Chronic kidney disease in felines and the use of SDMA for diagnosis: Literature review

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ABSTRACT

Due to the domestication process, tutors are increasingly concerned with ensuring better living conditions for their pets. This has reflected in the increased longevity of pets. Felines, due to anatomical, physiological and dietary aspects, have a certain predisposition to problems affecting the system renal.Com this, chronic kidney disease (CKD) is a progressive and irreversible disease, being an important cause of death in felines, especially with advanced age. Unfortunately, its initial signs are silent, becoming evident as the lesion progresses, thus allowing the worsening of the condition. Thus, when the diagnosis occurs, the evolution is already well established. Symmetrical dimethylarginine (SDMA) is a biomarker of renal function, correlated with glomerular filtration rate (TGF), and is used to evaluate the existence of Chronic Kidney Disease, because unlike the quantification of serum creatinine, it is not influenced by extrarenal mechanisms, for this reason it is considered more efficient. In 2015, SDMA became provisionally part of the International Society of Renal Interest (IRIS) classification of CKD as a complementary test of kidney function aiding in the classification of disease stages, thus allowing the identification of disease stages and substages. In this way, it is possible to better monitor and determine the most appropriate treatment for each patient.

Keywords: Biomarker, Precocity, Felines, Renal system.

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INTRODUCTION

The renal system has numerous functions of extreme importance in the body's homeostasis, due to: excretion of metabolic products and waste (aiding in detoxification), hormone production (allowing the processes of hematopoiesis and calcium and phosphorus balance), regulation of the volume and composition of the extracellular fluid (LEC), water excretion (regulating blood volume and pressure), excretion of ions (acting on electrolyte balance) and, consequently, influencing the regulation of the acid-base balance (HAGIWARA, 2014; REECE, 2017)

Currently, the assessment of quality of life has been shown to be increasingly important in the management of chronic diseases, since they have a negative impact on the lives of patients. In felines, due to their evolutionary process and consequently their eating, physiological and anatomical habits, they are highly affected by chronic kidney disease (CKD), an important and common nephropathy, being the main cause of death in this species, with a recently identified prevalence estimated at 1 to 3% in this species, among which 30% are over 15 years of age at diagnosis (ROBERTSON, 2015; LOURENÇO, 2019)

In the long term, this disease culminates in the appearance of toxic neurological changes secondary to the accumulation of residues of cellular catabolism, in some cases even adopting preventive measures, factors such as age, heredity, can cause the disease, especially if treated properly and in time, the animal can lead a healthy life despite some restrictions. (TOZZETTI, 2009)

Chronic Kidney Disease is characterized by the progressive and irreversible loss of nephrons, resulting from a range of kidney disorders, compromising at least 75% of their functional activity, culminating in the loss of excretory and concentrating functions of the kidneys. Thus, it is correlated with glomerular filtration rate (GFR) and functional renal mass. (MCGAVIN , 2013; ZACHARY, 2013; CRIVELLENTI, 2015)

Thus, research for more sensitive renal biomarkers is the focus of studies, as they can provide an early diagnosis, allow the establishment of appropriate therapy for each patient and improve their quality of life. (OLIVEIRA, 2020)

According to Lourenço (2019), one of the reference methods for assessing renal function, allowing the measurement of the glomerular filtration rate, corresponds to the verification of serum concentrations of urea and creatinine. These methods, because they are not used frequently, allow the use of alternative markers.

With this, the renal biomarker Symmetric Dimethylarginine (SDMA) has shown significant results in terms of early diagnosis of kidney disease, being able to detect kidney injury when 50% or less of the function is compromised. (OLIVEIRA, 2020)

This is because, according to Lourenço (2019), SDMA corresponds to a stable molecule, widely excreted by the kidney, making it a good choice as a renal biomarker, as its size and load allow it to be freely excreted by glomerular filtration. In addition, the dosage of this biomarker is extremely accurate, being used to carry out the early diagnosis of CKD, allowing the taking of renoprotective interventions that slow its progress, or aim to stabilize the disease.

The objective of this study was to perform a literature review regarding Chronic Kidney Disease in felines, the use of MDDA in the early diagnosis of Chronic Kidney Disease, in addition to evaluating its use and success by veterinary professionals in the veterinary medical routine.

LITERATURE REVIEW

FELINES AND THEIR RELATIONSHIP WITH KIDNEY DISEASE (CKD)

As discussed by Scholten (2017), cats have always played an important role in the history of human civilization, presenting adaptability, independence, and versatility. In this way, the author in her work demonstrates the importance of studies on the individuality of these animals, because even with great advances in the veterinary medical and surgical clinic of small animals, professionals and their owners are often unaware of the true nature of the cat and its normal behavior. This issue leads to a lack of understanding, which directly compromises the efficiency of diagnosis.

Therefore, Scholten (2017) made it clear that behavioral analysis is the initial measure for detecting various types of problems from different origins in domestic cats and serves as the main source of evidence for the evaluation of animal welfare. The author Lucca (2022), following the same line of reasoning, also raised in his work the importance of knowledge about the natural behavior of the species and well-being, since stress can lead to numerous losses.

Thus, the assessment of quality of life has been shown to be increasingly important in the management of chronic diseases, since they have a negative impact on the lives of patients. In cats, chronic kidney disease is the most common nephropathy and is the leading cause of death at ages above five years inclusive (FEITOR, 2021).

In cats, Chronic Kidney Disease (CKD) is considered the most common nephropathy, being associated with treatments and regular monitoring through the measurement of kidney function biomarkers. In addition, the International Renal Interest Society (IRIS) aims to facilitate the diagnosis and clinical management of this disease (Polzin, 2016).

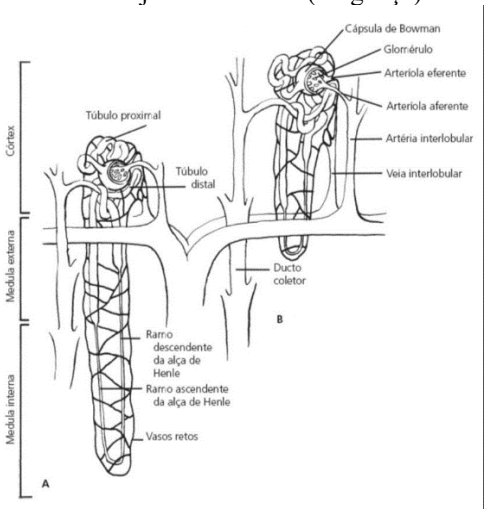
More recent studies suggest that CKD is higher (more than 40%) among felines aged 5 to 15 years, reaching a higher involvement (80%) in cats over 15 years of age (Marino et al., 2014).

Thus, kidney health over the last few years has drawn the attention of veterinarians, as the impairment of this organ in chronic renal failure is an important cause of morbidity and mortality in felines. Thus, Agopian (2016), in his study, proposes the biometric characterization of the kidneys of cats, Felis catus, under the macroscopic (length, height, width, weight and volume), mesoscopic (height of the cortex and medulla, and their interrelation) and microscopic (glomerular volume) aspects, in order to establish possible differences resulting from age, sex and bilateral symmetry.

Although more studies are needed on the possible existence of racial predisposition, apparently this disease is more common in the Maine Coon, Abyssinian, Siamese, Russian Blue, Burmese and Ragdoll breeds. The presence of a history of Acute Kidney Disease (ARD) or nephropathies, as well as the administration of nephrotoxic drugs are also considered risk factors (Maniaki & Finch, 2018; Langston & Eatroff, 2020)

Cats, as reported by Reece (2008) and Konig, Maierl and Liebh (2016) and Carvalho (2020), can have approximately 190,000 nephrons in each kidney, having a large number of long-loop juxtamedullary nephrons (Figure 1), which justifies the ability to concentrate their urine, and consequently the greater predisposition to diseases related to this system. Thus, kidney failure is a very common condition in the species, about 50% to 60% of cats will have some kidney dysfunction at some point in their lives, especially in senile animals. (PAZ, 2016).

