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Clinicopathological profile of canine renal disorders

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Abstract
Renal disorders rank the highest among the non infectious health problems in canines. It arises either as a primary renal issue due to damage to renal parenchyma, congenital renal problems as well as secondary renal problem subsequent to infectionsor impairment of other organs like hepatic involvement when the undetoxified toxins damage the kidneys. The spectrum of clinical signs in dogs with renal disorders varies depending on the intensity and duration of the insult like whether it is of acute or chronic in nature. In this review, we shall discuss the various attributes of canine renal disorders like the etiological agents ending in renal disorders, clinicopathological diagnosis and post therapeutic follow up in dogs suffering with renal problems.

Keywords: Kidney diseases, BUN, creatinine, urinalysis, urine protein creatinine ratio, urinary casts

Introduction
Kidney diseases are of serious concern in canine clinical practice apart from the infectious diseases caused by bacteria, viruses, hemoprotozoa and rickettsiales like Ehrlichiosis. They are associated with morbidity and mortality based on the stage in which they are presented. Polzin (2011) [1] reported that kidney diseases are common in dogs and cats and are often associated with poor prognosis when they are presented in later stages.

Etiology of renal disorders
Impairment of kidney function is attributed to multifactorial conditions. The major causes for the significant upsurge in kidney diseases in the recent past is due to improvement in the economic standards and attitude of the clients and subsequent change in the feeding quality of their pets. Pets are treated at par with and as a child especially in urban areas. They are often fed with much more than their metabolic requirements, in the form of treats and nutritional supplements which has led to many cases, of late presented with problems of obesity, fatty liver and kidney related ailments.

In addition to nutritional causes, irrational use of nephrotoxic drugs in therapy also has lead to calcification of kidneys, damage to the renal parenchyma and functional impairment of kidneys. The other causes of renal disorders include - congenital and developmental anomalies; circulatory disturbances like hypertension, ischemia; bleeding and clotting disorders; inflammation of kidneys-glomerulonephritis, pyelonephritis, interstitial nephritis and other components of urinary system; neoplasms of renal system either as a primary tumour or tumours metastatic from other organs like prostate, adrenals, liver etc.,

The major infectious diseases inflicting severe renal impairment in canine include the rat fever-leptospirosis and hemoprotozoan diseases like Trypanosomiasis and Babesiosis (Areshkumar *et al*., 2019) [20]. Canine Ehrlichiosis caused by *Ehrlichia canis* is the frequently encountered rickettsial disease in canine practice which is manifested with drastic reduction in the platelet count. Of late, immune mediated nephritis with variable prognosis is also diagnosed at large due to disturbances in immune regulation like as in Immune Mediated Hemolytic Anemia (IMHA).

Barnett and Cummings (2018) [2] have grouped the causes of renal failure into two major groups as intrinsic and extrinsic; the extrinsic causes of renal failure are cardiovascular disease obesity, diabetes, sepsis and lung and liver failure; the intrinsic factors leading to renal failure are glomerular nephritis, polycystic kidney disease, renal fibrosis, tubular cell death and stones.

Clinical signs

Dogs suffering with renal problems have nonspecific manifestations of illness like inappetance, loss of body weight, lethargy, depression to variation in micturition pattern like oliguria to polyuria. On physical examination, mucous membrane may be pale to blanched depending on the severity of anemia. On examination of the buccal cavity, uremic ulcers and halitosis may be observed. Pain may be evinced on palpation of the sublumbar region. Edema of the hindlimbs may be seen in few cases. Jeong *et al*. (2006) [3] have also reported emaciation, anorexia, depression, hemorrhagic vomiting and diarrhoea for 7-10 days before death in three dogs diagnosed with canine renal failure syndrome.

Diagnosis of renal disorders

Diagnosis of renal disorders is based on the history, clinical signs, physical examination of the animal, by abdominal ultrasonography and by laboratory examination viz. haematology, serum biochemistry, urinalysis etc.

Laboratory diagnosis of renal disorders

In dogs suspected for renal dysfunction, the following samples are collected for laboratory diagnosis: Blood in EDTA vacutainer for Complete Blood Count (CBC); Blood smears for the identification of blood parasites and associated anaemic changes, thrombocytopenia; Serum in clot activator tubes for Biochemical examination; urine samples for the determination of urine specific gravity, protein, presence and type of casts etc.

