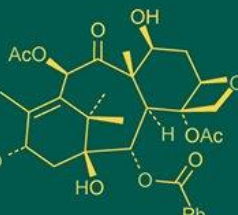
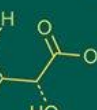
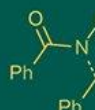


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Chronic kidney disease (CKD) in dog: A comprehensive review

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Abstract

Chronic Kidney Disease (CKD) is a prevalent and often progressive condition in dogs, with significant implications for their overall health and well-being. This review article aims to provide a comprehensive overview of CKD in dogs, encompassing its etiology, pathophysiology, clinical presentation, diagnostic approaches, staging, treatment options, and prognosis. The understanding of CKD in dogs has evolved over the years with advancements in diagnostics and therapeutic strategies, leading to improved management and outcomes for affected canines. This review will synthesize current knowledge on CKD in dogs to aid veterinarians in early detection, proper staging, and individualized management of canine patients with this debilitating condition.

Keywords: Chronic Kidney Disease (CKD), DOG, biomarkers

Introduction

Chronic Kidney Disease (CKD) is a progressive disorder of the kidney that is marked by functional and structural abnormalities due to a broad range of etiologies. The most frequent causes of chronic kidney disease globally are diabetes and hypertension (Ezekiel *et al.*, 2019) [23]. Indignation of kidney damage is estimated by glomerular filtration rate [GFR] (<60 ml/min/1.73 m²), albuminuria, hematuria, and deformities shown during ultrasonography that have been present for at least three months (Webster *et al.*, 2017) [85]. Around 10% of individuals globally suffer from CKD, which causes 1.2 million deaths per year. The most frequent kidney condition in dogs is CKD (Polzin *et al.*, 2005) [63]. Aging and particular breeds with hereditary renal disease are risk factors (Macdougall *et al.*, 1986; Sosnar *et al.*, 2003) [46, 78]. This condition has a significant and growing global impact (Bikbov *et al.*, 2020) [7].

Long-term disease progression may lead to end-stage kidney disease (ESKD), which would be associated with poor patient outcomes and the requirement for dialysis or kidney transplantation to improve kidney function. Rat models of human CKD may improve knowledge of the pathophysiological processes underlying the disease and enable the testing of more effective treatment alternatives. Up until now, there has been no specific drug to treat CKD patients to improve kidney function. So, the development of new therapies, drugs, and natural dietary supplements is highly required to decline the effects of CKD and slow or reverse the worsening of kidney function (Wang *et al.*, 2022) [83].

Stages of Chronic Kidney Disease

Chronic kidney disease is a progressive and an irreversible loss of kidney structure and function. When approximately one-third of the nephrons are destroyed, clinical symptoms arise, and azotemia is detected when 75% of renal function is affected (McGrotty, 2008) [49]. Loss of appetite, vomiting, weight loss, polydipsia, and polyuria are all symptoms of impaired kidney function (Grauer, 2005; Scottline, 2012) [29].

Chronic kidney disease is classified into four stages *i.e.* serum creatinine, proteinuria, symmetric dimethylarginine (SDMA), and blood pressure by The International Renal Interest Society (IRIS). It assists in the diagnosis, therapy, and prognosis of diseases.

Table 1: Stages of chronic kidney disease: On the basis of serum creatinine concentration

Stages of Chronic Kidney Disease	Indignation	Creatinine Concentration (mg/dl) in dogs
Stage 1	No azotaemia and Normal creatinine	< 1.4
Stage 2	Mild azotaemia with Normal/ mildly elevated creatinine	1.4 - 2
Stage 3	Moderate azotaemia	2.1 - 5
Stage 4	Severe azotaemia with high creatinine	> 5

Table 2: Substages of chronic kidney disease: Based on UPC ratio (Urine Protein-Creatinine ratio)

Proteinuric (P)	> 0.5
Non-Proteinuric (NP)	< 0.20
Borderline Proteinuric (BP)	0.2 - 0.5

Table 3: Substages of chronic kidney disease: On the basis of blood pressure & risk to target organ