Fig. 1. Types of mammalian nephron. A. néfron justamedulares (long alça) B. néfron corticais. Source: Reece, 2017



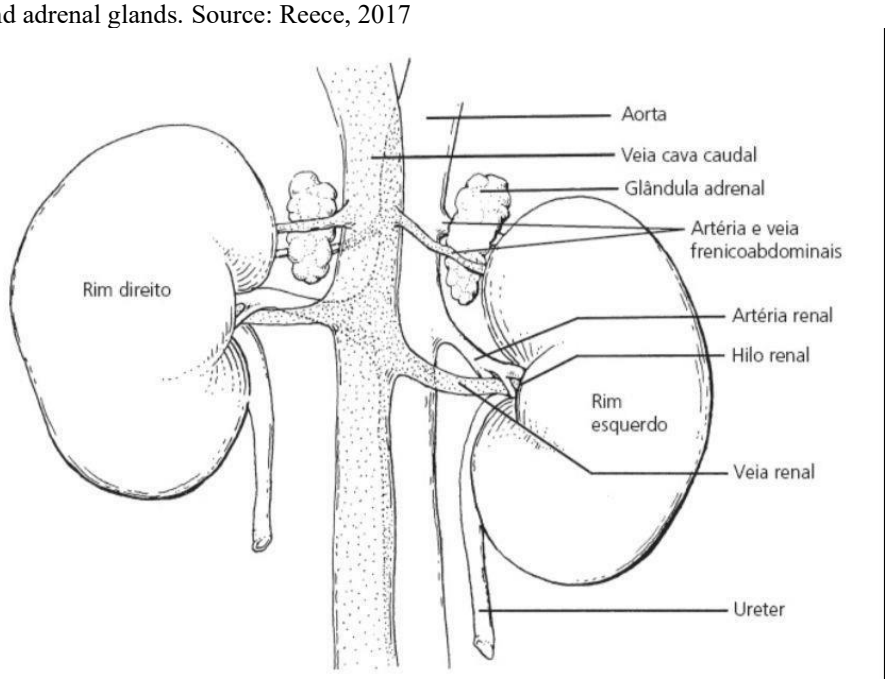
The main nephropathies in the feline species are: acute renal failure, chronic kidney disease, bacterial pyelonephritis, glomerulopathies, polycystic renal disease, amyloidosis, nephrotoxicosis and neoplasms (Anjos, 2014). This highlights the need for early diagnosis techniques, in order to allow the clinician to intervene as quickly as possible, and can delay the process of advancement and worsening of the disease. (PAZ, 2016).

RINS

The feline kidneys are located in the retroperitoneal space, being separated by the peritoneal envelope, caudomedial to the splenic cranial portion, lateral to the aorta, with an appearance similar to "beans". (KOGIKA, WAKI, MARTORELLI, 2015).

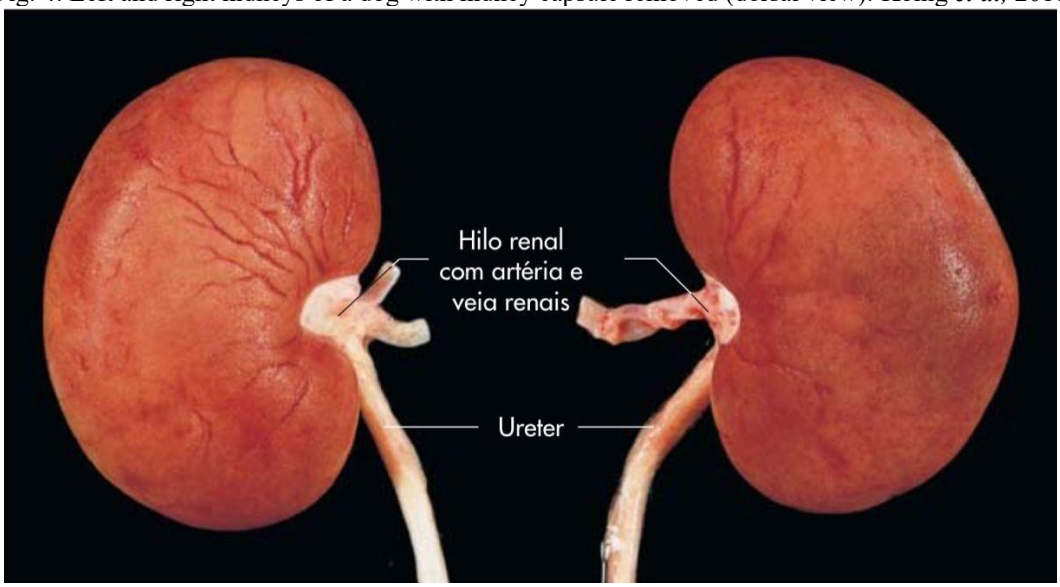
The renal system, Jericho (2015), Konig, Maierl and Liebh (2016) and Reece (2017), is then composed of the pair of kidneys, which are organs surrounded by fatty tissue, paired and suspended in the dorsal abdominal wall by a peritoneal fold and blood vessels, renal artery and renal vein, being responsible respectively for the irrigation and drainage of each organ. These vessels flow into the organ through the renal hilum (**Figure 3**), at the medial border, which is in the concave part of the organ, where it is also possible to find the nerves and lymphatic vessels, in addition to the ureter. They are located cranial to the mid-lumbar region, where in the feline species, the right kidney is positioned near the L1-L4 vertebrae, while the left kidney, the L2-L5. These are what can contribute to its localization during abdominal palpation (KOGIKA, WAKI, MARTORELLI, 2015).

Fig. 3. Ventral view of the kidney, showing the renal arteries, renal veins, and ureters and their position in relation to the aorta, vena cava, and adrenal glands. Source: Reece, 2017



Each kidney, Hagiwara (2014) and Reece (2017), has a cortical region and a medullary region **(Figure 4),** which we observe striations due to anatomical dispositions of the loops of Henle of the nephrons of long loops. In this region we also find the collecting tubules, which aim to conduct the glomerular filtrate to the renal pelvis and posterior to the urethra.

Fig. 4. Left and right kidneys of a dog with kidney capsule removed (dorsal view). Konig *et al,* 2016

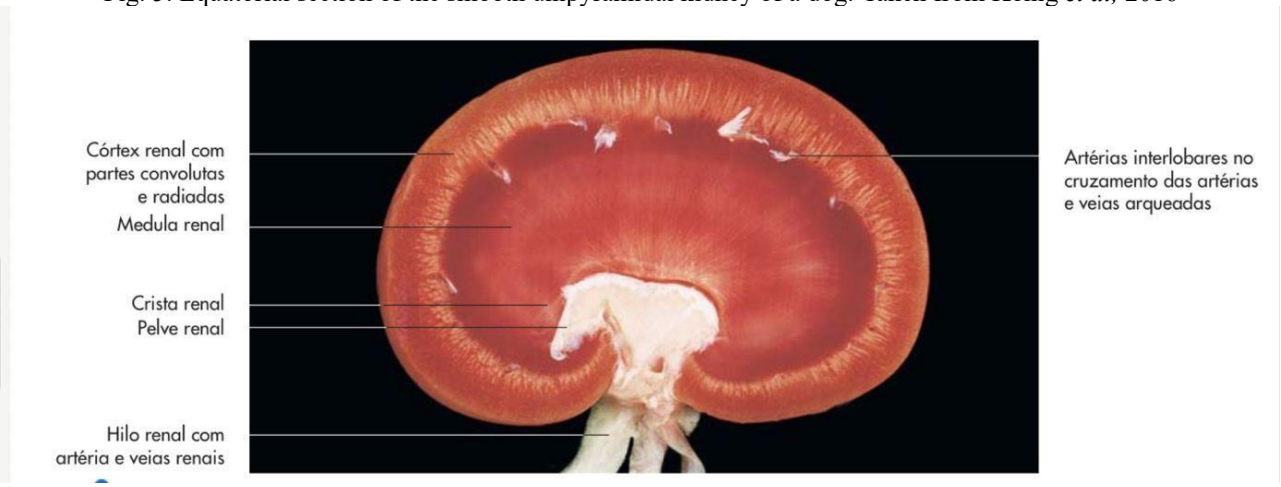


We observed in dogs and cats that the kidney is unilobar, composed of a group of nephrons and covered with a fibrous capsule; The parenchyma is formed by a medullary region and a cortical region. In small animals, the corticomedullary ratio is approximately 1:2 or 1:3. (KOGIKA, WAKI, MARTORELLI, 2015). A mean cortical renal thickness of 0.82 ± 0.14 cm and medullary thickness of 0.59 ± 0.06 cm have been described in healthy felines (DEBRUYN et al., 2012).