Complete Blood Count

In the blood sample, Hemoglobin (Hb), RBC count (Red Blood Cell count) and Packed Cell Volume (PCV) are analysed. The normal canine haematological values are Hb: 12-18g%, PCV: 37-55% and RBC: 5.5-8.5 millions/cmm (Duncan and Prasse, 1986) [4]. Animals with blood values falling below these limits are considered as anaemic. Blood smears are screened for the identification of parasites like *Trypanasoma evansi*, *Babesia canis*, *Babesia gibsoni and Ehrlichia canis*. Blood picture changes like hypochromasia and thrombocytopenia are critically looked for in the smear. In renal disorders due to hemoprotozoan infections thrombocytopenia is a common finding.

Serum Biochemistry

Serum biochemistry is performed to estimate the parameters like Blood urea nitrogen **(**BUN), creatinine and phosphorus along with other serum electrolytes like calcium, sodium and chloride for identifying renal involvement and assessing the degree of renal damage. The serum biochemical values are compared with the canine reference values (Boyd, 1984) [5].

Blood Urea Nitrogen (BUN)

The normal value of BUN in canine is 8.8-26 mg /dl. It is elevated in renal disorders due to reduction of glomerular filtration rate due to the extensive damage to the kidney parenchyma and in impaired blood flow to the kidneys due to hypertension and diabetes etc. BUN may also be elevated due to non renal causes, pre and post renal like high protein diet, dehydration, haemorrhage in the gastrointestinal tract and obstruction in the urinary tract due to calculi as of in ureter, bladder etc.

Creatinine

The normal value of Creatinine in canine is 0.5-1.6 mg /dl. Elevation of creatinine is a specific indicator of renal involvement unlike serum BUN which is a non specific marker which can be elevated due to diet, exercise and other non renal factors. However creatinine values within the normal limits does not rule out renal impairment as elevation of creatinine may be witnessed only when more than 75 per cent loss of functional nephrons occurs and not in early stages of the renal disease (Lefebvre, 2011) [6]. Hence normal creatinine values can camouflage the renal involvement in routine clinical practice. In such cases, urine specific gravity and casts may give a clue of early stage of renal impairment. Moreover pseudo elevation of creatinine may also occur due to deteriorated sample like old, hemolysed samples.

Serum electrolytes

Kidneys maintain the electrolyte balance of the body in addition to excretion of waste products and maintaining acid base balance. Hence when the functioning of kidneys is impaired, there is a disturbance in their balance reflected by elevation or reduction in the serum electrolyte values. The major electrolytes analysed in renal cases include calcium, potassium, sodium and chloride along with the mineral element phosphorus.

The normal value of Phosphorus in canine is 2.9-6.2mg /dl. Phosphorus may be elevated in renal diseases of long standing duration as the damaged nephrons cannot be excreted which affects the calcium phosphorus balance and end in secondary renal hyperparathyroidism. This condition further accentuates the serum phosphorus levels by causing depletion of bone calcium to maintain the calcium phosphorus balance. Polzin (2010) [7] stated that dogs with serum phosphorous range 6.6 to 7.8 mg/dL are reported to have 13% higher mortality than dogs with phosphorous levels within the reference range.

The normal value of Calcium in canine is 8.7-11.8 mg /dl. Elevated serum calcium levels are suggestive of congenital renal disease and renal failure. Damage to the renal parenchyma occurs due to nephrocalcinosis by the deposition of calcium and phosphorus which are unexcretable by the damaged tubules. Hikes and Morrison (1985) [8] proposed the causes of hypercalcemia induced by primary renal disease as: a) decreased excretion of calcium by the diseased kidney; b) decreased renal tubular degradation of Parathyroid hormone (PTH); c) PTH-induced hypercalcemia which increases complexed calcium; d) overcompensation by the parathyroid gland; and e) exaggerated response to vitamin D with resultant increase in intestinal absorption of calcium. However in chronic kidney diseases calcium levels may be reduced.

The normal value of Potassium in canine is 3.8-5.6 mEq/L. Hyperkalemia or increase in serum potassium levels occurs due to changes in the micturition pattern as in reduced urine output wherein potassium excretion is inefficient.