Sub-staging of Blood pressure	Systolic Pressure (mm of Hg)	Diastolic Pressure (mm of Hg)	Indignation	Risk to Target Organ
Arterial Pressure Stage 0	< 150	< 95	Normotensive	Minimal
Arterial Pressure Stage I	150 - 160	95-100	Borderline Hypertensive	Low
Arterial Pressure Stage II	160 - 179	100-119	Hypertensive	Moderate
Arterial Pressure Stage III	≥ 180	≥ 120	Severe Hypertensive	Severe

Causes of chronic kidney disease: Multiple factors have involved in pathogenesis of CKD, including polycystic kidney disease, calcauli, chronic toxicity, neoplasms, chronic glomerulonephritis, infections, inflammation and ischemia, amyloidosis, chronic pyelonephritis, hypercalcemic nephropathy, primary systemic hypertension etc (O'Neill *et al.*, 2013; Rudinsky *et al.*, 2018) [54, 73].

Diagnosis of chronic kidney disease: CKD is typically found inadvertently or as a result of routine screening of blood biochemical profile and urine testing. Mostly patients with kidney disease have symptoms like hematuria, albuminuria (foamy urine), nocturia, and frequent urination with flank pain. Patients with severe CKD may have tiredness, nausea, vomiting, anorexia, unexpected decrease weight, changes in their mental status, pruritus, dyspnea, and some time peripheral edema also observed (Skorecki *et al.*, 2016) [77].

Other Approach Detect the CKD

Laboratory examination: Urinalysis, Serum biochemistry, CBC, Doppler ultrasound, Biomarkers (Vinodhini *et al.*, 2021; Dunaevich *et al.*, 2020 and Wang *et al.*, 2019) [20, 82, 84].

Biomarkers

For a therapeutic intervention biomarker traits are tested and assessed as an indicator of normal physio-pathogenic processes, and pharmacological action of drugs. An ideal biomarker would detect the location and severity of damage while also correlating with renal function (Wang *et al.*, 2019) [84].

Markers of GFR

Creatinine: Creatinine is an endogenous byproduct of muscle metabolism (Peake and Whiting, 2006) [56]. The renal tubules are unable to absorb it; the glomerulus filters it. It serves as a marker for renal function. It is not an indicator of early renal insufficiency because about 75% of working nephrons disappear before creatinine goes over the reference level (Lefebvre, 2011) [44].

Cystatin C: Cystatin C is a cysteine proteinase inhibitor that produced by the nucleated cells and discharged into the

bloodstream (Monti *et al.*, 2012) [51]. The glomerulus filters it, and it is absorbed and catabolized in the proximal tubule cells, never entering the circulation again. It is the most effective biomarker for early-stage CKD detection. In early CKD dogs, CysC levels demonstrated higher sensitivity and specificity than other biomarkers (creatinine or SDMA) (Kim *et al.*, 2020) [41].

Urinary immunoglobulin G (uIgG): In CKD, elevated levels are related to glomerular damage. Higher glomerular permeability causes higher uIgG levels (Haraldsson, 2008) [32].

Symmetric dimethylarginine (SDMA): SDMA is produced by intracellular protein breakdown and released into the bloodstream. It is a precise and sensitive biomarker for measuring GFR. It is excreted by the kidney and increases in early CKD with a 40% loss in GFR, compared to a 75% decline required to raise creatinine levels (Relford, 2016) [70].

Markers of Tubular Dysfunction

Retinol-Binding Protein (RBP): It is generated in the liver, filtered by the nephrons, and almost reabsorbed in the proximal convoluted tubular cells following each of these processes (Raila *et al.*, 2010) [66]. Damage to the tubulointerstitial tissues that prevents reabsorption was observed in the urine (D'amico and Bazzi, 2003) [17]. It is important for monitoring CKD, especially in the latter stages of the disease.

α_1 -Microglobulin and β_2 -microglobulin: It is a valuable marker for proximal convoluted tubular dysfunction (Penders and Delanghe, 2004) [57]. Damage to the proximal tubules causes reduced reabsorption and is detectable in the urine.

N-acetyl- β -D-Glucosaminidase (NAG): It is an X-linked hereditary nephropathy in dogs (Nabiity *et al.*, 2012).