The renal parenchyma is surrounded by a resistant fibrous capsule, a thin and shiny fibroelastic membrane called the renal capsule, which enters the medial aspect of the kidney to line the walls of the renal sinus, protecting it from certain diseases. This capsule remains attached to the pelvis and blood vessels, and can be easily removed from a healthy kidney during postmortem examination, but adheres to it after the tissue has been marked by disease. (KONIG *et al,* 2016; VERLANDER, 2007, SANDOVAL, 2018)

The blood supply of this system is derived from the Abdominal Aortic Artery, which will branch into the renal artery, and from the renal parenchyma, into the interlobar artery (which will supply the renal lobe, the corticomedullary junction and the cortical region) **(Fig. 5**), and, subsequently, into glomerular capillaries (EVANS, DE LAHUNTA, 2010; KOGIKA, WAKI, MARTORELLI, 2015)

Fig. 5. Equatorial section of the smooth unipyramidal kidney of a dog. Taken from Konig *et al,* 2016



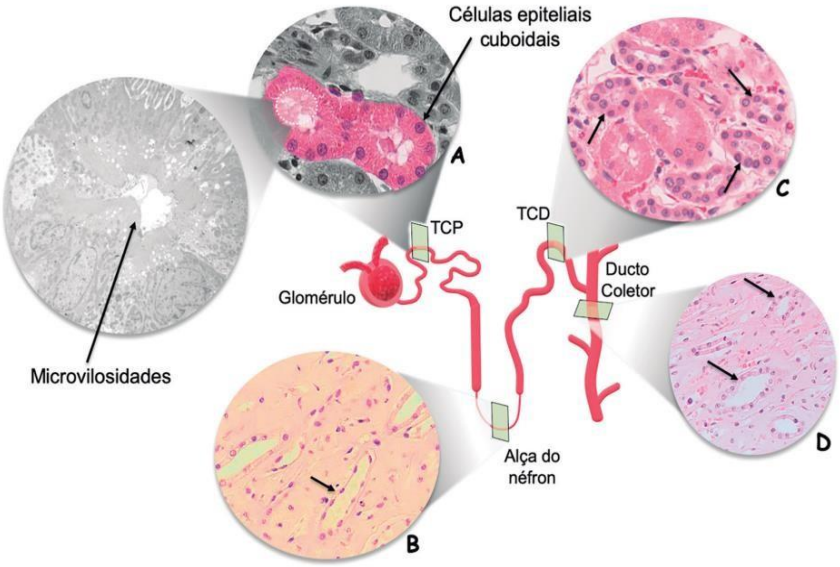
The wall of these capillaries has three layers (**Fig. 6**), the innermost portion being a continuation of the endothelium of the afferent arteriole, covered by a layer of endometrial cells, which have fenestrae, which allow the passage of water and other molecules of low molecular weight. The intermediate layer, consisting of a glomerular basement membrane (GBM) is another structure that offers resistance to the filtration of macromolecules. The third component of the filtration process is the epithelial layer, made up of podocytes, giving rise to the visceral leaflet of Bowman's capsule. (RIELLA, 2010; KOGIKA, WAKI, MARTORELLI, 2015; CRIVELLENTI *et al* 2021).

ANATOMOPHYSIOLOGY OF GLOMERULAR FILTRATION

Glomerular filtration rate (GFR) measures the amount of filter formed in the nephrons of both kidneys (in mL) per unit time (minutes) per body weight (in kg) of the animal. It is an extremely important parameter for verifying renal functionality, and with this, verifying Chronic Kidney Disease. (FINCH & HEIENE, 2017; NHANHARELLI, 2018)

Structurally, there are differences between the tubular segments (**Figure 9**), with histological differences related to different physiological functions. CRIVELLENTI *el al*, 2021

Figure 9 – Histopathology scheme of the renal tubules. A) Proximal convoluted tubule (TCP) and enlarging microvilli can be observed under electron microscopy. B) Nephron loop. C) Distal convoluted tubule. D) Collecting duct. Source: CRIVELLENTI *el al,* 2021



The filtration process has as its starting point the glomerulus, located in the renal cortex, and is composed of a filtration membrane containing three layers: fenestrated capillary endothelium, glomerular basement membrane and cells of the visceral epithelium of the glomeruli (podocytes). What determines the continuous filtration rate is the pressure of the blood inside this glomerulus, thus flowing the fluid into Bowman's capsule and, subsequently, into the proximal convoluted tubule also located in the renal cortex. Following this path, the fluid will be directed to the loop of Henle, which is divided into a thin and thick segment. Subsequently, this filtrate penetrates into the distal tubule, also located in the renal cortex. (SERAKIDES and SILVA, 2016, König *et al.,* 2021; CRIVELLENTI *et al* 2021)

Also in the renal cortex, the junction of the distal convoluted tubules will occur, to form each collecting tubule, which will launch the glomerular filtrate into the renal pelvis through the renal papillae. This filtrate is similar to plasma, however it does not have large amounts of proteins (macromolecules), because they do not cross the wall of the capillaries. On the other hand, small amounts of albumin end up being filtered, and due to the importance of this protein in the body, they are quickly absorbed from the proximal convoluted tubule. (Reece, 2008; COLVILLE *et al.*, 2010; VERLANDER, 2013; SERAKIDES and SILVA, 2016)

As the glomerular filtrate evolves along the renal tubules, substances that are unnecessary for the body maintain their path, while those that are necessary, especially almost all water and many electrolytes, are reabsorbed into the peritubular capillaries. This reabsorption process is favored due to the low blood pressure in this capillary network, with about 99% of this filtrate being reabsorbed, leaving a small portion that will contribute to the formation of urine. (Verlander, 2013; SERAKIDES and SILVA, 2016)

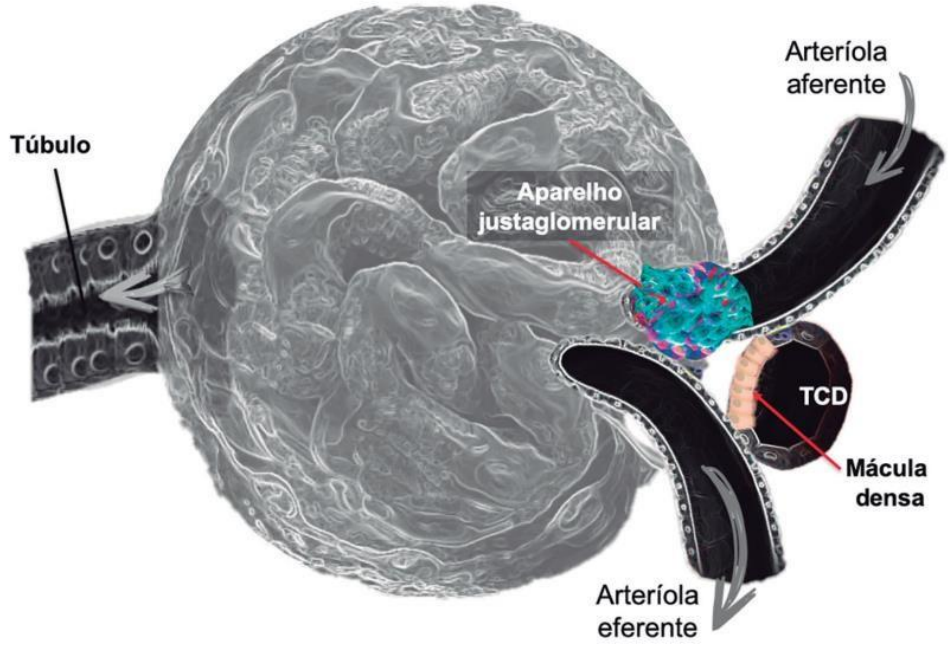
Tubular secretion is the process that occurs when substances pass from plasma through the epithelial cells, which line the tubules, to the tubular fluid, which is the second mechanism, after glomerular filtration, by which the nephron secretes undesirable substances into the plasma. Thus, urine is made up of substances that have been filtered and secreted, and this amount of glomerular filtrate formed per minute is called the Glomerular filtration rate. (COLVILLE, 2010; Verlander, 2013; SERAKIDES and SILVA, 2016)

The intensity of glomerular filtration is determined by three factors: glomerular pressure, plasma colloidsmotic pressure, and pressure in Bowman's capsule. Thus, there are some conditions that affect these factors and consequently the intensity of glomerular filtration, such as renal blood flow, constriction of the afferent arteriole, and constriction of the efferent arteriole. (SERAKIDES and SILVA, 2016)

Inside the kidneys, through local mechanisms, such as feedback, the intensity of glomerular filtration and renal blood flow is controlled. To achieve this, each nephron can trigger vasodilator feedback from the afferent arteriole or vasoconstrictor feedback mechanism from the efferent arteriole. (REECE, 2008, COLVILLE *et al.*, 2010; Konig *et al.*, 2020)

The juxtaglomerular complex (**Figure 10**) is formed by the macula densa (epithelial cells of the distal convoluted tubules in contact with the afferent and efferent arterioles) and by the juxtaglomerular cells (smooth muscle cells of the afferent and efferent arterioles that secrete renin). (COLVILLE, 2010, REECE, 2017)

Figure 10 – Macula densa and juxtaglomerular apparatus are closely linked and work to maintain the proper filtration rate. TCD: distal convoluted tubule. Source: CRIVELLENTI *el al*, 2021



In the event of a reduction in the flow of the glomerular filtrate, it will result in a low concentration of chloride and sodium ions in the macula densa, triggering a signal from the macula densa to dilate the afferent arteriole, with consequent increase in blood flow to the glomerulus and increase in glomerular pressure. The low concentrations of these ions (chloride and sodium) will also induce the juxtaglomerular cells to release renin, which, in turn, results in the formation of angiotensin II, responsible for the production of vasoconstriction of the efferent arterioles, culminating in the elevation of glomerular pressure. (SERAKIDES AND SILVA, 2016; FINCH & HEIENE, 2017)

