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Immune disorders in dogs with chronic kidney disease: Review

Geovanny Romano de Sousa[1*], Almir Pereira de Souza[2], Antônio Fernando Vaz de Melo[3], Rosangela Maria Nunes da Silva[3]

[1]Médico Veterinário, Universidade Federal de Campina Grande, Campus de Patos, Paraíba, Brasil
[2]Professor Titular do Curso de Medicina Veterinária da Universidade Federal de Campina Grande, Campus de Patos, Paraíba, Brasil
[3]Professor(a) Associado(a) do Curso de Medicina Veterinária da Universidade Federal de Campina Grande, Campus de Patos, Paraíba, Brasil
[*]Autor para correspondência: E-mail: geovannyrdesousamv@outlook.com

Abstract: The aim of this literature review was to identify the stages of chronic kidney disease in dogs that have greater immune dysfunction and which cellular components of the innate and humoral immune system are most affected by the retention of uremic toxins. Chronic kidney disease is characterized by being a serious and irreversible disease, but common in the practice of medical clinic for dogs and cats and usually affects those of advanced age. The consequences of chronic kidney disease can expand to other systems as the disease progresses; systemic arterial hypertension, hypertensive retinopathies and secondary renal hyperparathyroidism are examples of extra-renal impairment caused by chronic kidney disease. The Interest Renal Society (IRIS), established degrees of progression of renal impairment according to serum concentrations of symmetrical creatinine and dimethylarginine, biomarkers of kidney injury, which allows aid in diagnosis, classification of the degree of nephrological and systemic impairment and treatment affected patient. Studies in human patients demonstrate that, in the terminal stages of kidney disease, there is an impairment of the immune function of these patients, which contributes to the increase in the rate of deaths related to secondary infections, cancers caused by viruses and low responsiveness to vaccines. In Veterinary Medicine, despite the scarcity of research on immunosuppression in dogs with chronic kidney disease, some have observed, *in vitro* and *in vivo* environments, dysfunction in the innate and humoral immune system of dogs with advanced chronic kidney disease, due to the pro-inflammatory environment resulting from the retention of uremic toxins that had their clearance affected by impaired kidney excretory function. Stage III of chronic kidney disease in dogs requires greater care, not only to prevent the disease from progressing to stage IV, but also to prevent immune disorders that may result in death. The adoption of intervention criteria and measures aimed at preventing and / or minimizing these immunological disorders depends on the expansion of research on this topic to establish better clinical management for dogs with nephrological disorder.

Keywords: Diagnosis, extrarenal, immune system, IRIS, uremic toxins

Distúrbios imunológicos em cães com doença renal crônica: Revisão

Resumo. Objetivou-se com essa revisão de literatura, identificar os estágios da doença renal crônica em cães que apresentem maiores disfunções imunológicas e quais os componentes celulares do sistema imune inato e humoral que são mais acometidos pela retenção de toxinas urêmicas. A doença renal crônica é caracterizada por ser uma enfermidade grave e de caráter irreversível, porém comum na prática de clínica médica de cães e gatos e acomete, geralmente, os de idade avançada. As consequências da doença renal crônica podem se expandir para outros sistemas à medida que a progressão da doença se instala; hipertensão arterial sistêmica, retinopatias hipertensivas e o hiperparatireoidismo

renal secundário são exemplos do comprometimento extrarrenal causado pela doença renal crônica. A Interest Renal Society (IRIS), estabeleceu graus de avanço do comprometimento renal de acordo com as concentrações séricas de creatinina e dimetilarginina simétrica, biomarcadores de lesão renal, o que permite auxílio no diagnóstico, classificação do grau de comprometimento nefrológico e sistêmico e tratamento do paciente acometido. Estudos em pacientes humanos demonstram que, em estágios terminais da doença renal, nota-se acometimento da função imunológica desses pacientes, o que contribui para o aumento da taxa de óbitos relacionados a infecções secundárias, cânceres causados por vírus e baixa responsividade a vacinas. Na Medicina Veterinária, apesar da escassez de pesquisas acerca da imunossupressão em cães com doença renal crônica, alguns já se observou, em ambientes *in vitro* e *in vivo*, a disfunção no sistema imune inato e humoral de cães com doença renal crônica em estágio avançado, decorrente do ambiente pró-inflamatório resultante da retenção de toxinas urêmicas que tiveram sua depuração afetada pelo comprometimento da função excretória dos rins. O estágio III da doença renal crônica em cães requer maiores cuidados, não somente para evitar a progressão da enfermidade para o estágio IV, mas também evitar distúrbios imunológicos que possam resultar em óbito. A adoção de critérios e medidas de intervenção que visam prevenir e/ou minimizar esses distúrbios imunológicos dependem da ampliação de pesquisas acerca desse tema para estabelecer melhores condutas clínicas aos cães com desordem nefrológica.