Neutrophil Gelatinase-Associated Lipocalin (NGAL): The renal proximal convoluted tubule, the Loop of Henle (LOH), and the collecting ducts contain epithelial cells containing the iron-carrying protein referred to as lipocalin (Schmidtott *et al.*, 2006) [75]. It's easy to find in urine, plasma, or serum samples. Damage to the tubules promotes higher release.

The Tamm Horsfall Protein (THP) (uromodulin): It is a glycoprotein produced by the cells lining the Distal Convoluted Tubules (DCT) and the thick ascending limb of LOH. (Raila *et al.*, 2003)^[67]. It is helpful to determine distal tubular damage and reduced THP levels in dogs with CKD. The average value in healthy dogs is 0.26 mg/dl.

Kidney Injury Molecule-1 (KIM-1): It is a transmembrane tubular protein that increased after kidney injury and appears in the urine after ischemic damage. The KIM-1 can be detected by the urine dipstick test.

Fibroblast Growth Factor-23: It is a phosphatonin that osteocytes produce in response to elevated levels of phosphorus and PTH (Harjes *et al.*, 2017)^[33]. Early on in canine CKD, FGF-23 concentrations rise. The concentrations rise in proportion to the severity.

Proteinuria: Urinary Albumin Concentration (UPC) or dipstick tests serve to quantify proteinuria (Lees *et al.*, 2005)^[43]. According to Yalcin and Cetin (2004)^[87], the kind of proteinuria can reveal the severity and origin (glomerular, tubular, or both) of nephron damage. Glomerular injury increases protein filtration. Protein leakage from tubular epithelial cells and reduced protein reabsorption are both possible effects of tubular injury (D'Amico and Bazzi, 2003)^[17]. Tubular injury causes modest proteinuria, whereas glomerular damage frequently causes significant proteinuria. According to Lees *et al.* (2005)^[43], UPC levels below 2 are indicative of tubular proteinuria, while levels above 2 are indicative of glomerular proteinuria. Microalbuminuria screening can identify CKD in its early stages.

Ultrasound: According to Monteiro and Froes (2009)^[50], ultrasonography is the best imaging diagnostic for detecting renal illness. (Nyland *et al.*, 2005; Hanamura *et al.*, 2012 and Novellas *et al.*, 2007)^[31, 52, 53]. It offers information about the kidney's size, shape, parenchymal composition, and other abnormal internal structures such as stones, cysts, tumors, etc.

Contrast-Enhanced Ultrasonography (CEUS): Makes it possible to evaluate tissue perfusion (Dong *et al.*, 2013)^[19]. Contrast media was injected intravenously @ 0.01 ml/kg, and the ensuing images were recorded for three minutes using harmonic imaging software.

ARFI (Acoustic Radiation Force Impulse) Elastography: The cortical and medullary regions' shear-wave velocities and the tissue deformation were also measured. Elastography is a technique that assesses the stiffness of tissues (Holdsworth *et al.*, 2014)^[34]. "Virtual Touch Tissue Quantification" software was used to create gray tissue elastograms for ARFI elastography. The stiffness of the kidneys determined how they were categorized: (i) softer or deformable tissues are represented by lighter gray tones; (ii) Dark gray tissues are more stiff and non-deformable. Both CEUS and ARFI elastography have been shown to be effective diagnostic methods for CKD (Cruz-Da *et al.*, 2021). Increased cortical echogenicity is a sign of CKD in its early stages. Reduced renal size, inappropriate lines, and loss of corticomedullary distinction are signs of CKD in its later stages.

Doppler ultrasound: Increases: evaluation of renal perfusion (reduced in CKD). Color Doppler imaging can be utilized to show intrarenal artery flow in dogs (Saraiva, 2010)^[74]. According to Baltazar *et al.* (2016)^[5], pulsed-wave Doppler ultrasound is more effective at measuring renal parenchymal perfusion. In a normal color Doppler image, the intra-renal vessels are clearly visible. In CKD,

color Doppler imaging of the intra-renal arteries hardly ever shows hypovascularization (Novellas *et al.*, 2007)^[52]. Other methods, i.e., radiology, magnetic resonance imaging, renal biopsy, renal scintigraphy, and renal clearance tests, are helpful in CKD diagnosis.