This increase in glomerular pressure results in increased blood flow, resulting in an increase in filtration intensity until the required level is reached. Thus, vasodilation of the afferent artery is one of the most important mechanisms for self-regulation of blood flow. (COLVILLE, 2010)

When there is a drop in renal blood flow, the glomerular filtration rate will also be affected, suffering a decrease. Due to this reduction, a feedback effect is generated in the juxtaglomerular complex, resulting in dilation of the afferent arteriole, allowing greater blood flow through the glomerulus and greater filtration. (HAGIWARA, 2014)

In cases of very low glomerular filtration, it would result in a slowdown of the fluid by the renal tubules, and with this practically all of it would be reabsorbed, thus compromising the elimination of necessary catabolic products. On the other hand, if the intensity of glomerular filtration were high, the glomerular filtrate would pass so quickly through the renal tubules that they would be unable to absorb the substances that should be preserved in the body, resulting in numerous losses. That is why it is extremely important to maintain the constancy of the glomerular filtration rate. (HAGIWARA, 2014; SERAKIDES and SILVA, 2016)

Thus, the proximal convoluted tubule, the longest segment, has epithelial cells with high metabolism, with a large number of mitochondria, to maintain the processes of rapid active transport. Thus, the primary function of these cells is the absorption of 70% of the glomerular filtrate. (COLVILLE, 2010; VERLANDER, 2013)

In this segment, there is an important active reabsorption of glucose and amino acids, in addition to sodium, calcium, potassium, chloride and phosphate ions. Hydrogen ions represent the most important substance secreted by active transport, filtered urea, approximately 30 to 40% is reabsorbed in these tubules, and creatinine does not have reabsorption by nephrons, but becomes more concentrated as the reabsorption of other substances occurs. (SERAKIDES and SILVA, 2016; REECE, 2017)

The first two-thirds of the TCP are called the "pars convolute" and followed by the final third called the "pars recta". This differentiation is not only present in the name, but in structure

and function. The CPET epithelium is subdivided into three types: segment 1 (S1), which makes up the initial short segment of CPET; segment 2 (S2), which makes up the rest of the CPT and the cortical part of the pars recta; and, finally, segment 3 (S3), composed of the medullary segment of the pars recta. CRIVELLENTI *el al,* 2021

In sequence, the small segment of the loop of Henle, responsible for urine concentration, has a thin epithelium, with absence of cells on the brush edge and a reduced number of mitochondria, indicating minimal metabolic activity. REECE, 2008; REECE, 2017.

This capacity in concentration is proportional to the length of the loop of Henle, with the descending branch being highly permeable to water and moderately permeable to urea, sodium and most other ions. While the ascending branch has less permeability to water and solutes (urea and ions). (COLVILLE, 2010; HAGIWARA, 2014, CARVALHO, 2020)

The thick segment of the loop of Henle has taller epithelial cells, similar to those of the proximal tubule, but its cells have a rudimentary brush border, and they are highly adapted for the reabsorption of sodium and potassium ions. On the other hand, this segment is almost completely impervious to water and urea. (VERLANDER, 2013; HAGIWARA, 2014)

Regarding the distal tubule, its first half has characteristics similar to the thick segment of the ascending ramus of the loop of Henle. Its cells absorb most ions, but in relation to water and urea they are almost completely impermeable. (COLVILLE, 2010; HAGIWARA, 2014)

The final portion of the distal tubule and the cortical portion of the collecting tubule have epithelium that is almost completely impermeable to urea. These two segments absorb sodium ions at a speed controlled by aldosterone. In these segments, the active secretion of potassium ions also occurs, controlling the concentration of these ions in the body's extracellular fluids. In these segments it is also possible to find a special epithelial cell, known as an intercalated cell, responsible for actively secreting hydrogen ions. Related to water, its permeability only occurs in the presence of antidiuretic hormone (ADH), in order to provide a means to control the degree of dilution of urine (SERAKIDES and SILVA, 2016).

The collecting tubule has cuboid cells in the composition of its epithelium, which have a smooth surface, and few mitochondria. The permeability of water, in this segment, is also controlled by ADH, and in relation to urea, it has slight permeability. An important characteristic of this segment is related to the ability to secrete hydrogen ions, in this way, the final portion of the distal convoluted tubule and the collecting tubule play an important role in controlling the acid-base balance of body fluids. REECE, 2008, REECE, 2017; HAGIWARA, 2014

Thinking about the acid-base balance, the first systems associated with this maintenance are the body plugs and pulmonary control (from the excretion of carbon dioxide), thus forming

the first line of defense in maintaining the pH of extracellular fluids. (SERAKIDES and SILVA, 2016 ; REECE, 2017)

With this in mind, the normal blood pH is approximately 7.4, so the kidneys also participate in this correction of the acid-base imbalance, performing the correction of metabolic alkalosis by the excretion of alkaline urine with excess bicarbonate ions, or in metabolic acidosis by increasing the reabsorption of bicarbonate, by the secretion of hydrogen ions or by the excretion of ammonia. (VERLANDER, 2013; SERAKIDES and SILVA, 2016)

During embryonic development, the urinary system is closely associated with the genital system. Both have a mesodermal origin, from the urogenital crest, located along the posterior wall of the abdominal cavity.(SERAKIDES and SILVA, 2016)

The primary function of the kidneys consists of the formation of urine, thus keeping the composition of body fluids within the physiological parameter. (KONIG *et al,* 2016, Carvalho, 2020)

To understand renal function, according to Serakides and Silva (2016) and Garcia (2011), understanding the functionality performed by nephrons is essential, precisely because they are responsible for maintaining the physiological integrity of the volume and constituents of the extracellular fluid. This is possible due to the ability to conserve water, fixed cations, glucose and amino acids; elimination of nitrogenous products from protein metabolism (urea, creatinine, uric acid, and urates); plasma clearance of excess sodium, potassium and chloride ions; elimination of excess hydrogen ions to maintain the pH of body fluids and elimination of endogenous and exogenous organic compounds. In addition to these functions, the kidneys also have endocrine functions, producing the hormone renin (responsible for the conversion of angiotensin I into angiotensin II, involved in the process of arterial constriction and consequently increased blood pressure), bradykinin (causes the dilation of blood vessels), erythropoietin (stimulates the process of erythropoiesis), in addition to the production of 1,25dihydroxycholecalciferol and prostaglandins. (KONIG *et al,* 2016; SERAKIDES and SILVA, 2016; POLZIN, 2017)

Erythropoietin synthesized in the kidneys, according to Serakides and Silva (2016) and Verlander (2017), is a glycoprotein produced by interstitial and/or endothelial cells of the peritubular capillaries of the cortical and medullary regions, in occurrence of a reduction in blood oxygen concentration, so it acts directly on the stimulation of erythropoiesis by the bone marrow.

Renin, according to Serakides and Silva (2016), is also a glycoprotein synthesized by the cells of the juxtaglomerular complex, in which there is a decrease in blood pressure due to the reduction in extracellular volume. Renin converts angiotensinogen into angiotensin I, which is

then converted into angiotensin II, exerts an effective vasoconstrictor action, in addition to causing the stimulation of aldosterone release by the adrenal cortex, resulting in increased sodium reabsorption and, consequently, water reabsorption from the renal tubules. These effects corroborate the elevation of blood pressure.

In addition to these activities, according to Serakides and Silva (2016) and Polzin (2017), the kidneys are also involved in the final stage of transformation from the inactive form of vitamin D to the biologically active form, that is, they convert 25hydroxycholecalciferol, which originates from the hepatic pathway, into 1,25dihydroxycholecalciferol, essential in the process of intestinal calcium absorption.

The secretion of prostaglandins, according to Serakides and Silva (2016), is carried out through the cells of the interstitium, the collecting ducts, and the wall of the renal arteries through the action of cyclooxygenases 2. Prostaglandins have little influence on the maintenance of blood pressure under normal conditions. However, in periods of hypotension, they exert a great contribution to the regulation of renal blood flow, sodium and water transport, and glomerular filtration, precisely by the release of renin and antidiuretic hormone and, indirectly, by the release of angiotensin II, aldosterone, and kallikrein.

Thus, according to Serakides and Silva (2016) and Takasa (2017), when using non-steroidal anti-inflammatory drugs (NSAIDs), great care must be taken with the dose, period of administration and hydration status of the patient, since the vasodilation performed by prostaglandins in the medullary region can be suppressed due to the inhibitory action of NSAIDs on the synthesis of cyclooxygenases 2. Thus, the medullary region, which usually already has less blood supply compared to the cortical one, can suffer ischemia process, resulting in necrosis of the renal papillae and extensive areas of the medullary region.