Palavras-chave: Diagnóstico, extrarrenais, IRIS, sistema imune, toxinas urêmicas

Introduction

Chronic kidney disease (CKD) is an irreversible pathological condition that is characterized by the dysfunction of at least 75% of the nephrons, culminating in excretory, hydroelectrolytic and endocrine deficits (Jericó et al., 2015). The causes of CKD are very different and it is often not possible to determine them, but among them they are hereditary, produced or acquired (Nelson & Couto, 2015). The patient with CKD can be according to the chronic kidney disease table by the International Renal Interest Society. This table classifies patients with CKD into four series that require the urea concentration (URE), creatinine (CRE), symmetrical methylarginine (SDMA) and blood pressure (BP) (IRIS, 2019). The diagnosis of the CKD patient must be evaluated with the clinical history of the animal, change the clinical examination, laboratory tests and imaging tests, especially the size of both rinses (Queiroz & Fioravanti, 2014). From this, together with the interpretation of the data presented in the exams, it is possible to determine the stage of CKD in which the animal is, according to the IRIS table. The treatment consists of maintaining the patient's renal function, that is, a conservative therapy that aims to stop the degeneration of the nephrons, considering that the potential of this disease is irreversible (IRIS, 2019).

Immunosuppression in CKD is still a poorly understood event in Veterinary Medicine; however, it is among the causes of mortality in human patients with advanced stage CKD (Akar et al., 2011). In studies, cells induced in the immune system are not determinants of neutrophil function. Possible cell changes can be generated in human cells, as secondary, immune cells caused by the immune system, but can also be changed for the immune system (Betjes, 2013; Syed-Ahmed & Narayanan, 2019).

The aim of this review explains in years the greatest concern with chronic kidney disease the effects that promote circulation by the pro-proposal-epidemiology objective evolve the deleterious effects to the body's immunity in the environment of immunological diseases.

Chronical kidney disease

CKD is a disease considered common in the clinical routine of dogs, being one of the factors that can lead to mortality. The irreversible character of the disease is characterized by the dysfunction of at least 75% of the nephrons present in both kidneys; unlike acute renal failure (ARI), the animal no longer has mechanisms that can promote a restoration of renal function. The impairment of two thirds of renal function causes in the affected animal’s numerous disorders that are related to the physiological functions of the kidney, among them, the excretory, endocrine, hydroelectrolytic and metabolic functions (Zachary et al., 2012).

Etiology

The etiology of CKD has a multifactorial occurrence and it is often not possible to identify it, although acquired, congenital and familial etiologies are cited, in the same way as the etiology, CKD has different sites of origin (Table 1). CKD still has different morphophysiological segments to be compromised, in addition, it has an insidious evolution and often, when diagnosed, presents itself in a very advanced stage of renal and systemic involvement (Jericó et al., 2015; Oliveira et al., 2020; Queiroz et al., 2015).

Table 1. Origin and causes of chronic kidney disease in dogs and cats.

Origin	Causes
Renal glomeruli	Glomerulopathies, amyloidosis, immune-mediated diseases, Cushing's syndrome, periodontitis, feline immunodeficiency virus (FIV), feline panleukopenia, caliciviruses, leishmaniosis, pyometra and ehrlichiosis.
Kidney tubules	Nephrotoxins, viral infections (Adenovirus type 1), bacterial infections (Pyelonephritis, and leptospirosis), Faconi syndrome, primary renal glycosuria, inflammatory and ischemic causes.
Extra cell space	Pyelonephritis, kidney stones and leptospirosis.
Vascular disorders	Diabetes *mellitus*
Biochemical disorders	Cystinuria
Hereditary/Idiopathic kidney disease	_____

Source: Adapted from Jericó et al. (2015).

Other causes can result in CKD, such as primary heart failure, primary systemic arterial hypertension, renal neoplasms, hyperthyroidism, and AKI progression injury. Regardless of the primary cause (tubular, interstitial or vascular) CKD can affect several structures simultaneously and as a result the functional tissue (nephron) will be replaced by fibrous tissue and viable nephrons will make a homeostatic mechanism in order to supply, in a compensatory way, the absence of degenerated nephrons even in a limited way (Jericó et al., 2015; Nelson & Couto, 2015).

Clinical signs

From the moment that there is impairment of renal function resulting from the gradual reduction of nephrons, the first indication of renal failure is the inability of the kidneys to concentrate urine, therefore, polyuria and compensatory polydipsia will be observed in these patients, however, in feline patients, due to the functional characteristic of the nephrons of this species of having a high capacity to concentrate urine, polyuria is observed in terminal stages of CKD when the kidneys are already affected in about three quarters of the number of nephrons (Ettinger et al., 2002; Jericó et al., 2015).

Clinical manifestations are closely linked to the degree of functional impairment of the kidney, and there may be symptomatic animals or animals with nonspecific symptoms where it is only possible to diagnose CKD through tests that use biomarkers of kidney damage and imaging tests or animals that show clinical signs in very advanced degrees of the disease, with classic symptoms together (Scardoeli, 2017).

According to the IRIS (2019), dogs in stage I and II of kidney disease tend to be asymptomatic, so it is important to use kidney markers to aid diagnosis in these stages. In stage III, in addition to polyuria and polydipsia, the affected dog begins to show signs of hyporexia, slight weight loss and sporadic episodes of vomiting. Stage IV, the terminal stage of the disease, is characterized as the stage with the greatest clinical manifestations, such manifestations affect several systems: gastrointestinal, bone, cardiovascular, respiratory, endocrine and hematopoietic (Figures 1 and 2).

