Evaluation of the applicability of SDMA for early diagnosis of CKD in felines and survey of staging and tests used in routine practice

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ABSTRACT

Felines, due to anatomical, physiological and dietary aspects, have a certain predisposition to problems affecting the renal system, highlighting chronic kidney disease (CKD). This disease is a progressive and irreversible disease, being an important cause of death in felines, especially with advanced age. Unfortunately, due to its initial signs being silent, it ends up resulting in late diagnoses, resulting in the appearance of clinical manifestations only during the worsening of the condition. Thus, the symmetric dimethylarginine biomarker (SDMA) has been raised as an alternative for assessing the existence of CKD early when compared to the quantification of serum creatinine, and in 2015 it was incorporated as a method for staging according to the International Society of Renal Interest (IRIS), representing a complementary test and aid in the classification of the stages of this disease, especially in the substages. Thus, the reason for this research was to disseminate a questionnaire to verify the applicability of this biomarker in the routine of veterinarians, in addition to addressing other important issues within this theme.

Keywords: Biomarker, Precocity, Felines, Renal system.

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INTRODUCTION

Currently, the assessment of quality of life has become increasingly relevant in the treatment of chronic diseases, due to the significant negative impact that these conditions have on patients. In felines, Chronic Kidney Disease (CKD) is particularly prevalent due to its evolutionary characteristics, such as eating, physiological, and anatomical habits. CKD is a common nephropathy of great importance, being the main cause of death in this species. Recent studies estimate that the prevalence of CKD in cats ranges from 1 to 3%, and 30% of diagnosed cases occur in felines over 15 years of age (RELFORD, 2016; LOURENÇO, 2019).

Chronic Kidney Disease is defined by the progressive and irreversible loss of nephrons, resulting in impairment of at least 75% of renal function. This negatively affects the excretory and concentrator functions of the kidneys, and is directly related to glomerular filtration rate (GFR) and renal functional mass (MCGAVIN, 2013; ZACHARY, 2013; CRIVELLENTI, 2015).

In the long term, CKD can lead to the emergence of toxic neurological changes due to the accumulation of waste products from cellular metabolism. Even with preventive measures, factors such as age and heredity can contribute to the manifestation of the disease. However, with adequate and timely treatment, it is possible for the animal to have a healthy life, despite some limitations (TOZZETTI, 2009).

Research into more sensitive renal biomarkers has been an important area of focus, as these markers can enable early diagnosis, allow the choice of appropriate therapies, and improve patients' quality of life (OLIVEIRA, 2020). According to Lourenço (2019), traditional methods for assessing kidney function, such as measuring serum urea and creatinine levels, are less used today, which makes room for the use of alternative biomarkers.

In this sense, the biomarker Symmetric Dimethylarginine (SDMA) has shown significant results for the early detection of CKD, being able to identify the disease even when less than 50% of kidney function is compromised (OLIVEIRA, 2020). This is because SDMA is a stable molecule and is widely excreted by the kidneys, making it a good biomarker due to its size and load that facilitate its excretion by glomerular filtration. In addition, the measurement of SDMA is very accurate, being used for early diagnosis of CKD and allowing the implementation of renoprotective interventions that can slow the progression of the disease or stabilize it.

The objective of this study is to investigate the application of the SDMA biomarker in veterinary practice, in addition to exploring other aspects related to CKD, such as diagnostic tests and staging, among other pertinent issues.

METHODOLOGY

A descriptive field research with a quantitative approach was carried out in order to evaluate and discuss the use of the renal biomarker: SDMA, to verify the knowledge of veterinarians regarding this theme, in addition to its use, allowing the verification of its applicability in the veterinary clinical routine of felines. To achieve the objective of the proposed work, a virtual multiple-choice questionnaire was structured, made through the Google Forms platform. The questionnaire in question was composed of 08 questions, where the variables analyzed included: Definition of Chronic Kidney Disease, staging, tests used in the routine for diagnosis, the advantages and disadvantages of the use of SDMA, the use by the participants of it in the clinical routine, and finally the relationship between SDMA and Serum Creatinine. In the questionnaire, it was mandatory to confirm the reading of the Informed Consent Form (ICF), in order to ensure that all the information collected was in accordance with the consent of the interviewees, ensuring the ethical commitment to use the data in accordance with the ethical precepts of the country, according to Resolution 466/12, safeguarding confidentiality and reliability. To identify the participants, their full name and CRMV were requested, thus ensuring that the participants would in fact be veterinarians, avoiding risks of damage to the results achieved. And as the last item for the identification of the participants, the area of activity was requested, in order to better interpret the results. For greater distribution of the questionnaire, the means for dissemination and sharing were: Instagram, Facebook, and Whatsapp. The data were collected from October 5 to October 25, 2023.