Other Risk Factors for CKD

Numerous other factors like inadequate nutrition and dehydration heighten the risk of CKD (Kazancioglu, 2013 and Banerjee *et al.*, 2017)^[6, 40]. African Americans and Pacific Islanders are substantially more probable to develop end-stage kidney disease (ESKD) than white people are (USRDS Annual Data Report, 2018). Hypertension, diabetes, and obesity are becoming more common, which contributes to this (Grams *et al.*, 2016)^[28].

However, genetic factors probably also play a part. To be more specific, it has been shown that recessive risk alleles in the apolipoprotein L1 (APOL1) gene contribute to an increased likelihood of developing kidney disease (Genovese *et al.*, 2010 and Tzur *et al.*, 2010)^[27, 80]. Compared to people with 0 or 1 risk allele, those with 2 risk alleles had a 2-fold more risk for developing CKD and a 29-fold more risk of developing certain conditions related to chronic kidney disease, like focal HIV-associated nephropathy and segmental glomerulosclerosis. These conditions affect about 13% of African Americans (Kopp *et al.*, 2011; Foster *et al.*, 2013; Parsa *et al.*, 2013; Grams *et al.*, 2016 and Peralta *et al.*, 2015)^[24, 28, 42, 55, 58].

The sickle cell trait, which is seen in around 8% of individuals of African American descent, has been linked to a heightened susceptibility to renal disease. Compared to people without sickle cell anemia trait, people have sickle cell anemia trait are 1.8-time more chance of getting chronic kidney disease (CKD) with reduced glomerular filtration rate (3 mL/min/1.73 m²), and a 1.9-time higher chance of getting albuminuria. African and Americans peoples have about 8% more risk of kidney disease due to the sickle cell anemia trait (Naik *et al.*, 2014).

Management of Chronic Kidney Disease (CKD)

1. Managing Gastrointestinal Signs of Uremia

Almost all parts of the Gastrointestinal (GI) tract can exhibit abnormalities in dogs and cats with uremia. parotiditis, stomatitis, Uremic breath, oral ulceration, nausea, vomiting, anorexia, intestinal perforation with oral or gastrointestinal hemorrhage, constipation/diarrhea, and intestinal obstruction are some of the gastrointestinal side effects of uremia. Abnormalities may be mild or severe. Utilizing H₂ blockers, like Ranitidine and Famotidine, to reduce gastric acidity is a common method of treating anorexia, nausea, and vomiting. Using antiemetics i.e. ondansetron hydrochloride, a neurokinin (NK-1) receptor antagonist such as aprepitant, rolapitant, and casopitant, and a substance such as sucralfate to protect the mucosa (Israel *et al.*, 1986; Perkovic *et al.*, 2002)^[38, 59].

2. Managing Metabolic Acidosis

Alkalinization treatment is advised for canines and felines with CKD stages 1 to 4 when the pH of blood and bicarbonate concentration falls below the normal range. Acidosis can be treated by providing buffers diet. When nutrition alone is insufficient, administering an alkalinizing salt, such as potassium citrate at a dose of 40-60 mg/kg orally twice or thrice a day or sodium bicarbonate at a dose

of 8-12 mg/kg orally twice or thrice a day, has the benefit of treating both hypokalemia and acidosis with a single medication. Blood gas analysis should be done 10-14 days after starting alkalization therapy to evaluate response, and dosage should be changed until normalization (Wesson and Simoni, 2009; De-Brito-Ashurst, 2009) [18, 86].