For the kidneys to perform their functions efficiently, the following are necessary: normal urine elimination, adequate blood perfusion, and functional kidney tissue. To perform their functions well, the kidneys carry out three essential processes: glomerular filtration and tubular resorption and secretion. (SERAKIDES and SILVA, 2016; KONIG *ET AL* 2021)

CHRONIC KIDNEY DISEASE IN FELINES

Chronic Kidney Disease is a syndrome linked to the progressive alteration of the excretory and endocrine functions of the kidney related to extensive (more than 70%) and irreversible lesions of the renal parenchyma. It may or may not result in a drop in the Glomerular Filtration Rate (GFR), depending on the stage. It is characterized by a permanent increase in urea and blood creatinine due to a drop in urinary density. (MORAILLON, 2013)

The term renal failure was recently replaced by renal disease, where through the staging of the severity of the disease, it provides a better understanding, communication and application of the necessary management guidelines. (ROUDEBUSH, 2009)

Chronic renal failure (CKD) occurs due to the inability of the kidneys to perform their functions, as a result of the progressive and gradual loss of kidney tissue over a prolonged period (months or years). Commonly, it is irreversible and is the end result of many kidney diseases, usually but not necessarily, chronic. CRF is not synonymous with chronic kidney disease, so there can be CRF without chronic kidney injury, and vice versa. In CKD, several extrarenal lesions can be observed. Regardless of whether or not uremia is of renal origin, the lesions that result from uremia are similar and are primarily intrarenal and multisystemic. (COLVILLE, 2010; SERAKIDES and SILVA, 2016)

It is the most common urinary tract disorder in cats, being responsible for high rates of morbidity and mortality, having several origins, which, however, are often unknown. It consists of a structural kidney injury, for at least 3 months, due to its insidious evolution, resulting in the occurrence of irreversible damage, observing a 50% drop in GFR. (GUSSO, 2021; JERICÓ, 2015; MARCUZ, 2022)

The feline species, according to Reece (2008) has 190,000 functional nephrons in each kidney, which compared to other species, such as cattle (4,000,000), is a small number. Normal TGF values in felines are 2 to 4 ml/min/kg. These are dependent on adequate renal blood flow, the number of functional nephrons and both tubular and interstitial blood pressure, thus being a method that is not so simple to measure (THRALL *et al.,* 2015; CRIVELLENTI *et al* , 2021).

Chronic renal failure corresponds to a pathology commonly found in dogs and cats, with prevalences of 0.5 to 7% and 1.6 to 20%, respectively, being one of the frequent affections in the feline species, increasing with age, and can thus reach 80% in geriatric cats. Although there is no racial and age predilection, morbidity and mortality are predominant in older dogs and cats (WAKIL et al., 2010; MARIANO *et al*, 2014).

This system is so important that according to Paz (2016), about 20% to 25% of the total body flow is destined to the kidneys, evidencing the need for a greater volume of blood flow when compared to other organs. Thus evidencing its susceptibility to injuries, justified due to its unique anatomical and functional characteristics, such as the significant blood supply from cardiac output, its filtering and biotransforming function.

Thus, due to the high need for blood flow, associated with these particularities, they confer greater vulnerability to injuries and possible pathologies, especially of a toxic, ischemic and infectious nature (PAZ, 2016; PAIVA, 2018)

The distribution of renal circulation is not uniform, approximately 90% irrigates the renal cortex and 10% is destined to the medullary region. Therefore, it is justifiable that a more vascularized region is more susceptible to lesions caused by toxins, while the portion with small blood supply presents more problems in the case of systemic hypotension, easily suffering ischemic episodes. (Langston, Estroff, 2010; Paz, 2016)

In terms of symptomatology, we can separate them into three phases, namely: Installation Phase (initial), State Phase (uremic CKD) and Terminal Phase. The installation phase is characterized by being silent, where I will observe the increase in water consumption and the decrease in urinary density. However, urea and creatinine levels may be normal. In the second phase, the animal may present dehydration, asthenia, weight loss, digestive signs (dysorexia, vomiting, diarrhea, ulcers, anemia (due to a drop in erythropoietin synthesis), arterial hypertension, bone demineralization (linked to secondary hyperparathyroidism) that causes pain, lameness. (MORAILLON, 2013)

Finally, in the terminal phase, we may observe oliguria or anuria, worsening of the animal's general condition (asthenia, thinness, anorexia, dehydration), worsening of digestive problems, modified respiratory curve (metabolic acidosis), nervous signs, tremors, uremic coma. In addition, we also observed a very significant increase in urea and creatinine. (MORAILLON, 2013)

In summary, the main manifestations observed in clinical routine will be apathy, anorexia, emesis, weakness, dehydration, polyuria, polydipsia, constipation, diarrhea. Treatment should be carried out based on the stage of the disease and individualized according to the case of each patient. (MARCUZ, 2022)

After the onset of the disease, due to the lesions and loss of nephrons, there is a compensatory increase in the glomerular filtration rate (GFR) of each patient, with an increase in the intraglomerular pressure of the remaining nephrons. The increase in flow in the capillary causes an increase in the passage of proteins and thus, greater filtration of them (NHANHARELLI, 2018)

Its clinical treatment is palliative. The therapeutic goal is to normalize fluid balance, resolve hemodynamic inadequacies, and promote urine formation. (PALUMBO, 2011).

Currently, due to evolutionary processes, it has allowed the emergence of some advanced renal therapies, such as: renal replacement therapy (dialysis and hemodialysis), kidney transplantation and stem cell therapy. However, these techniques have some limitations such as the associated costs that are often impeding their realization, their availability and the fact that they require further investigation (Jepson & Syme, 2017)

In chronic kidney disease, there is usually destruction of all renal structural components. Thus, in the advanced stages of many nephropathies, it is difficult or even impossible to define the primarily injured structure. (SERAKIDES and SILVA, 2016)

Kidney lesions, according to Polzin (2011), can be represented macro or microscopically, requiring the use of imaging techniques for the detection of macroscopic morphological changes, analysis of serum or urine samples for functional analysis, and tissue biopsy for the detection of histological changes of the parenchyma.

Thus, due to the relevance of the kidneys in physiological processes, as well as the maintenance of the body's homeostasis, studies for the determination of renal biometric parameters are fundamental, since they can serve as a reference for future clinical evaluations. The information obtained in morphometric studies determines parameters that can be used as a reference both in clinical studies and to compare possible changes resulting from various diseases. Some of them can highlight the importance of understanding the functioning of the kidneys. (AGOPIAN, 2016)

In both medicine and veterinary medicine, different stains and additional methodologies are required for the diagnosis of nephropathies, including light microscopy (LM), transmission electron microscopy (TEM), and immunofluorescence (IF) (CRIVELLENTI *et al*, 2021)

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE

Chronic renal failure, according to Colville (2010), Chew, Dibartola and Schenck, 2012; Serakides and Silva, 2016; Fidalgo, 2019, can be characterized by the occurrence of uremia and azotemia, due to Pre-renal, Renal and Post-renal occurrences. Uremia is a biochemical disorder in which there is an increase in the levels of urea and creatinine, among others, being associated with clinical signs and lesions, on the other hand, azotemia is a term mistakenly used as a synonym for uremia, however it refers only to the elevation of blood urea and creatinine concentrations, without presenting clinical signs and systemic lesions.

PRERENAL CAUSES

Prerenal occurrence is due to decreased blood supply to the kidneys, which can be due to congestive heart failure, circulatory shock and hypovolemia (severe hemorrhages and dehydration). Thus, due to this decrease in blood supply and consequently renal perfusion, the glomerular filtration rate is reduced, thus retaining in the blood the unnecessary and toxic substances that should be eliminated through urine. (COLVILLE, 2010; SERAKIDES and SILVA, 2016)

In addition, this reduction in vascularization can result in ischemia, with consequent degeneration and necrosis of the cells of the tubular epithelium. In this way, prerenal azotemia can be supplanted by azotemia of renal origin. It is unlikely that a process of prerenal uremia will occur, since the causes mentioned above can lead to the death of the animal or cause ischemic nephrosis before causing prerenal uremia. Therefore, the most common is the occurrence of prerenal azotemia (SERAKIDES and SILVA, 2016; FIDALGO, 2019)

RENAL CAUSES

Renal occurrence occurs due to acute or chronic injuries that will reflect in the reduction of renal function to levels incompatible with normality. Thus, at the renal level, the most important changes that occur are the loss of functional nephrons and the decrease in GFR. This decrease leads to an increase in plasma concentrations of substances that would normally be eliminated from the body through renal excretion, such as amino acids, peptides, ammonia, aliphatic and aromatic amines, creatinine, gastrin, renin, urea, uric acid, glucagon, growth hormone, among others (SERAKIDES and SILVA, 2016; POLZIN, 2007)

And due to this increase in the concentrations of these substances, the so-called uremic syndrome can originate, which according to Grauer (2007) and Rodriguez (2012) encompasses water and sodium imbalance, anemia, carbohydrate intolerance, neurological and gastrointestinal tract changes, osteodystrophy, immunodeficiency and metabolic acidosis.