CKD staging

The IRIS, created in 1998, established parameters for staging dogs and cats with CKD according to serum levels of CRE, ERU and, more recently, SDMA (Table 2). Staging aims to diagnose, monitor and treat patients with CKD to provide them with a better quality of life. In addition to CKD staging by CRE and SDMA dosage, there are sub-stagings, which subclassify CKD according to BP and proteinuria/creatinine ratio (UP/C).

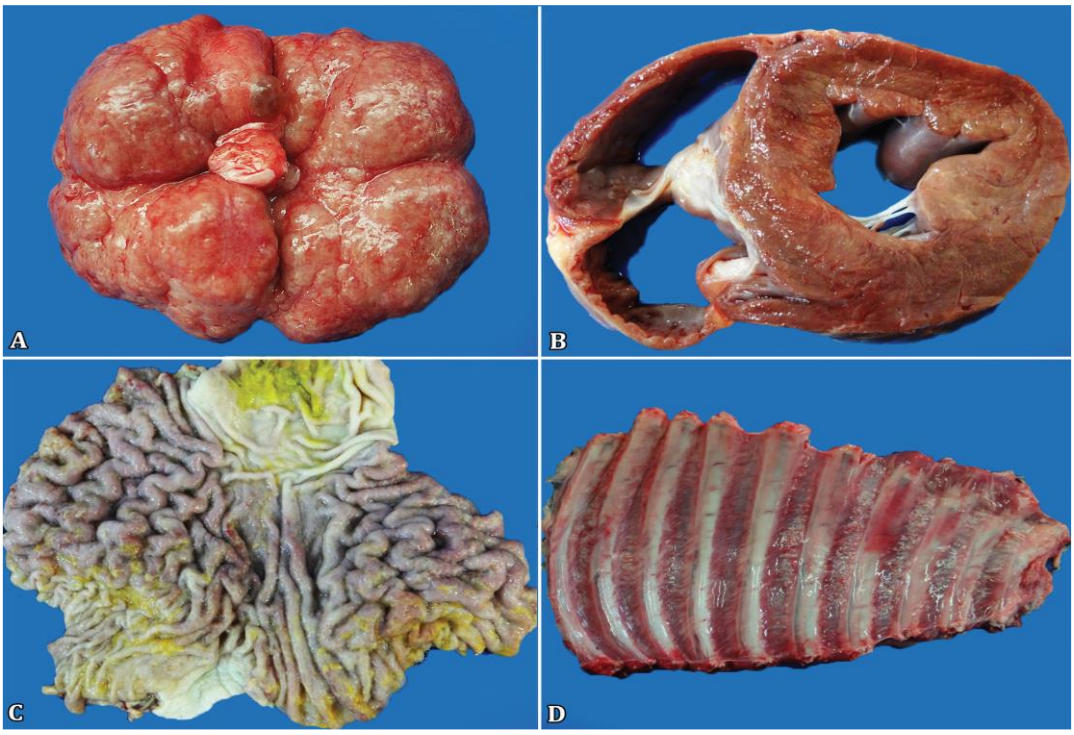

Figure 1. Renal and extrarenal lesions of dogs with uremic syndrome. (**A**) Canine kidney with presence of irregularities under the surface and retraction of the parenchyma, (**B**) Focus of dystrophic mineralization in the myocardium, (**C**) Uremic gastropathy with edema under the mucosa, (**D**) Presence of mineralization in the intercostal muscles.

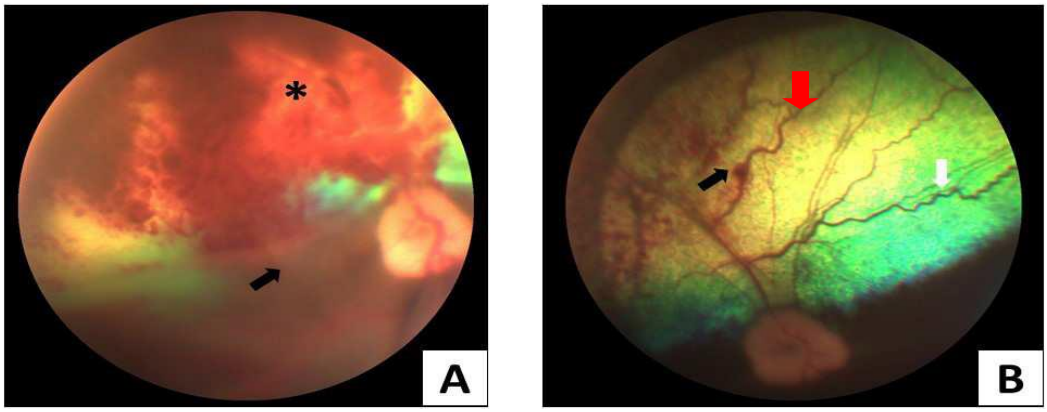

Figure 2. Hypertensive retinopathy in a dog diagnosed with CKD. (**A**) Presence of extensive hemorrhage in a tapetal area present in the eye fundus (asterisk). Retinal displacement in non-tapetal area of the eye fundus (arrow); (**B**) Bleeding areas adjacent to retinal vessels (black arrow). Tortuosity of retinal vessels (red arrow). **Source:** Adapted from Queiroz et al. (2015) and Cardoso et al. (2019).