3. Managing Proteinuria

In canines and felines, proteinuria is linked to the advancement of CKD (Jacob *et al.*, 2005; Syme *et al.*, 2006) [39, 79]. For canines and felines with CKD stage-2, stage-3, and stage-4 with urine protein-creatinine ratios over 0.5 and 0.4, respectively, as well as for canines and felines with CKD stage 1 and protein-creatinine ratios higher than 2.0, therapy intended to minimize proteinuria is advised to achieve urine protein-creatinine ratio in the normal range by the treatment with a renal diet and give an ACE-I (Lees *et al.*, 2005) [43]. Starting with oral dose 0.25-0.5 mg/kg every 12 to 24 hours of (ACEIs) benazepril and enalapril in canines and felines with CKD (Plumb, 2008) [60]. Enalapril @ 2.0 mg/kg/d has been shown to slow the progression of CKD in dogs (Grodecki *et al.*, 1997) [30]. Serum potassium levels should be carefully examined before increases the dosage of ACE-I because hyperkalemia is a major side

effect of ACE-I, because it is primarily excreted by hepatic rather than renal means, benazepril has traditionally been favored over enalapril. Check the serum creatinine levels before and one to two weeks after starting treatment since ACE-I therapy can occasionally cause a noticeable deterioration in renal function.

4. Managing Hypertension

In order to treat canine hypertension, Angiotensin Converting Enzyme Inhibitors (ACEi) are typically the first medication of choice (Brown SA and Henik RA, 1998; Brown, S.A. and Henik, 2000) [11, 12]. These medications reduce blood pressure in three different ways by inhibiting conversion of angiotensin I into angiotensin II so that reduce production of angiotensin II, a potent vasoconstrictor, causes vasodilatation and lowers blood pressure (Adams, 2001; Ganong, 2001) [1, 2, 26]. Second, angiotensin II directly encourages Na⁺ absorption in the kidney's proximal convoluted tubule (Adams, 2001; Ganong, 2001) [1, 2, 26]. This results in an expansion of the intravascular volume and a corresponding rise in blood pressure. Last but not least, angiotensin II induces aldosterone release, which additionally encourages renal salt resorption (Adams, 2001; Ganong, 2001) [1, 2, 26].

Table 4: Frequently prescribed antihypertensive drugs and their doses (Acierno, M.J. and Labato, M.A. 2004)

Class	Drugs	Canine Dose
ACE inhibitor	Enalapril	0.5-1.0 mg/kg PO q12-24h
	Benazepril	0.25-0.5 mg/kg PO q12-24h
Ca ²⁺ Channel blocker	Amlodipine	0.05-0.1 mg/kg PO q24h
Beta blocker	Atenolol	0.25-1.0 mg/kg PO q12-24h
	Propranolol	2.5-10 mg/dog PO q8-12h
Alpha blocker	Prazosin	0.5-2.0 mg/dog q12h
ARB blocker	Losartan	1mg/kg PO q 24
Aldosterone inhibitor	Spironolactone	1-2 mg/kg PO q 12

Calcium channel blockers, despite dramatically decreasing blood pressure, have been proven in studies on people and diabetic dogs to aggravate renal impairment when administered alone to manage hypertension (Brown and Henik, 2000) [12].

The first choice in treating feline hypertension is now calcium channel blockers, for illustration. One of the most frequently suggested hypertension medications for canine and feline is amlodipine besylate. The afferent glomerular arteriole is selectively dilated by these medications, leading to glomerular hypertension (Brown SA, Henik RA, 2000; Mathur *et al.*, 2004) [12, 48]. In dogs or cats where the initial antihypertensive drug proved to be successful in lowering blood pressure to the desired level, beta-blockers are an appropriate supplementary therapy (Brown and Henik, 1998) [11]. There are B₁-adrenergic receptors in the heart and B₂ adrenergic receptors in lungs. Blocking the B₂ receptors can result in unfavorable bronchial constriction, despite the fact that blocking the B₁ adrenergic receptors will reduce the blood pressure by the decreasing in heart rate (Adams, 2001) [1, 2]. Therefore, only B₁-selective antagonists, such as atenolol, should be used as beta-blockers. The stimulation of blood vessel alpha-receptors results in vasoconstriction, which raises blood pressure and increases systemic vascular resistance (Adams, 2001) [1, 2]. These receptors are specifically blocked by alpha-blockers, which cause vasodilation. A powerful alpha-inhibitor called prazosin has been utilized both as a adjunctive and primary treatment for

canine hypertension. According to recent research, medications that inhibit aldosterone can protect the kidneys, heart, and brain from the adverse effects of hypertension (Epstein, 2001; Hostetter *et al.*, 2003) [21, 36]. In addition to mildly lowering blood pressure, inhibiting aldosterone can also reduce the fibrosis that hypertension induces in particular target organs (Epstein, 2001; Hostetter *et al.*, 2003) [21, 36]. Hypertension Losartan Intervention for Endpoint Reduction (Os *et al.*, 2008).