RESULTS AND DISCUSSION

The first question presented to the participants was related to the definition of Chronic Kidney Disease, which was found by 41.4% that it is a progressive and irreversible loss, 20.7% indicated that it leads to a decrease in functioning, characterized by an irreversible loss of renal function, already installed for at least three months. In addition, 10.3% indicated that it is characterized by progressive and reversible loss of renal function, and early diagnosis is an important form of treatment to recover the injured mass.

Thus, CKD is defined when functional, progressive and irreversible kidney damage has occurred for at least three months, which will consequently result in an average impairment of 50% of GFR, and it is possible to observe clinical symptoms due to compromised functionality (SILVA, 2018; GUSSO, 2021).

Thus, analyzing the results obtained, we observed that there was a great division and doubt among the participants as to the correct definition and consequence of this disease, thus emphasizing the importance of knowing its progressive, chronic and established character for at least three months, with only 27.6% of the interviewees who indicated the option of characterization by the

progressive and irreversible loss of renal function, already installed for at least three months. This is the most complete option, referring to the definition of CKD.

Thus, not having a curative treatment, but a palliative treatment due to irreversible damage to functional cells, the main therapeutic objective is to normalize water balance, resolve hemodynamic inadequacies and promote urine formation (PALUMBO, 2011). That is why early diagnosis is such an important measure, aiming to prevent the numerous damages that this pathology entails.

Thus, early diagnosis is essential for treatment to be carried out as soon as possible, slowing the progression of the disease, minimizing its complications, and improving the patient's quality of life. Likewise, the collaboration of the tutor and the commitment of the Veterinarian are fundamental for the success of the therapy. (SILVA, 2018)

Next, the participants were asked about the performance of Renal Disease staging, and 27.6% indicated yes, against 24.1% who reported performing the times and finally, 20.7% did not use it because they belonged to another area of activity.

Veterinary medicine develops and improves over time, it has a vast area of activity, but it is erroneously summarized as the clinic and surgery of small and large animals (SOUZA, 2022). That is why it is understandable that many professionals who work in other areas of activity are unaware of the topic addressed, precisely due to the extensive breadth of knowledge within this profession.

Regarding the CKD staging system in cats, according to the International Renal Interest Society (IRIS), it is formed by four stages, according to the fasting serum creatinine or SDMA value, presence or absence of proteinuria, and systolic blood pressure according to the degree of risk of target organ damage and whether there is evidence of target organ damage or complications. In association, urine density can also be assessed (IRIS, 2019; FACHINI, 2023; IRIS, 2023).

Staging is initially based on fasting blood creatinine or fasting blood SDMA, assessed on at least two occasions in the stable patient. It is important to note that the patient must be hydrated and stable (IRIS, 2023).

Care should be taken when interpreting the SDMA value in young animals with concentrations higher than the reference value, as well as the presence of existing comorbidities and prerenal factors (SARGEENT *et al*., 2021).

This evaluation should be done in conjunction with anamnesis, general clinical analysis and diagnostic evaluations, such as X-rays, abdominal ultrasound, laboratory tests such as: blood count, serum biochemistry and urinalysis, in order to rule out other diseases that may be involved (GUSSO, 2021; FACHINI, 2023; MARCUZ, 2022; IRIS, 2023).

Thus, related to the diagnosis, complementary tests such as X-rays, abdominal ultrasound, blood count, serum biochemistry, and urinalysis are carried out based on the anamnesis (MARCUZ, 2022). Thus, as a result of the third question, related to the tests requested in the routine for diagnosis,

it was observed that the main tests used were: Urea and Creatinine (72.4%), Urianalysis (72.4%), Physical exams and anamnesis (65.5%) and Ultrasonography (62.1%). Thus, SDMA demonstrated, importantly, a low use in the routine by the participants, reaching a value of 37.9%. Representing practically half of its use, when compared to the other tests.

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 patient's degree of renal impairment and the staging of the lesions are determined (SILVA; MARCUSSO, 2017).

An important evaluation performed in the small animal clinic is Urianalysis, a simple, non-invasive, inexpensive laboratory test method capable of providing important information related to the urinary tract (GOLDSTEIN, 2005). According to Garcia (2011), urinalysis is a key of great diagnostic importance, as it evaluates the ability of the kidneys to concentrate, whether there is an acute, chronic, inflammatory, infectious, neoplastic process, among others.