Table 2. Staging and clinical considerations of chronic kidney disease in dogs.

Stage	CRE*, µmol/l, mg/dl	SDMA*, µmol/l, mg/dl	Clinical considerations
I	<125 <1.4	<18	Normal CRE serum concentrations and normal or slightly increased serum SDMA levels. Abnormal findings on imaging exams, abnormalities on palpation, biopsy with changes, increases in serial collections of CRE and SDMA levels.
II	125 – 250 1.4 – 2.8	18 – 35	Serum CRE concentrations or slightly increased, mild renal azotemia. Slight increase in SDMA. Presence of discrete clinical signs.
III	251 – 440 2.9 – 5.0	36 – 54	Moderate renal azotemia. Other extrarenal signs may be present, characterizing early or late stage III.
IV	>440 >5.0	>54	Increased risk of systemic signs resulting from uremia crises.

Source. Adapted from IRIS (2019). *CRE = creatinine; *SDMA = symmetrical dimethylarginine.

Diagnosis

The diagnosis of CKD is made through anamnesis, clinical history, physical examination findings and complementary exams. Imaging tests can help diagnose the etiology of CKD through the visualization of kidney stones or pyelonephritis (Jericó et al., 2015; Nelson & Couto, 2015).

Among the possibilities of complementary tests for the diagnosis of CKD, the standard are laboratory tests such as the performance of serum biochemistry to observe the markers of kidney injury, urinalysis, electrolyte measurement, blood count, blood gas analysis and serum phosphorus and ionized calcium (Nelson & Couto, 2015).

When observing the increase in serum fractions of URE and CRE, it is assumed the accumulation of nitrogenous compounds in the bloodstream. The serum concentration of CRE has been shown to be the best indicator, indirectly, of glomerular filtration rate (GFR). Reference limits for CRE and URE in dogs can range from 0.8 mg/dl to 1.8 mg/dl and 30 mg/dl to 75 mg/dl, respectively (Ettinger & Feldman, 2002; Jericó et al., 2015; Nelson & Couto, 2015).

According to Nelson & Couto (2015), in dogs, isosthenuria occurs when there is nephron dysfunction above 67%. The presence of proteinuria is indicative of the progression of CKD and a sign of glomerular hypertension and, together with inactive urinary sediment, suggests primary glomerulopathy.

There is the possibility of bacteriuria and pyuria in response to isosthenuria, which favors microbial growth and the development of lower urinary tract infection (UTI). The patient may have a UTI because the immune response is suppressed as a result of uremia. In these cases, monitoring of the affected patient with these changes should be recommended in order to avoid an ascending UTI that could cause more damage to the remaining nephrons, such as pyelonephritis (Girndt et al., 2001; Jericó et al., 2015; Nelson & Couto, 2015). According to Lamoureux et al. (2019), in a retrospective study with 201 cases of CKD in dogs, pointed out that 32% of the cases had a diagnosis of bacteriuria, however, only 8% had clinical signs of UTI.

The assessment of serum sodium and chloride levels is important for managing the patient's fluid therapy and important for patients with polyuria and for monitoring losses (hypochloremia) and accumulations (hyperchloremia); in patients with CKD, serum potassium is usually within reference values, except in cases of anuria or oliguria (Jericó et al., 2015; Nelson & Couto, 2015).

The hemogram brings the possibility of evaluating the type of anemia, where normocytic normochromic anemia is more frequently observed due to a deficit in the production of erythropoietin (EPO). The observation of hematocrit (Ht) should be related to the dosage of total proteins (PT), as dehydration can influence Ht (Jericó et al., 2015; Nelson & Couto, 2015).

Blood gas analysis results may indicate the presence of metabolic acidosis, the type, size and varied changes of acid-base imbalance when they exist. Simultaneously, clinical manifestations occur on the part of the patient leading to the loss of bicarbonate and HCl (Jericó et al., 2015).

The observation of serum concentrations of phosphorus and ionized calcium makes it possible, indirectly, to evaluate renal phosphorus excretion and an interpretation of the metabolism of these minerals in the patient's body (Jericó et al., 2015).

Treatment

IRIS (2019) recommended that the therapy of patients affected with CKD be appropriate for their staging, in this way, the aim is to preserve the remaining renal function and provide a better survival to the animal. However, according to Jericó et al. (2015), it is important to emphasize that the dog may present, within the same stage, clinical and laboratory variations according to the nephrological and systemic involvement.

Protocols with the use of angiotensin-converting enzyme (ACE) inhibitors, gastric mucosal protectors, antiemetics, mineral and/or hormonal supplements to combat anemia and, in advanced cases, the use of dialysis therapy, must be individualized according to the renal and systemic clinical manifestations of each patient (Queiroz & Fioravanti, 2014; Jericó et al., 2015).