The normal value of Sodium in canine is 140-154 mmol/L. In chronic kidney diseases, reduction in sodium levels occurs as in polyuria when sodium is not efficiently reabsorbed. The causes of hyponatremia include hypotension, pain, and renal injury which activate the sympathetic nervous system; renin angiotensin-aldosterone system and antidiuretic hormone release (Prowle *et al*., 2010) [9]. These changes subsequently result in decreased renal perfusion, decreased glomerular filteration rate (GFR) and increased proximal tubular reabsorption of sodium and water in advanced renal failure

(Di Bartola, 2006) [10]. The normal value of Chloride in canine is 102-117 mmol/L and altered chloride values may also occur due to the inapt electrolyte balance by the damaged kidneys.

Urinalysis

Urinalysis is a simple and non-invasive method of assessing the functions of kidney. It is done by subjecting the urine to physical, chemical, microscopic, cultural and cytologic examination to identify the pathological constituents and changes.

Urine Volume

The amount of urine produced per day by normal animal is dependent upon several variables like diet, fluid intake, weather, exercise etc. Normal urine output for adult dogs is approximately 20-50ml/kg body weight per day. Any degree of insult to the kidneys is often manifested with altered urine volume and frequency like oliguria in early stages, polyuria in later stages and anuria in terminal stages of renal failure. Hence, the pet parent is suggested to observe for the volume and pattern of urination of their pets for a 24 hour period to have a reliable information on the per day urine volume and micturition pattern as they may be overlooked often.

Specific Gravity

Specific gravity of urine is an indicator of the concentrating or diluting ability of the kidneys and it is determined by Refractometer, Urinometer and Uri strips. All components of urinalysis is interpreted with reference to specific gravity of urine to have a meaningful and efficient diagnosis as variation in urine volume, polyuria or oliguria may otherwise show a hike or decrease in the components despite their presence within the normal range.

The normal range of specific gravity in dogs is 1.025 (1.010-1.060). Altered urine specific gravity thus gives a clue of renal involvement and it is further confirmed by other diagnostic tests as specific gravity may also be altered due to fluid therapy, dehydration etc.

Protein

Protein may be detected in urine, in renal cases with inflammation of the renal system like glomerulonephritis, pyelitis, urethritis, ureteritis and cystitis. It may also be seen as in non-renal conditions like protein losing enteropathy, hemoglobinuria and myoglobinuria. Protein may also be detected in urine due to physiological conditions like animals fed with excess protein diet, due to muscular exertion in police dogs etc., Hence proteinuria should always be interpreted with care to rule out the physiological and non renal causes.

Harley and Langston (2012) [11] stated that an increase in urinary protein excretion correlates with decrease in survival independent of any other factor; proteinuric renal disease progresses more rapidly than non proteinuric renal disease but the reduction in urinary protein excretion slows down the progression of renal disease and renal interstitial inflammation in humans and dogs. Hence the authors further proposed to diagnose and reduce the level of proteinuria as the proteinuria itself can contribute further to the ongoing renal damage.

Urine protein: creatinine ratio (UPC)

In addition to estimating the urine protein, the quantity of protein excreted in urine in comparison to quantity of creatinine excreted in urine (UPC) is done to assess the magnitude of protein loss in urine due to renal diseases and to have a meaningful interpretation.

$$\text{UPC} = \frac{\text{Urine protein (mg/dl)}}{\text{Urine creatinine (mg/dl)}}$$

The normal value of UPC in dogs is less than 0.5. Harley and Langston (2012) [11] have stated that UPC values > 0.5 in dogs is significant and values > 0.2 are borderline cases which warrant investigation. Dogs with any form of kidney disease that also have proteinuria (UPC > 0.5) have a worse prognosis and shorter long-term survival than non-proteinuric animals with kidney disease (Littman, 2011) [12]. Higher UPC values indicate significant proteinuria due to severe damage to the kidneys like renal amyloidosis when part of the kidney tissue is replaced by amyloid tissue leading to its functional impairment.

However, UPC values may be misleading if it has more cellular elements like RBCS as in haemorrhage or WBCs as in infection or inflammation of one or more components of the urinary system. In such cases UPC interpretation becomes void.