5. Managing of Hypokalemia & Hyperkalemia

The most effective therapy for hypokalemia is oral supplementation, whereas in case of mild hyperkalemia, a advice for renal diet with the least amount of potassium in it may be beneficial. Oral sodium polystyrene (potassium binders) can limit dietary potassium absorption. In patients that are hyperkalemic and on ACE inhibitors, keep an eye on them and lower the dosage if necessary. Avoid providing potassium supplements to any patients with hyperkalemia (Ramos *et al.*, 2021) [68].

6. Managing of Hyperphosphatemia

Since plasma phosphorus levels and GFR are related in the opposite way, phosphate retention as renal function decreases is an important early sign of renal secondary hyperparathyroidism. When a diet alone is unable to control hyperphosphatemia than phosphate binders are combined with renal diet. These drugs combine with dietary phosphate

to form nonabsorbable complexes in the Gastro Intestinal Tract (GIT). Aluminum hydroxide, Frequently used as a first-line treatment, nonetheless, toxicity in dogs has been recorded when administered in excess of prescribed doses. @ 30-100 mg/kg/d, calcium salts, such as calcium acetate, carbonate, citrate, and carbonate of lanthanum, To create capsules of the proper size, compounding may be necessary. Aluminum hydroxide may also be used with it; the latter's dosage required for reduced the latter's synergistic effects. Sevelamer hydrochloride, 30 mg/kg/d In general, a greater dose of phosphate binder (within the approved dosage range) is needed for successful correction, the more severe the hyperphosphatemia. These medications must be taken with food; if meals or treats rich in phosphate are given without a phosphate binder, their effectiveness is reduced. The goal of treatment should be to follow the IRIS CKD stage recommendations (Rastogi *et al.*, 2021)^[69].

7. Managing of Anemia

The cause of the chronic, progressive, nonregenerative anemia of CKD is a lack of erythropoietin. If CKD patients have new or severe anemia, one should always take GI ulcers causing blood loss into consideration. If overall Packed Cell Volume [PCV] is under 20% and you have moderate to advanced anemia, darbepoietin hormone enhancement is a thing to reflect on. Therefore, it is advised that all patients undergoing erythropoietin therapy take iron supplements. When starting EPO or DPO, at the very least, an intramuscular injection of iron dextran (50-300 mg) should be given. In both dogs and cats, administering r-HuEPO raised RBC and reticulocyte counts, hemoglobin concentration, and Hct. Clinical well-being evaluations, such as hunger, energy, weight growth, alertness, strength, and playfulness, all showed varying degrees of improvement. Inconsistent evidence of negative effects, such as anemia, anti-r-HuEPO antibody development, convulsions, systemic hypertension, and iron insufficiency, was seen in dogs and cats. (Cowgill *et al.*, 1998)^[15]. Once the target PCV is reached, monitor PCV weekly and reduce the frequency of dosage. At the initial administration of darbepoietin medication, some individuals may develop hypertension; hence, blood pressure should be closely monitored. Because human erythropoietin can lead to the development of anti-erythropoietin antibodies that can react with one another and potentially destroy the patient's endogenous erythropoietin, leaving the patient dependent on transfusions, darbepoietin, a synthetic form of erythropoietin, is thought to be less antigenic than human erythropoietin. Consider receiving a blood transfusion if the anemia is severe.