Prognosis

The prognosis of dogs with CKD depends on several factors, such as early diagnosis, staging and patient monitoring. Patient treatment is not aimed at reestablishing renal function, but at stabilizing and improving clinical signs (Queiroz, 2016). The reasons that can result in a poor prognosis are the presence of severe anemia, acid-base and electrolyte imbalance and progressive azotemia (Nelson & Couto, 2015).

Immunosuppression in uremic dogs

Uremia is characterized as a toxic and polysystemic syndrome that causes, in different ways, several changes in the patient, such as gastropathy, stomatitis, hemorrhagic diarrhea or not, thrombopathy, alterations in the respiratory and cardiac systems, acid-base and electrolyte imbalances (Cohen et al., 1997).

According to Betjes (2013) and Syed-Ahmed & Narayanan (2019), in human patients, there is a correlation between immune system disorders and advanced degrees of uremic state. The progression of kidney disease causes the retention of uremic toxins in the body, generating a pro-inflammatory uremic environment that causes changes in the cells of the innate and humoral immune system. Such a uremic environment, as kidney disease progresses, results in a decline in these circulating cellular components, low chemotactic activity, phagocytic deficit, increased cellular oxidative metabolism, and induction of apoptosis.

Ample recent studies have sought to elucidate the deleterious effects of uremic syndrome in patients with CKD. Due to the progression of CKD in the patient, these substances that would be excreted in non-uremic patients, result in the clinical picture of uremia. The uremic picture causes several deleterious effects to different tissues of the body, especially on the cardiovascular system (Barreto et al., 2014).

According to the European Database of Uremic Solutes (EUTox-DB), there are prerequisites that must be met for a compound to be classified as a uremic toxin (Table 3). Altogether, according to EUTox-DB (2003), there are more than 130 uremic toxins listed in the database, with the possibility of increasing the number of these toxins in the coming years.

Table 3. Necessary prerequisites for characterization of uremic toxins

Chemically identified and accurately measured;
Plasma/total body levels should be higher than non-uremic patients;
High concentrations should be correlated with the patient's clinical spectrum, which disappears as the concentrations of uremic compounds decrease;
Ex vivo, *in vivo* or *in vitro* research must prove the biological activity of these compounds, and finally, experimental concentrations of this molecule in these studies must be compatible with those identified in body fluids or tissues of patients known to have uremic status;
Total serum levels should be at higher values than in non-uremic individuals.

Source: Adapted from Barreto et al. (2014).

Uremic toxins can also be classified according to their physicochemical characteristics and their removal by dialysis therapy: I- Small, water-soluble, with a maximum molecular weight (MP) of 500 daltons (DA). Included in this group are URE, CRE and guadinines (GUA), which are easily removed by dialysis. These do not necessarily have deleterious effects on the organism; II – Medium-sized uremic toxins: moderately high MW compounds (above 500 DA). Removal occurs by dialysis membranes with pores large enough for passage. These compounds, for the most part, are characterized as peptides and can cause deleterious effects to various tissues. Examples of this group are Fibroblast growth factor (FGF23), Parathyroid hormone (PTH) and leptin; III- Compounds conjugated to proteins: Generally, of low MW. Indoxyl sulfate (SI) and Para-cresol (P-Cresol) are part of this group and have several toxic effects and are difficult to remove by dialysis therapies (Barreto et al., 2014).

The pro-inflammatory environment and the immunological compromise generated by uremic toxins can favor an increase in secondary infections, such as periodontitis, stomatitis and gingivitis. The infectious condition can result in systemic inflammation, atherosclerotic diseases or cardiovascular

diseases, the latter two being the main causes of death in human patients with end-stage chronic kidney disease (Akar et al., 2011).

In dogs, studies on immunosuppression caused by uremia are scarce. However, studies realized by Barbosa et al. (2010), reproduced in an *in vitro* environment, suggest that, *in vivo*, as in humans, uremia compromises innate immunity through changes in neutrophil metabolism. The impairment of innate immunity caused by uremia, observed by changes in the oxidative metabolism of neutrophils, is also described as a factor in the dysfunction of the patient's humoral immunity. Decreased lymphocyte population, low immune responsiveness to vaccines were observed as consequences of cellular involvement of the humoral immune system of dogs in stage III and IV of CKD (Borin-Crivellenti et al., 2014; Kralova et al., 2010).

Several factors influence the immune response of these patients (Figure 3), the presence of uremic toxins in the bloodstream, poor nutrition, chronic inflammation and involvement of the parathyroid gland affect both pathways. of the organism, innate and acquired (Syed-Ahmed & Narayanan, 2019).