In addition, it is important to remember the functions of hormonal formation such as erythropoietin and catabolism of several peptide hormones, resulting in hormonal changes reflecting on the pathogenesis of this disease. (TREVISAN, 2016)

Justifying the occurrence of osteodystrophy that occurs secondary to hyperparathyroidism, due to the attempt to maintain plasma concentrations of calcium and phosphorus. The occurrence of proteinuria and glomerulosclerosis can also be justified by the increase in GFR in an attempt to maintain adequate functionality, developing hyperfiltration, which leads to injury and loss of functional nephrons (GRAUER, 2007; TREVISAN, 2016)

Systemic arterial hypertension can also contribute to the progressive loss of nephrons, causing irreversible glomerular lesions through increased intraglomerular pressures and glomerulosclerosis. (GRAUER, 2007)

Acute renal failure is characterized by azotemia (renal azotemia), among other biochemical alterations. Chronic renal failure is characterized by uremia and can be used as a synonym for renal uremia (SERAKIDES and SILVA, 2016)

POSTRENAL CAUSES

The postrenal occurrence may be due to complete obstruction of the urinary flow, the most common being in the bladder and urethral region, and rarely bilateral urethral obstruction, which will only result in azotemia or uremia in cases where the contralateral kidney is altered. It can be due to causes intrinsic to the lower urinary tract, such as urolithiasis, bladder and urethral tumors. Or extrinsic factors, such as uterine tumors, prostatic hyperplasia, severe prostatitis and bladder paralysis caused by spinal cord injuries. (COLVILLE, 2010; SERAKIDES and SILVA, 2016)

CAUSES OF CHRONIC KIDNEY DISEASE (CKD) IN CATS

Among the causes of CKD in felines, we can mention chronic tubulointerstitial nephritis of unknown cause, being the most common pathological diagnosis. Chronic pyelonephritis or chronic glomerulonephritis, both of which can be difficult to differentiate histologically when compared to chronic tubulointerstitial nephritis. In addition, we can mention: Amyloidosis (of familial origin in Abyssinian cats) and Polycystic kidney disease (of familial origin in Persian cats). **(** CHEW, DIBARTOLA and SCHENCK, 2012**)**

Among other causes we can also mention: Hypercalcemic nephropathy, Progression after AKI, Chronic obstructive uropathy (such as hydronephrosis as a consequence of ureteral urolithiasis), Neoplasm (such as renal lymphoma), Acromegaly (excessive production of growth hormone) resulting in renomegaly. Piogranulomatous nephritis due to feline infectious peritonitis (FIP), hypokalemic nephropathy (kalopenic). And finally, due to chronic toxicity (associated with food, drugs and environmental toxins) and primary systemic hypertension. **(** CHEW, DIBARTOLA and SCHENCK, 2012**).**

DISORDERS CAUSED BY CKD

Uremia

The biochemical disorders of uremia are characterized by alterations in the control of extracellular fluid volume and basic acid and electrolyte balance, in the metabolism of hormones, and in the excretion of products from protein catabolism. (SCHENCK, 2012)

Uremia occurs from the reduction of GFR by 75%, which so far adaptive measures by intact nephrons have been performed with the objective of maintaining renal function at adequate levels. However, with this high impairment, resulting in a significant reduction in GFR, undesirable substances such as sulfates, phosphates, urea, uric acid, creatinine, etc. begin to occur. Thus, the verification of urea and creatinine concentrations are important parameters in this phase for renal evaluation. SERAKIDES and SILVA, 2016; CRIVELLENTI *et al*, 2021.

Uremic toxins refer to any compound that accumulates in excess due to decreased kidney function and contributes to the clinical signs of uremia.

These toxins are composed of guanidine, products of bacterial metabolism (such as polyamines, aliphatic amines, untamed), myoinositol, oligoelements, and medium molecules. (CHEW, DIBARTOLA and SCHENCK, 2012)

Uremia, whether of renal origin or not, can lead to extrarenal and multisystem lesions in various systems, such as the digestive system (stomatitis, glossitis, ulcerative and necrotizing esophagitis, necrosis of the tip of the ear (rare), ulcerative and hemorrhagic gastritis, hemorrhagic pancreatitis), respiratory system (pulmonary edema, mineralization of the subpleural connective tissue of the intercostal spaces), cardiovascular system (ulcerative atrial endocarditis and mucoarteritis), locomotor and endocrine system (fibrous osteodystrophy, rubber jaw). (SERAKIDES and SILVA, 2016; CRIVELLENTI *et al*, 2021)

In the urinary system (fibrosed and mineralized kidneys, nephrocalcinosis may occur), in the hematopoietic system (aregenerative anemia in uremia occurs due not only to a reduction in the synthesis of erythrocytes, but also due to hemolysis and hemorrhage), in the nervous system (animals may not present macroscopic lesions, but may present neurological and motor signs, which characterize uremic encephalopathy). (SERAKIDES and SILVA, 2016; CRIVELLENTI *et al*, 2021)

Dehydration

The dehydration caused will be triggered by a decrease in tubular reabsorption and associated with a loss of responsiveness to ADH, in addition to lesions in the medullary region of the kidneys, which may be aggravated by vomiting and diarrhea, which occur in cases of uremia. SERAKIDES and SILVA, 2016; CRIVELLENTI *et al*, 2021.

Metabolic acidosis

The decrease in tubular secretion causes potassium retention, which can lead to cardiotoxicity, and hydrogen ions, which leads to acid-base imbalance. Due to this imbalance, associated with the reduction of ammonia production by the distal convoluted tubules and collecting duct, associated with a decrease in the reabsorption of bicarbonate ions, results in metabolic acidosis. (SERAKIDES and SILVA; CRUZ, 2016)

Vitamin D and Calcium Deficiency

Due to kidney injury, the transformation of 25hydroxycholecalciferol into 1,25-dihydroxycholecalciferol is compromised due to the kidney being injured, resulting in deficient

formation of the active form of vitamin D. In this way, calcium deficit can lead to tetany (spasmodic contractions of skeletal muscles) and muscle weakness. SERAKIDES and SILVA; PEREIRA, 2013; POLZIN *et al*., 2016)

This reduction of calcium concentrations in the extracellular medium results in increased excitability of the nervous system, due to the increased permeability of the axon membrane of neurons to sodium ions. With this, the triggering of the action potential is facilitated, where the nerve fibers spontaneously discharge, thus sending a series of nerve impulses directed to the skeletal muscles, triggering tetanus muscle contractions. SERAKIDES and SILVA, 2016; POLZIN *et al.*, 2016)

Phosphorus Retention

Because the kidneys are unable to excrete phosphorus through the urine, hyperphosphatemia and absolute hypocalcemia develop, and this calcium reduction is aggravated by the kidneys' inability to convert 25-hydroxycholecalciferol into 1,25di-hydroxycholecalciferol. SERAKIDES and SILVA, 2016; PEREIRA, 2013; CRUZ, 2016)

In addition, the parathyroid glands are stimulated to produce parathyroid hormone, resulting in excessive bone resorption in order to try to balance the serum levels of calcium and phosphorus. However, parathyroid hormone also increases the renal excretion of phosphorus, however, as the kidneys do not respond to it, phosphorus retention occurs in the body. Result in a condition of secondary renal hyperparathyroidism. SERAKIDES and SILVA, 2016; PEREIRA, 2013; CRUZ, 2016)

Deficient Erythropoietin Training

Due to the injury, the kidneys start to have their ability to form erythropoietin compromised, resulting in minimized synthesis of erythrocytes by the bone marrow, resulting in an aregenerative anemia, with a variable aspect in relation to severity. (SERAKIDES and SILVA, DiBARTOLA; WESTROPP, 2015)

DIAGNOSIS

The frequency of diagnosis has increased significantly in the last decade. The sharp increase in the prevalence of CKD may be an improvement in the recognition of the disease or a real increase in its incidence in the feline population. (VALENTE, 2019)

To identify renal failure, the following can be performed: anamnesis, complementary tests such as radiographs, abdominal ultrasound, laboratory tests (**Table 2**), such as: blood count, serum biochemistry and urinalysis. Unfortunately, the diagnosis usually tends to occur only in

the more advanced stages of the disease due to the appearance of clinical signs (**Table 1**) that are caused by the great loss of renal function. (GUSSO, 2021; MARCUZ, 2022)

CLINICAL SIGNS

The clinical manifestations (Table 1) of the disease are not always evident or may not even exist, which is the case of asymptomatic patients. (KOGIKA et al., 2015). With regard to the anamnesis of felines with CKD, polyuria and polydipsia are the signs that owners most easily recognize, although they only appear when the ability to concentrate urine is already lost and there is a loss of 67% of kidney function. The onset and presentation of clinical and biochemical episodes that occur in patients with CKD may vary, depending on the nature, severity, duration, speed of progression of the underlying condition, presence of a coexisting disease, but not related to the patient's age and species, and administration of therapeutic agents (POLZIN et al., 2010). 37 Some animals affected by CKD may present clinical manifestations such as loss of body weight and muscle mass, polyuria and polydipsia, hyporexia or even 13 anorexia, vomiting, halitosis, gastroenteritis and gastric ulcerations (BARTGES, 2012)

Table 1. Aspects of chronic kidney disease

Anemia arregenerativa
Apetite diminuído com mais de 3 meses de evolução
Azotemia
Diminuição do tamanho renal
Halitose urêmico
Osteodistrofia renal
Pelame ressequido e quebradiço
Perda de peso corporal por mais de 3 meses
Presença de poliúria e polidipsia por mais de três meses
Sinais clínicos discretos

Fonte: adaptado de Polzin, 2011.