Urinalysis is composed of a macroscopic and physicochemical analysis of the urine, in addition to sedimentoscopy (FETTMAN; REBAR, 2006). Through the evaluation of urine density (UD) it is possible to verify the capacity of urinary concentration, reflecting the capacity of dilution and concentration by the kidneys, which in case of CKD will be altered, an isosthenuria can be observed, with a value between 1,008 and 1,012 (POLZIN *et al*., 2000; WATSON; LEFEBVRE; ELLIOTT, 2015).

The fourth question was about the participants' knowledge of SDMA and their experience with it. Thus, 13.8% were found to have no satisfactory experience with it, associated with 17.2% who had no experience with its use. 41.4% had a satisfactory experience, while only 10.3% reported that they had an excellent experience.

Then, in the fifth question, the participants' knowledge regarding the advantages of this biomarker was verified, and the following were found: early diagnosis of CKD (54.6%), greater accuracy of GFR compared to creatinine (51.7%) and is not influenced by loss of lean mass, animal condition and age (41.4%). It was observed that no participant checked the option of its use to verify other diseases, besides AKI and CKD, and it was possible to verify the lack of knowledge regarding the broad applications that this biomarker can assume, since it can be used to verify other diseases.

There are many pathologies that can lead to secondary kidney failure. Thinking about this line of reasoning, the use of SDMA would be an interesting alternative for renal monitoring due to these diseases. Thus, in cats, the literature talks about the use of SDMA in cases of Polycystic Kidney Disease, lymphoma with renal infiltration, urinary tract infection (UTI) (DITTRICH, 2023; MEDEIROS, 2023). Since this biomarker can be used as a tool to assist in monitoring the renal

system, thus preventing damage and allowing preventive measures to be taken against the damage and disorders that occur as a result.

A high concentration of SDMA reflects a poor Glomerular Filtration Rate (GFR). Both primary kidney disease and secondary kidney damage, such as concomitant diseases, can lead to elevated SDMA concentrations. (IDEXX, 2017)

Thus, thinking about this same line of reasoning, we can highlight its use in cases of inflammatory diseases, since they predispose to kidney damage, and we can highlight the use of SDMA in cases of leptospirosis, pyometra, septic shock, amyloidosis, renal lymphoma, renal infarction, congestive heart failure, hypoadrenocorticism, bladder rupture, ureteric trauma, renal trauma, anesthesia, surgical trauma, non-steroidal anti-inflammatory drugs, among others, which can cause an irreversible loss of functional nephrons, thus compromising renal function (BICHARD, 2003).

Among the causes of infectious diseases that can affect the urinary system, due to glomerular lesions, the following can be highlighted: due to bacteria (post-streptococcal glomerulonephritis, infective endocarditis, shunt nephritis (Staphylococcus epidermidis), rickettsia, chlamydia, mycoplasma). Virus-related: Immunodeficiency syndrome (FIV), Infectious hepatitis, Epstein Barr (Infectious mononucleosis), Feline Herpes virus. Referring to Protozoa, one can think of Malaria and Toxoplasmosis. And finally, about Helminths: Schistosomiasis, Visceral Leishmaniasis, Filariasis, Trichinosis, Strongyloidiasis, Opistorachiasis, Trypanosomiasis (VILELA, 2022).

In addition, interstitial nephritis can be caused due to infections, bacterial and viral septicemias. In cats, we can highlight: Feline cholangiohepatitis, Feline leukemia (FELV), FIV, Feline infectious peritonitis, Systemic arterial hypertension, Hypokalemia (low levels of serum potassium) (VILELA, 2022).

In dogs, the literature already reports on the use of SDMA for the evaluation and monitoring of renal functionality in dogs affected by Leishmaniasis, Ehrlichiosis and Leptospirosis (GULTEKIN, 2023; VIEIRA, 2022). Leptospirosis is a classic example of Interstitial Nephritis, especially in dogs. Therefore, the use of SDMA is interesting, especially in endemic areas. (VILELA, 2022)

In addition to the advantageous precocity of elevation compared to 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.

Another important point that is raised as an advantage of SDMA would be the non-influence of extrarenal factors on serum concentrations, since it has been established that creatinine is affected by more non-renal factors than SDMA, such as lean body mass, age, and diet.

SDMA more accurately reflects GFR, especially in geriatric cats. This is due to the lack of influence of SDMA in relation to lean body mass, unlike what happens with creatinine, which is decreased in older animals with weight and muscle mass loss (HALL *et al*., 2014a).

Another importance about the specificity of SDMA is that lean body mass does not affect it, being even more reliable and can be used in animals with great weight and muscle mass loss, such as in animals with hyperthyroidism (HALL *et al.*, 2015).