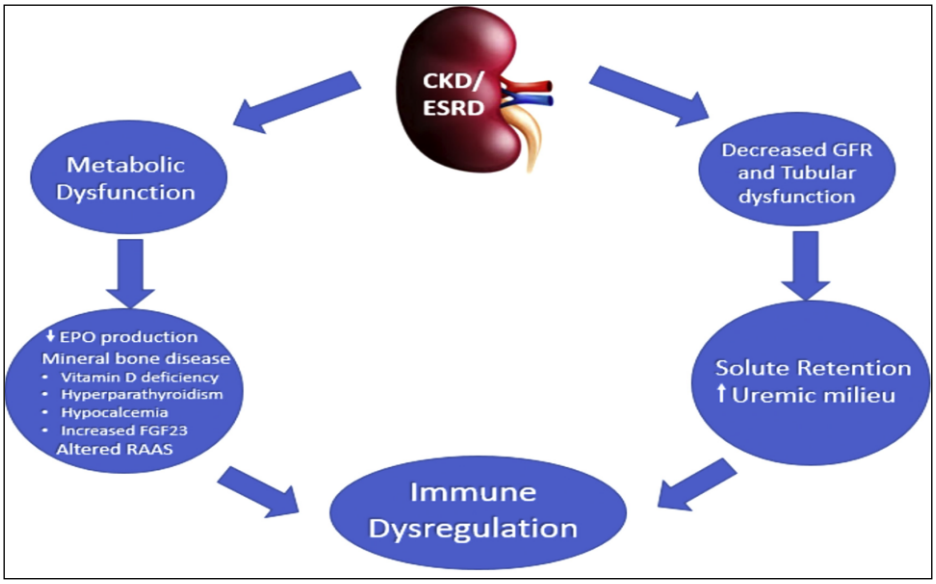

Figure 3. Multisystem consequences of CKD. **Source:** Syed-Ahmed & Narayanan (2019).

Oxidative stress of leukocytes in chronic kidney disease

Free radicals, or reactive oxygen species (ROS), are highly reactive atoms or molecules with one or more unpaired electrons in their outer shell and arise when oxygen interacts with certain molecules. The formation of ROS is a result of the process generated by the metabolism of oxygen through the action of mitochondria, the main cellular responsible for the source of energy (Liguori et al., 2018).

The enzymatic and non-enzymatic cellular antioxidant system has the function of inhibiting or minimizing the deleterious effects caused by the production of ROS. Studies show that oxidative stress is a potential factor in deaths in patients with CKD and in the development of other comorbidities such as SAH, vascular endothelium dysfunction and inflammatory precursor (Barbosa et al., 2010).

CKD is closely related to the increased incidence of severe infections, especially in patients with advanced stage of kidney disease, this condition corresponds to about 20% of deaths in human patients, which reflects the immunological dysfunction in these patients, especially those who are undergoing dialysis procedures (Lopez et al., 2017). Patients with renal disorders usually have a weakened nutritional status, with a deficit in vitamins and minerals, therefore, there is a deficiency in the performance of the enzymatic and non-enzymatic antioxidant system, such as catalase, glutathione peroxidase, vitamin C, vitamin E and beta-carotenes. The decline in the function of this antioxidant system results in a greater production of ROS, which consequently causes renal and extrarenal cellular changes (Liguori et al., 2018). The immunological alteration observed in human patients with CKD and in veterinary medicine demonstrates that oxidative stress has a significant impact on the induction of immune dysfunctions (Lopez et al., 2017).

The accumulation of uremic toxins observed in dogs with end-stage CKD has caused, mainly to neutrophils, changes in their oxidative metabolism, increasing ROS concentrations and, consequently, the rate of apoptotic induction of these cells (Barbosa et al., 2010; Bosco et al., 2017; Silva et al., 2013). Studies realized by Kralova et al. (2010) and Borin-Crivellenti et al. (2014) demonstrated, in advanced stages of CKD in dogs, a decrease in the population of lymphocytes, which suggests not only a deficiency in innate cellular immunity with the involvement of neutrophils, but also in humoral immunity.

Immunosuppression in dogs with stage I and II of CKD

Dogs with stage I CKD are usually asymptomatic and present with other renal abnormalities such as changes in imaging tests, abnormalities on palpation and biopsy, and changes in serial URE and CRE collections. In stage II of CKD, there are slight increases in URE, CRE and SDMA concentrations and discrete clinical signs, such as inappetence and sporadic vomiting (Jericó et al., 2015; IRIS, 2019).

Studies by Brum et al. (2012), demonstrated (Table 4) that in a group of ten dogs diagnosed with stage II CKD, aged between four and nine years, six patients (60%) had leukocyte values within the reference values, two patients (20 %) had leukopenia and two other patients (20%) had leukocytosis, that is, dogs diagnosed with stage II CKD are not predisposed to bacterial infections due to the low concentrations of circulating uremic toxins that could cause defense cells high oxidative stress and , consequently, a higher rate of induction of apoptosis.

Table 4. Percentage of dogs diagnosed with stage II chronic kidney disease with normal leukocyte count, leukopenia and leukocytosis.

Groups	Stage II
Normal white blood cell count	60% (n=6)
Leukopenia	20% (n=2)
Leukocytosis	20% (n=2)

Source: Brum et al. (2012).

There are reports of human patients in early stages of CKD who would have increased neutrophil oxidative metabolism agents and oxidizing agents that could eventually, due to a cumulative effect, cause cellular damage to the immune system in more advanced stages of CKD, affecting the production of superoxide and accelerating the induction of apoptosis (Silva et al., 2013).