COMPLEMENTARY EXAMS

In complementary tests, tests should be used to assess renal concentration capacity, glomerular permeability, and especially glomerular filtration rate (GFR), which is routinely evaluated indirectly through the quantification of markers that must be eliminated from the body through the urinary tract. With the use of such tests, the degree of renal impairment of the patient and the staging of the lesions are determined. (SILVA; MARCUSSO, 2017)

Among some of the most common alterations, we observed azotemia and hyperphosphatemia in serum biochemistry during the advancement of chronic kidney disease (CKD), resulting from reduced glomerular filtration rate (GFR). (GARCIA, 2011)

Thus, currently the laboratory diagnosis of Kidney Injury is extensively performed by means of serum biochemistry of creatinine, however, it does not have the ability to detect mild degrees of loss of renal function, due to its low sensitivity, making it unfeasible to measure it as an early diagnosis method, being feasible in patients with a reduction of 75% in GFR, indicating moderate to severe renal involvement. Classifying it as a late marker due to neglect of the early stages of the injury. (POLETTO, 2016; PAIVA, 2018).

In addition, creatinine is interfered with by several factors that are independent of the kidneys, such as eating time, muscle mass index, and age, which compromises its role as a marker of this organ. (PAIVA, 2018)

Serum creatinine concentration is not capable of detecting mild degrees of loss of renal function, due to its low sensitivity, making it impossible to measure it as an early diagnosis method, being feasible in patients with a reduction of 75% in GFR, indicating renal impairment of moderate to severe intensity. (POLETTO, 2016).

Table 2 - Complementary laboratory tests for the diagnosis of feline chronic kidney disease.

Marcadores sanguíneos	Marcadores urinários	Imagenologia
Acidose metabólica	Diminuição da gravidade urinária	Modificação de tamanho e contorno renal
Elevação na concentração da ureia	Proteinúria	Alterações na densidade do parênquima renal
Elevação da concentração de creatinina sérica	Cilindrúria	Mineralização tecidual
Hiperfosfatemia	Cistinúria	
Hipercalemia ou hipocalemia	Alteração no pH urinário	
Hipoalbuminemia		

Fonte: adaptado de Polzin, 2011.

STAGING OF CKD FOR SOCIETY INTERNATIONAL RENAL INTEREST (IRIS) 2023

Thus, the diagnosis and management of CKD, due to being a routine reality in the clinical practice of small animals, can be classified into stages by IRIS (International Renal Interest Society), which formulated the CKD guidelines for staging and treatment of patients, standardizing management and diagnostic practices. This classification considers the stages of

the disease according to the time of evolution and the presence of markers of kidney injury (CHEW, DIBARTOLA and SCHENCK, 2012, VALENTE, 2019; OLIVEIRA, 2020)

This planning for the classification of Kidney Disease outlined by IRIS aimed to support the application of appropriate clinical guidelines for the diagnosis, therapy and prognosis of this disease. In order to allow a correct knowledge of the evolution of kidney injury, patients with diseases that predispose to CKD, without clinical and laboratory alterations, are considered to be stage 01 (DALTON, 2011)

This staging system will continue to evolve through new research and new clinical studies, in order to diagnose kidney disease in advance, which will allow the institution of preventive, treatment and monitoring measures, which will delay the progression of the disease, improving the quality of life of patients with kidney disease. (GUSSO, 2021).

Staging of chronic kidney disease (CKD) is performed after the diagnosis of CKD, in order to facilitate appropriate treatment and monitoring of the patient. Staging is initially based on fasting blood creatinine or fasting blood SDMA, assessed on at least two occasions in the stable patient. SDMA may be a more sensitive marker that is less impacted by the loss of lean body mass. It is important to note that the patient must be hydrated and stable. After this, the feline can be understaged based on proteinuria and systemic blood pressure. (IRIS, 2023).

Table 3. Staging of CKD based on blood creatinine and SDMA concentrations

CÃES Creatinina sanguínea SDMA	**GATOS** **Creatinina sanguínea** **SDMA**	COMENTÁRIOS
<125 µmol/l <1.4 mg/dl <18	<140 µmol/l <1.6 mg/dl <18	Creatinina sanguínea normal ou aumento normal ou leve SDMA de sangue. Alguma outra anormalidade renal presente (como, capacidade inadequada de concentração urinária sem causa não renal identificável (em gatos, não em cães), palpação renal anormal ou achados de imagem renais, proteinúria de origem renal, biópsia renal anormal resultados, aumentando a creatinina sanguínea ou SDMA concentrações em amostras coletadas em série). Persistentemente concentração elevada de SDMA no sangue (>14 µg/dl) pode ser usado para diagnosticar DRC precoce
125 –250 µmol/l 1.4 – 2.8 mg/dl 18 - 35	140 – 250 µmol/l 1.6 – 2.8 mg/dl 18 - 25	Creatinina normal ou levemente aumentada, azotemia renal leve (a extremidade inferior da faixa está dentro das faixas de referência para creatinina para muitos laboratórios, mas a insensibilidade de concentração de creatinina como um teste de triagem significa que pacientes com valores de creatinina próximos ao limite superior limite de referência frequentemente apresentam falha excretora). levemente SDMA aumentado. Sinais clínicos geralmente leves ou ausentes.
251 – 440 µmol/l 2.9 – 5.0 mg/dl 36 - 54	251 – 440 µmol/l 2.9 – 5.0 mg/dl 26 - 38	Azotemia renal moderada. Muitos sinais extrarrenais podem ser presentes, mas sua extensão e gravidade podem variar. Se sinais estão ausentes, o caso pode ser considerado como estágio inicial 3, enquanto a presença de muitos ou marcados sinais sistêmicos pode justificar a classificação como estágio avançado 3.
>440 µmol/l >5.0 mg/dl >54	>440 µmol/l >5.0 mg/dl >38	Aumento do risco de sinais clínicos sistêmicos e urêmicos crises

Table 3. Staging of CKD based on blood creatinine and SDMA concentrations. IRIS (2023). Adapted by Rafaela Cristina

Table 4. Proteinuria Substaging

CÃES (VALORES)	GATOS (VALORES)	SUBESTÁGIO
<0.2	<0.2	Não proteinúrico
0.2 to 0.5	0.2 a 0.4	proteinúrico limítrofe
>0.5	>0.4	proteinúrico

Source: Adapted from Iris (2023).

Canine and feline patients with persistent proteinuria should be reassessed at 2 months and reclassified as appropriate. Veterinarians may offer treatment for cats persistently in the borderline proteinuric range or microalbuminuria, considering the association with proteinuria of this level and progressive kidney disease in the cat (see treatment guidelines). Proteinuria may decrease as renal dysfunction worsens, and therefore may be less frequent in dogs and cats in stages 3 and 4. Response to any treatment given to reduce glomerular hypertension, filtration pressure, and proteinuria should be monitored at intervals using UP/C. IRIS (2023)

Table 5. Blood pressure understaging

Pressão arterial sistólica (mm Hg)	Pressão arterial Subestágio	Riscos futuros de Danos aos Órgãos alvos
<140	Pressão normal	Mínimo
140 – 159	Pré- Hipertenso	Baixo
160 – 179	Hipertenso	Moderado
≥180	Severamente Hipertenso	Alto

Source: Adapted from Iris (2023).

Canine and feline patients should be evaluated by multiple measurements. The final classification should be based on multiple systolic blood pressure determinations, preferably made during repeated visits of the patient to the clinic on separate days, but acceptable if during

the same visit, at least 2 hours apart, between determinations. Patients are under-staged for systolic blood pressure according to the degree of risk of target-organ injury and whether there is evidence of target-organ injury or complications. IRIS (2023)

REVIEW OF STAGING AND SUBSTAGING AFTER TREATMENT

The stage and substages assigned to the patient should be reviewed appropriately as changes occur. For example, a substantial increase in the concentration of creatinine or SDMA in the blood may warrant reassignment to a higher stage. Or, in patients assigned to antihypertensive (or antiproteinuric) treatment, the classification of the patient in the reassessment should be adjusted according to the need, according to the new blood pressure, instead of the original state previously. IRIS (2023)

TREATMENT

According to Iris (2023), all treatments for chronic kidney disease (CKD) need to be adapted to each patient. Serial follow-up of these patients and treatment adapted according to the response to treatment is ideal.