Casts

Urinary casts, sometimes known as the poor man's renal biopsy, are objects formed within the renal tubules (Tietze, 2011) [13]. The Tamm horsfall mucoprotein secreted by the renal tubules gets conglomerated as casts. They are formed in the renal tubules due to high concentration of urine in the lumen of the tubules and resemble like the shape of the tubules. On microscopic examination of the urine sediment, casts appear as cylindrical bodies. The various urine casts include hyaline casts, granular casts, waxy casts, fatty casts, epithelial casts, red cell casts and leucocytic casts.

Hyaline casts is seen in mild stage of renal impairment. Granular casts are seen in severe damage to the kidneys as due to ischemia, protein induced nephropathy *viz*. haemoglobin and myoglobin, administration of nephrotoxic drugs etc. Epithelial cell casts is seen in acute nephritis. Fatty casts are seen due to damage inflicted on the renal tubules as in Diabetes mellitus in dogs. Erythrocytic casts with the organisation of RBCs is seen during haemorrhage in the kidney tubules. Leukocytic casts are suggestive of inflammatory and infectious causes associated with urinary tract infection, abscess, pyelonephritis etc (Benjamin, 1978) [14].

Urine gamma glutamyl transferase (GGT): creatinine ratio

Urine (GGT): creatinine ratio is a test of choice to assess renal tubular damage in dogs with known history of treatment with aminoglycosides for any underlying disease process. It is calculated by dividing the Urine GGT (IU/l) by Urine creatinine (mg/dl). The value of Urine GGT/creatinine ratio is reported as 0.15 in healthy dogs. Rivers *et al.* (1996) [15] from their research findings suggested that urine GGT-to-creatinine ratio can be superior as an early indicator of aminoglycoside-induced nephrotoxicity in dogs.

More often, GGT is employed as an indicator of hepatic involvement. Hence to rule out hepatic issues, serum GGT levels are estimated simultaneously with Urine GGT/creatinine ratio. In dogs with purely renal involvement, urine GGT/creatinine ratio are elevated against the serum

GGT which is within the normal limits. If liver is affected, then both serum GGT and urine GGT/creatinine ratio are elevated which clearly implies that the pathology of illness is confined to liver.

Acute Kidney Injury (AKI) AND Chronic Kidney Disease (CKD)

Acute Kidney Injury (AKI) is a condition commonly encountered in dogs with unfavourable to guarded prognosis when they are not diagnosed and treated promptly. The Acute Kidney Injury Network (AKIN) has described AKI as "functional or structural abnormalities or markers of kidney damage including abnormalities in blood, urine, or tissue tests or imaging studies present for less than three months." AKI in dogs is most commonly caused by reduction in blood flow to the kidneys, due to detrimental effects of drugs, toxins, hemoprotozoan diseases, leptospirosis and sepsis etc. Because of the rigorous insult to the kidneys in a short span, the kidneys are severely affected, especially the tubules, resulting in failure to excrete the metabolic end products of the body. In ultrasonography, kidneys may appear enlarged or even normal in size in AKI.

Chronic kidney disease (CKD) is more commonly seen in older dogs though it has been diagnosed in other age group dogs as well. It has been diagnosed as a primary entity as well as secondary viz. as an aftermath phenomenon of a previous episode of AKI in dogs. O'Neill *et al.* (2013) [16] have reported that the prevalence of CKD increases to up to 15% in dogs over 10 years of age. In CKD the history of weight loss, inappetance, poor skin and body coat, altered micturition pattern like polyuria shall be observed for more than three months indicating the pathology of longer duration unlike AKI which occurs as a sudden episode. In ultrasonography, kidneys may appear smaller in size.

International Renal Interest Society (IRIS) Grading of AKI and Staging of CKD

The International Renal Interest Society (IRIS) has graded AKI and CKD so as to have an effective therapeutic intervention.

Grading of AKI (2016) [17]

IRIS AKI Grade I includes Non Azotemic dogs with a blood creatinine <1.6 mg/dl.

IRIS AKI Grade II includes dogs with mild azotemia with a blood creatinine 1.7 – 2.5 mg/dl. It also includes animals that have an increase from their baseline creatinine concentration of ≥0.3mg/dl during a 48 hour interval associated with pre-existing CKD.