8. Managing of Secondary Hyperparathyroidism

A frequent consequence of Chronic Kidney Disease (CKD), Secondary Hyperparathyroidism (SHPT), is associated with higher mortality (Rodriguez-Ortiz and Rodriguez, 2020; Block *et al.*, 2004; Ganesh *et al.*, 2001; Horl, 2004)^[8, 25, 35, 71]. As chronic renal disease worsens, a complicated disorder called secondary hyperparathyroidism emerges. The retention of phosphorus, as well as the drops in calcium and vitamin D levels, increase the production of parathyroid hormone and the pace at which parathyroid cells divide. As the condition worsens, parathyroid development changes from diffuse to nodular, making the gland less sensitive to being reduced (Rodriguez-Ortiz and Rodriguez, 2020)^[71]. It

is a key component of the mineral and bone pathology associated with chronic renal disease and is crucial to the onset of bone disease and vascular calcification. As a result, maintaining appropriate levels of mineral metabolism parameters is a key component of managing chronic renal disease in an effort to delay or stop the onset of secondary hyperparathyroidism (Rodriguez-Ortiz and Rodriguez, 2020)^[71]. Parathyroid Hormone (PTH) production is stimulated by hyperphosphatemia, hypocalcemia, and a gradual decrease in calcitriol levels, all of which have long been known to contribute to the genesis of SHPT (Llach, F. and Forero, F. V. 2001)^[45].

9. Activated Vitamin-D metabolites

Calcitriol: Treatments with calcitriol assist patients with renal secondary hyperparathyroidism in reducing PTH or preventing its growth. In addition to a slightly calcemic effect, anti-proliferative effects, and genomic effects that reduce PTH production, this is mostly accomplished. It is preferable to monitor blood ionized calcium, serum phosphorus, and PTH concentrations simultaneously when treating CKD patients with calcitriol to demonstrate effective and secure management of renal secondary hyperparathyroidism (Andress, 2006)^[3]. Due to the possibility of soft-tissue mineralization, it shouldn't be given until hyperphosphatemia has been under control. The first dose of calcitriol should be 2.0-2.5 ng/kg every 24 hours. (Polzin, 2011)^[62]. The recommended daily dose of calcitriol is no more than 5.0 ng/kg. Lifelong treatment is necessary to achieve the desired effect of reduced renal mortality (Porsti, 2008; Cheng and Coyne 2007)^[13, 65].

10. Maintaining Hydration

Chronic dehydration, a major CKD consequence that frequently worsens renal function and causes episodes of acute uremia, appears to be especially dangerous for dogs and cats with the disease. Chronic dehydration can increase the risk of AKI as well as anorexia, lethargy, weakness, constipation, and prerenal azotemia. In order to treat and prevent recurrent bouts of dehydration and their clinical implications, dehydrated individuals should be rehydrated either orally or parenterally. Patients experiencing symptoms symptomatic of chronic or recurring dehydration may be evaluated for long-term subcutaneous fluid treatment. (weak evidence supports this recommendation) (Roudebush *et al.*, 2009 and Polzin *et al.*, 2008)^[64, 72]. The main advantages of subcutaneous fluid treatment can include increased activity and hunger, as well as decreased constipation. A balanced electrolyte solution (such as lactated Ringer's solution) is given subcutaneously as needed every 1-3 days for long-term administration.

11. Dialysis

Hemodialysis is a potentially life-saving medical procedure that uses a dialyzer, or artificial kidney, to purify the blood. It utilizes contact between the patient's blood and the extracorporeal dialyzer's semipermeable membrane to remove substances from the bloodstream, including BUN, creatinine, electrolytes, minerals, anions, cations, certain medications, toxins, and extra fluid. It is distinguished from peritoneal dialysis, which employs a patient's peritoneum as the dialysis membrane, by the extracorporeal dialyzer (Bloom and Labato, 2011)^[9].

12. Kidney Transplant

Given that canine patients have greater rates of morbidity and death than human and feline patients, kidney transplantation is having less success in canine patients. (Broaddus, 2006; Aronson, 2016) [4, 10]. Many of the consequences of renal failure can be alleviated with a successful kidney transplant.

Conclusion

This comprehensive review aims to enhance the understanding of chronic kidney disease in dogs, emphasizing the significance of early diagnosis and individualized management. As ongoing research continues to shed light on the pathophysiology and treatment options, veterinarians can implement evidence-based strategies to improve the lives of dogs affected by this challenging condition.

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