According to Crivellenti (2015), the treatment can consist of antiemetics (in cases of vomiting), use of fluid therapy and hydration, where animals in stages 3 and 4 may not be able to compensate for polyuria with polydipsia, making them chronically dehydrated (hyporexia, constipation, prerenal azotemia, and predisposition to acute kidney injury). That is why it is important to use an esophageal tube or subcutaneous route to administer water and electrolytes. Hypertension control should also be performed, and a calcium blocker may initially be used. Control of hyperphosphatemia is required, treatment of hypocalcemia, control of hypokalemia, treatment of proteinuria (increased U-P/C).

According to Crivellenti (2015), anemia should also be treated, which can be through the supplementation of water-soluble vitamins, use of mucosal protectors, iron supplementation, hormone therapy or blood transfusion. Treatment for metabolic acidosis, urinary tract infection (rarer compared to dogs, and should be guided by culture and antibiogram results), hemolysis and peritoneal dialysis when necessary, and in the last cases kidney transplantation should be performed.

Research has shown that high-protein diets increase filtration glomerular hyperemia cause renal hyperemia and increase renal volume by causing hypertrophy of the tubular epithelium and increased glomerular volume. These effects are mediated by the increase in insulin-like growth factor 1 (IGF1). Hyperfiltration results from vasoconstriction in the efferent arteriole, which consequently increases glomerular pressure; however, this increased

pressure in the glomerular capillaries predisposes to glomerular injury. In patients suffering from kidney disease, low-protein diets have a protective effect on kidney function by reducing the formation of toxic metabolites such as phosphate, uric acid, and urea. (SERAKIDES and SILVA, 2016)

In cats, according to Crivellenti (2015), whose anorexia has persisted for more than 3 days, esophageal or gastric tubes should be used, representing an important difference compared to dogs.

Studies with animals and humans carried out by Ramezani (2014), point to the use of prebiotics and probiotics, verifying that they can play therapeutic roles in maintaining a metabolically balanced intestinal microbiota and reducing the progression of patients with CKD with complications associated with uremia.

RENAL BIOMARKER: SDMA (SYMMETRICAL DIMETHYLARGININE)

Symmetric Dimethylarginine (SDMA) is one of the most current molecules and recently inserted in renal evaluation in small animal clinics, especially when the goal is early access to CKD. (PAIVA, 2018)

SDMA is a small molecule, measuring around 202 Da, from the intracellular methylation of the amino acid arginine, first isolated 48 years ago, from human urine (KAKIMOTO and AKAZAWA, 1970). In veterinary medicine, SDMA was first studied 12 years ago, aiming at a correlation with LR (PEDERSEN, 2006; TATEMATSU et al., 2007).

Symmetric Dimethylarginine results from protein methylation, with approximately 90% excreted by the kidneys, with no tubular reabsorption (Braff, Obare, & Yerramilli, 2014; El-Khoury et al., 2016). Thus, as discussed by Braff et al. (2014), its serum concentration is closely correlated with the Glomerular Filtration Rate. SDMA is a methylated presentation of arginine, originating after enzymatic proteolysis inside nucleated cells, released into the bloodstream, for subsequent renal excretion, directly correlated to GFR, without suffering extrarenal interference, as occurs with RCs (BURESOVA et al., 2019).

A study covering 18 studies in humans found that SDMA correlated strongly with the main markers of renal function, mainly serum creatinine (Crs) and Glomerular Filtration Rate, and is therefore considered an endogenous marker of function (KIELSTEIN et al., 2006). Thus, in studies to be carried out in dogs and cats, the same correlation was verified, being proposed, similar to humans, as an endogenous marker of renal functioning (PEDERSEN, 2006; JEPSON et al., 2008; BRAFF et al., 2014; NABITY et al., 2015; HALL et al., 2016).

SDMA, as previously reported, is a new, accurate renal biomarker used to calculate Glomerular Filtration Rate (GFR), initially estimated and used in humans, and is more sensitive

than serum creatinine to assess renal dysfunction (RELFORD; ROBERTSON; CLEMENTS, 2016), included as part of the IRIS guidelines, modified in 2015, for staging early and advanced CKD (HALL et al., 2017), allowing for an early diagnosis of patients in stage IRIS I (Hall, Yeramilli & Obare 2014)

In 2015, SDMA was incorporated into the International Renal Interest Society (IRIS) Chronic Kidney Disease (CKD) staging guidelines, which recognized it as a renal function test that complements the determination of serum creatinine in the evaluation of renal patients (RELFORD et al., 2016). Thus, SDMA presents itself as an interesting biomarker for the early diagnosis of CKD, both in dogs and cats, although more studies are needed for a better understanding of its action and determination of possible extrarenal influences.

A relevant fact for the use of SDMA would be for the diagnosis of chronic kidney disease (CKD) in cats with hyperthyroidism, since this disease leads to an increase in the Glomerular Filtration Rate and a reduction in muscle mass, covering the levels of serum creatinine, which can silence and hinder the identification of Kidney Injury (BOAG et al., 2007; PETERSON, 2016).

Following this line of reasoning, Peterson et al. (2016) proposed the use of SDMA in these cases, however in only one third of the 206 felines evaluated was the test effective in predicting azotemia, although it was a more sensitive marker in predicting creatinine elevation. Similar to the idea of this study, an IDEXX® fact sheet presented data from a retrospective survey, in which in a population of 2,000 feline patients with chronic kidney disease and hyperthyroidism, SDMA was able to identify 20.6% of CKD as opposed to 3.5% of serum creatinine.

The literature reports on the use of SDMA not only for the evaluation of chronic kidney injuries, but also for the detection of other alterations, such as acute injuries and in patients with kidney stones, although it does not allow the distinction between diseases (HALL et al., 2014a; DAHLEM et al., 2017; HALL et al., 2017). In addition, according to Nabity et al. (2015), this marker also has the ability to monitor the progression of the injury, and can be used for this purpose.

Recently, Pelander et al. (2019), conducted a study to compare the performance in the global diagnosis of SDMA and serum creatinine for the detection of Glomerular Filtration Rate (GFR) when it was reduced, observing that the two respective markers had a similar diagnostic value.

Thus, for serum creatinine (CRs) and SDMA, the existence of a nonlinear correlation with GFR is assumed, and as there is a decrease in filtration rate, there will be a serum increase in both markers. However, the value of one marker will not directly influence the result of the

other, and the level of CRs may not yet be noticed while that of SDMA is already a concern (BURESOVA et al., 2019; PETERSON et al., 2018).

It is important to work on the thought that, probably, no marker used individually is sufficient to assess kidney function and damage. Thus,[for the execution and construction of a diagnosis of CKD, multiple findings must be taken into account, such as: clinical presentation, physical examination, laboratory and imaging tests (POLZIN, 2011; RELFORD et al., 2016, (HOKAMP and NABITY, 2016). Thus, in this context, markers can help in the early detection of such evidence (POLZIN, 2011).

With this in mind, an early test to screen patients with suspected chronic kidney disease is important so that interventions can be initiated as soon as possible, seeking to delay the progression of the disease (HALL et al., 2014b; HOKAMP and NABITY, 2016)

According to Hall et al. (2014a), the increase in SDMA occurs, on average, 17 months before serum creatinine. Studies also suggest that it is not influenced by muscle mass in dogs and cats (Hall et al., 2014b, 2015; Nabity et al., 2015). Thus, early Chronic Kidney Disease should be suspected when SDMA is elevated and serum creatinine is unchanged. Therefore, the measurement of this biomarker is recommended in the diagnosis of non-azotemic cats and in cases of muscle atrophy (Polzin, 2016).

Reis (2019) carried out in his work carried out a survey to evaluate the behavior of the renal biomarkers symmetric dimethylarginine (SDMA), serum creatinine (CRs) and the urinary protein:creatinine ratio (UPC) in apparently healthy cats and cats with chronic kidney disease. Where it was found that, for symptomatic cats for CKD, it will be necessary to be substaged according to the IRIS (2017) criteria (UPC, CRs, PAS and SDMA) and to carry out renoprotection measures in an attempt to control the progression of the present CKD. And for apparently healthy cats, the behavior of SDMA was within the normal range for the species, with a borderline urinary creatinine value (UPC), suggesting quarterly or semiannual monitoring and follow-up, according to clinical evaluation.

FINAL CONSIDERATIONS

According to the information above, emphasizing all the indispensable functions of the kidneys, it is important to observe the importance of studies and research on new alternative ways to evaluate and diagnose pathologies of the urinary system in felines, especially chronic kidney disease. In this way, through the use of early markers, it is possible to ensure greater longevity for felines, preserving their well-being and living conditions. It is worth mentioning that even though it is a promising biomarker, according to data in the literature, it is necessary to combine other parameters to diagnose CKD, not using SDMA individually.

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