IRIS AKI Grades III includes dogs with a blood creatinine 2.6-5 mg/dl, Grade IV includes dogs with a blood creatinine 5.1-10 mg/dl, and Grade V includes dogs with a blood creatinine>10 mg/dl. Grade III, IV and V define animals with documented AKI and progressively greater degrees of parenchymal damage and functional failure (uremia).

After grading, the animals are further subgraded as Non oliguric/ Oligoanuric and requiring renal replacement therapy.

IRIS Staging of CKD (modified 2019) [18]

IRIS CKD staging is based on fasting blood creatinine concentration and blood SDMA concentration. If serum or plasma SDMA is persistently >18 µg/dl in a dog whose creatinine is <1.4mg/dl (IRIS CKD stage 1 based on creatinine), this canine patient should be staged and treated as an IRIS CKD Stage 2 patient. If serum or plasma SDMA is persistently >35 µg/dl in a dog whose creatinine is between 1.4 and 2.8 mg/dl (IRIS CKD stage 2 based on creatinine), this canine patient should be staged and treated as an IRIS CKD Stage 3 patient. If serum or plasma SDMA is persistently >54 µg/dl in a dog whose creatinine is between 2.9 and 5.0 mg/dl (IRIS CKD stage 3 based on creatinine), this canine patient should be staged and treated as an IRIS CKD Stage 4 patient. After staging, the animals are further substaged based on proteinuria and blood pressure.

Based on the above clinicopathological investigation and grading and staging of renal disorders discussed, renal impairment is diagnosed and is further classified as Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) as the two conditions warrant different strategic therapeutic intervention ranging from embracing of renal diet, withdrawal of nephrotoxic drugs administration, Dialysis, Continuous renal replacement therapy etc.,

Clinicopathological follow up of renal cases in dogs

Despite the clinical significance, diagnosing and staging renal disease can be difficult as AKI and CKD have a narrow rim of demarcation. AKI dogs after therapeutic intervention may progress to CKD and dogs with CKD have more predisposition to develop AKI on exposure to nephrotoxic drugs, hemoprotozoan diseases etc.

The general stages which the animal mostly surpass in renal dysfunction whether of acute or chronic onset include an early stage without symptoms or with nonspecific symptoms like inappetance, depression etc., Serum biochemistry may not show elevation of creatinine. However urine specific gravity and casts may be seen on microscopic examination as early indicators of renal involvement. Further, if the animal has undergone an insult of sufficient intensity then clinical signs suggestive of renal involvement with significantly elevated serum creatinine levels may be seen which is often diagnosed and treated as AKI. Dogs, especially older dogs and dogs affected with and treated for AKI may show symptoms of renal involvement with mild to moderately elevated serum creatinine levels. Such cases are diagnosed and treated as CKD. Very often, dogs may also be presented as end stage renal failure with alarming clinical signs suggestive of renal involvement, impairment of vital parameters and very high serum creatinine levels wherein intervention like haemodialysis or Continuous Renal Replacement Therapies (CRRT) is ventured to otherwise save the animal.

Following therapeutic and manage mental intervention, clinicopathological follow up at regular intervals is an indispensable step to assess the progression of the renal pathology as to monitor whether the condition is getting worse or is showing positive signals of recovery. Blood sample is collected and CBC is done to see whether the HB, PCV and RBC values are within the normal limits. If the kidney functioning has become normal post treatment and management, then erythropoietin synthesis would have been resumed and is witnessed by seeing the nucleated RBCs, polychromasia and reticulocytes in the blood smear. Absence of such features and finding normochromic, normocytic anaemia indicates that the condition is mostly of chronic kidney disease. Kralova (2010) [19] stated that normochromic, normocytic anemia is the most frequently noted hematological change in patients with chronic renal failure. Serum biochemistry is further carried out to look for reversal to normal creatinine values and other electrolytes. If

there is no improvement in any of these parameters, the case may beanalyzedcritically to rule out any other pathological condition or etiological agent precipitating the renal problem and hampering recovery and the prognosis can be considered un favourable.

Conclusion

Biochemical and haematological testing are a boon in pet animal practice as regular physical health checks may facilitate early detection of renal diseases before they presented clinically allowing earlier intervention and better health outcomes and to monitor the improvement post therapeutic intervention.

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