. Clark WF, Parbtani A, Philbrick DJ, et al. Dietary protein restriction versus fish oil supplementation in the chronic remnant nephron model. *Clin Nephrol* 1993;39:295-304.

69. Schreiner GF, Klahr S. Diet and kidney disease: the role of dietary fatty acids. *Proc Soc Exp Biol Med* 1991;197:1-11.

70. Fernandes G, Chandrasekar B, Luan X, Troyer DA. Modulation of antioxidant enzymes and programmed cell death by n-3 fatty acids. *Lipids* 1996;31:S91-S96.

71. Matthews KR, Homer DB, Thies F, Calder PC. Effect of whole linseed (*Linum usitatissimum*) in the diet of finishing pigs on growth performance and on the quality and fatty acid composition of various tissues. *Br J Nutr* 2000;83:637-643.

72. Yokozawa T, Dong E, Kawai Y, et al. Protective effects of some flavonoids on the renal cellular membrane. *Exp Toxicol Pathol* 1999;51:9-14.

73. Kuhlmann MK, Horsch E, Burkhardt G, et al. Reduction of cisplatin toxicity in cultured renal tubular cells by the bioflavonoid quercetin. *Arch Toxicol* 1998;72:536-540.

74. Chen H, Zuo Y, Deng Y. Separation and determination of flavonoids and other phenolic compounds in cranberry juice by high-performance liquid chromatography. *J Chromatogr A* 2001;913:387-395.

75. Naguib YM. A fluorometric method for measurement of oxygen radical-scavenging activity of water-soluble antioxidants. *Anal Biochem* 2000;284:93-98.

76. Ishikawa Y, Kitamura M. Bioflavonoid quercetin inhibits mitosis and apoptosis of glomerular cells *in vitro* and *in vivo*. *Biochem Biophys Res Commun* 2000;279:629-634.

77. Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. *Transplantation* 1998;66:147-152.

78. Hu L, Yu T, Jia Z. Experimental study of the protective effects of astragalus and salvia miltiorrhiza bunge on glycerol induced acute renal failure in rabbits. *Zhonghua Wai Ke Za Zhi* 1996;34:311-314. [Article in Chinese]

79. Rubin SI. Chronic renal failure and its management and nephrolithiasis. *Vet Clin North Am Small Amin Pract* 1997;27:1331-1354.

80. Kronfeld DS. Dietary management of renal senescence and failure in dogs. *Aust Ver J* 1994;71:328-331.

81. Leibetseder JL, Neufeld KW. Effects of medium protein diets in dogs with chronic renal failure. *J Nutr* 1991;121:S145-S149.

82. Henegar JR, Bigler SA, Henegar LK, et al. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* 2001;12:1211-1217.