Immunosuppression in dogs with stage III and IV of CKD

Dogs affected with CKD in stages III and IV show a decrease in the production of the anion of bactericidal function for neutrophils, superoxide. Other changes at the cellular level for neutrophils are a decrease in oxidative metabolism and an increase in the rate of spontaneous apoptosis induction of these immune system cells, which are extremely important for the innate immune system of the dog with kidney disease. In dogs, as in humans, CKD causes greater induction of neutrophil apoptosis when compared to healthy patients (Silva et al., 2013). However, according to Brum et al. (2012), dogs in stage III and IV of CKD, in the majority, presented leukocytosis that may be related to the presence of infectious diseases (Table 5).

Table 5. Percentage of dogs diagnosed with stage III and IV chronic kidney disease with normal leukocyte count, leukopenia and leukocytosis

Groups	Stage III	Stage IV
Normal white blood cell count	69,4% (n=25)	36% (n=9)
Leukopenia	8,4% (n=3)	28% (n=7)
Leukocytosis	22,2% (n=8)	36% (n=9)

Source: Brum et al. (2012).

This decrease in neutrophilic oxidative metabolism and other changes that affect the phagocytic capacity of neutrophils, pointed out by Pereira et al. (2015), indicates the immunosuppressive action of the uremic state in the nephropathic patient, as already demonstrated, in an in vitro environment, by

Barbosa et al. (2010) and Silva et al. (2013) and demonstrated in dogs with uremic syndrome and in neutrophils of healthy dogs after use of uremic plasma (Tables 6 and 7) by Bosco et al. (2017).

Table 6. Non-stimulated (NE) neutrophil viability and apoptosis (mean and standard deviation) and in the presence of camptothecin (CAM) induction measured by Annexin System V-PE in flow cytometry in healthy (n = 16) and uremic dogs (n = 16)

Parameter	Healthy	Uremic	p-Value
Viability (NE)	98,76 ± 0,21	98,17 ± 0,82[a]	0.0087
Viability (CAM)	85,15 ± 3,30	77,88 ± 4,12[a]	0.0001
NE apoptosis rate (%)	0,30 ± 0,12	0,48 ± 0,27[a]	0.0288
CAM apoptosis rate (%)	7,91 ± 2,48	15,73 ± 4,02[a]	0.0001

[a] Statistically significant difference by unpaired Tukey test. **Source**: Bosco et al. (2017).

Table 7. Viability and apoptosis (mean and standard deviation) of neutrophils from healthy dogs incubated in RPMI 1640 medium (Control) or with the addition of uremic plasma (50%) in the absence (not stimulated, NE) or in the presence of camptothecin induction (CAM) (n = 12).

Parameter	Healthy	Uremic	p-Value
Viability (NE)	98,18 ± 0,27	98,42 ± 0,86[a]	0.0164
Viability (CAM)	79,91 ± 5,18	64,18 ± 10,43[a]	0.0011
NE apoptosis rate (%)	0,38 ± 0,20	1,36 ± 0,79[a]	0.0020
CAM apoptosis rate (%)	19,38 ± 4,49	34,53 ± 10,80[a]	0.0018

[a]Statistically significant difference by unpaired Tukey test. **Source:** Bosco et al. (2017).

In humans, impairment of adaptive immune activity has also been reported due to the uremic environment and to dialysis therapy and its complications (Table 8). Alterations such as linear decrease in the count of $CD4^+$, $CD8^+$ and $CD45^+$ lymphocytes, decrease in proliferation, induction of apoptosis by activation and deficiency of T lymphocytes, greater pro-apoptotic activity of naïve T lymphocytes, pre-activation of antigen-presenting cells and production of Pro-inflammatory cytokines by Th1 and Th2 lymphocytes that act on innate and adaptive immunity favor infections and low or no response to vaccines in patients with end-stage CKD (Betjes, 2013; Syed-Ahmed & Narayanan, 2019).

Table 8. Changes in cells of the adaptive immune system under uremic conditions

Adaptive immune system cell	Normal function	Status in uremic environment	Changes under uremic syndrome
Regulatory T lymphocytes	Antigen presentation (CD4+), Cytotoxic responses to virus-infected cells and tumor cells (CD8+)	Decrease	Deficit immune response to vaccines, high risk of severe infections, increased risk of cardiovascular disease, increased pro-inflammatory environment.
Effector T lymphocytes	Suppression of T lymphocyte-mediated immune responses	Decrease	Reduction in IL-2 production and reduction in suppressive activity.
B lymphocytes	Antigen presentation and antibody production	Decrease (naïve and memory cells)	Deficit in serological responses.
γδ T lymphocytes	Unknown	Unknown	Unknown

Source: Adaptado de Betjes (2013) and Syed-Ahmed & Narayanan (2019).

According to Lemesch et al. (2016), human patients with end-stage CKD and undergoing hemodialysis had a higher mortality due to bacterial infections when compared to patients undergoing peritoneal dialysis, however, in Veterinary Medicine, studies by Perondi et al. (2020), demonstrated that dogs undergoing hemodialysis, where non-permanent central venous catheters were used, had a prevalence of irrelevant bacterial contamination, positively impacting the survival of these dogs with advanced-stage CKD and undergoing renal replacement therapies.

Intervention measures under immunological disorders

Due to the progressive loss of nephrons and replacement of functional tissue by fibrous tissue, CKD is characterized by irreversibility and the use of drug therapy aimed at maintaining the remaining nephrological function (Quimby et al., 2013).

The use of mesenchymal stem cells (MSCs) has emerged in veterinary medicine as an alternative treatment with the aim of tissue regeneration, reduction of the pro-inflammatory environment and immunomodulation (Malard et al., 2020). Studies by Malard et al. (2020) demonstrated that the use of MSCs in dogs and cats with CKD favored, as a result of the paracrine effect of this cell therapy, the fight against inflammation, a decrease in the rate of apoptotic induction, immunomodulation and protection of the architecture and remaining renal function, corroborating the studies performed by Perico et al. (2018), where it was observed that the benefits of using cell therapy in human patients with CKD stem from the immunomodulatory action of MSCs, where they acted under the innate and adaptive immune system, preventing the activation and proliferation of lymphocytes, favoring maturation of dendritic cells and causing the reprogramming of monocytes and macrophages from the pro-inflammatory state to the anti-inflammatory state.

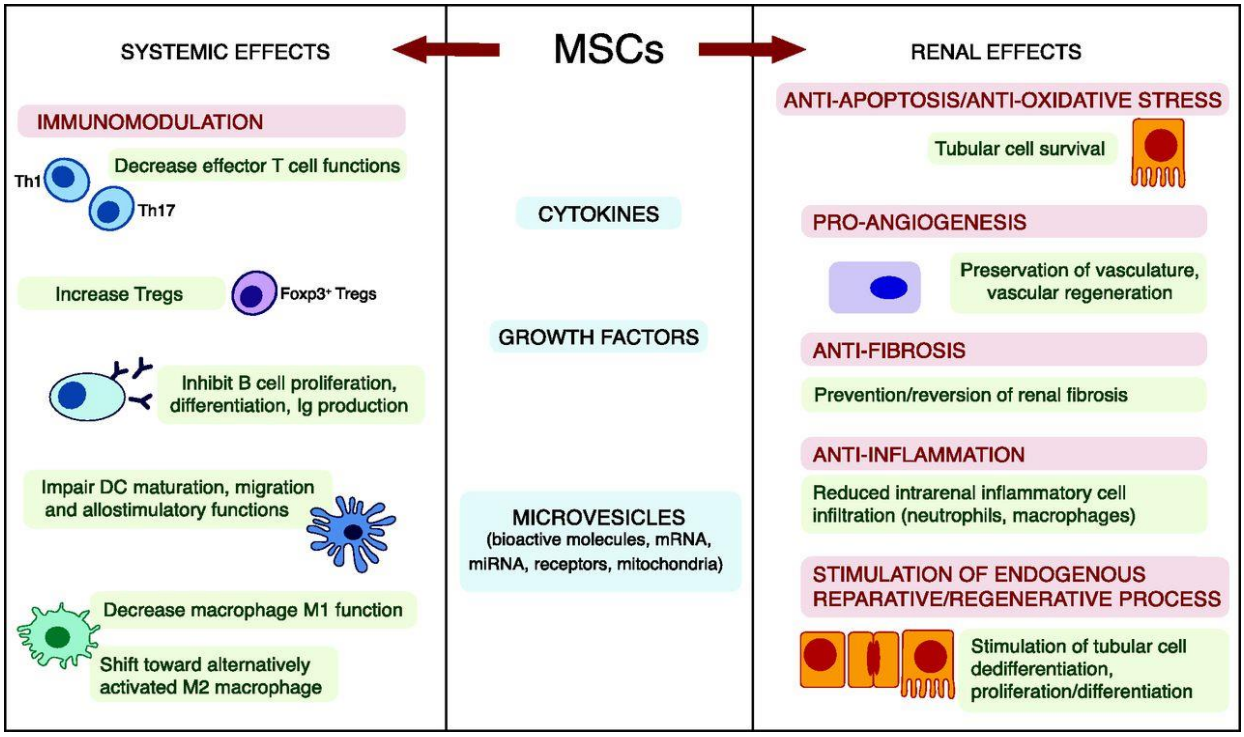

Figure 4. Renal and systemic effects of mesenchymal stem cells. **Source:** Perico et al. (2018).

Furthermore, it was demonstrated by Saad et al. (2017) and Rota et al. (2018) that in human patients, growth factors and cytokines released by MSCs act providing better patient survival by limiting podocyte loss, rarefaction of glomerular capillaries, stimulation of M2-type macrophages, decreased oxidative stress of cells tubular and increased angiogenesis.

Conclusions

CKD is a serious disease in the Small Animal Medical Clinic and the professional must pay attention to the stage of the affected patient and establish not only a therapy that aims to maintain the remaining renal function, but also carry out effective monitoring approaches and measures so that this patient has, in the smallest possible ways, deleterious effects on your body.

Immunosuppression in CKD should receive greater attention from the moment the animal is classified in stage III of the disease, aiming at the full impact that the pro-inflammatory environment caused by uremia can cause to the cells of the immune system, predisposing this patient to conditions of secondary infections.

In Veterinary Medicine, the use of interventional therapies, even at an experimental level, such as the use of halogen stem cells, would make it necessary to expand research to determine criteria for use that can provide dogs affected by CKD with a better clinical management, interventional therapy and, consequently, prognosis.

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