However, as discussed by Sargent *et al*., (2021) SDMA and creatinine can also be affected by racial and biological variability and prerenal causes of GFR reduction, such as dehydration. Associated with this information, in the field of human medicine, SDMA has been found to be affected by several disease states, including diabetes, sepsis, and thyroid disease, in the absence of impaired kidney function (Sargent *et al*., 2021; and Mack *et al.*, 2021).

Although veterinary research is limited, in a study involving 37 cats by Langhorn *et al.* (2018) found that SDMA is significantly lower in cats that had diabetes mellitus compared to healthy controls. Thus, partially in disagreement with the literature, thus demonstrating its susceptibility to influences.

Subsequently, to verify its applicability in the clinical routine by veterinarians, an important value was found, 20.7% who did not use it, that is, who had a routine of CKD, but who really did not use it, and 10.3% who did not use it in the routine, that is, who ended up not facing cases of CKD in the routine, so they did not use it. It was found that 13.8% said they used it in most cases, 20.7% used it sometimes. Thus, it is possible to observe the low or non-applicability of this biomarker in the clinical routine.

Subsequently, which can be raised as possible justifications for its low use in clinical routine, the main disadvantages of the use of SDMA considered by the participants were questioned, with the highest cost (51.7%) being pointed out by more than half of the participants. In sequence, we observed the arrival of animals in an advanced stage in the routine, making early diagnosis impossible (44.8%) and difficulty in authorization by (41.4%).

One of the great difficulties faced in the medical clinic of small animals, as observed in the results found in this research, is the lack of authorization by tutors to carry out the necessary exams, as reported by the authors Alcantara (2019), Marques (2020) and Borges (2022). Due to the growth in cost, many tutors have restrictions on carrying out exams, and since this information provided is often essential by the clinician for screening, directing and even helping to diagnose certain damages,

it forces the veterinarian responsible for opting for palliative treatments, and even assuming presumptive diagnoses.

Subsequently, less pointed out by the participants, it was found: need to associate them with other tests, which will add value (34.5%), difficulty in understanding by tutors or veterinarians about their use and need (20.7%), lack of knowledge (13.8%) and difficulty in interpreting their results (3.4%).

In the clinical routine, it is often necessary for the tutor to understand the need for the exam to be performed, so that the authorization to be performed can occur. Thus, as found in this research, 20.7% have doubts about its use and interpretation, and with this, the veterinarians themselves may end up not requesting the exam due to doubts in its interpretation, or even not being able to resolve the doubts of the tutors about its operation, thus not being able to justify the need for its performance.

In agreement with the results obtained, Oravev (2021) in his work also reported on the tutor's non-authorization to perform the SDMA exam, being affirmed by IRIS (2019), the concentrations of SDMA important for confirmation or correction to a more advanced stage. Thus, Jericho *et al.* (2015) emphasizes that the success of the treatment and reduction of the progression of kidney injury depends on the collaboration of the owner.

Oravev (2021), also in his study, demonstrated the importance of performing laboratory and imaging tests, emphasizing the importance of early diagnosis, because the sooner the clinician's intervention occurs, the better the patient's prognosis. After the staging of the animal, the correct treatment for the stage is initiated, thus seeking to delay the progression of the disease, minimize complications and improve the patient's quality of life.

We commonly observe in the clinical routine the low demand by tutors for check up appointments, aiming to monitor the health of their *pet* and consequently preventing the emergence of possible diseases. According to what was observed by D'Almeida (2023), in which the casuistry followed in his work, of 48 consultations in felines, only (18.75%) was related to prophylaxis, divided between vaccination, FIV/FELV testing, and within this value, only 3 consultations (6.25%) were check up. Thus, even knowing the numerous benefits of keeping *pet appointments* up to date, many tutors reject this practice.

For this reason, the diagnosis usually occurs only in the most advanced stages of Chronic Kidney Disease, which, due to the great loss of kidney function, results in the appearance of clinical signs (MARCUZ, 2022). It is at this time that owners tend to seek veterinary support, again justifying the low use of SDMA due to its unfeasibility, since it would no longer be possible to carry out an early diagnosis.

Finally, as the last question, it was verified about the participants' knowledge regarding the relationship between the increase between SDMA and serum creatinine, and it was found that 41.4%

of the participants checked the correct option, which reports the increase in SDMA with 25% of injury, and Creatinine with 75%, and only 13.8% selected the wrong option, which stated that SDMA increases with 30% of kidney injury. The other most important portion, 27.6%, reported not having knowledge, associated with 10.3% not having knowledge or being in doubt because they belonged to another area of activity.

With this in mind, 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 or more, indicating moderate to severe renal involvement. It classifies it as a late marker due to neglect of the early stages of 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).

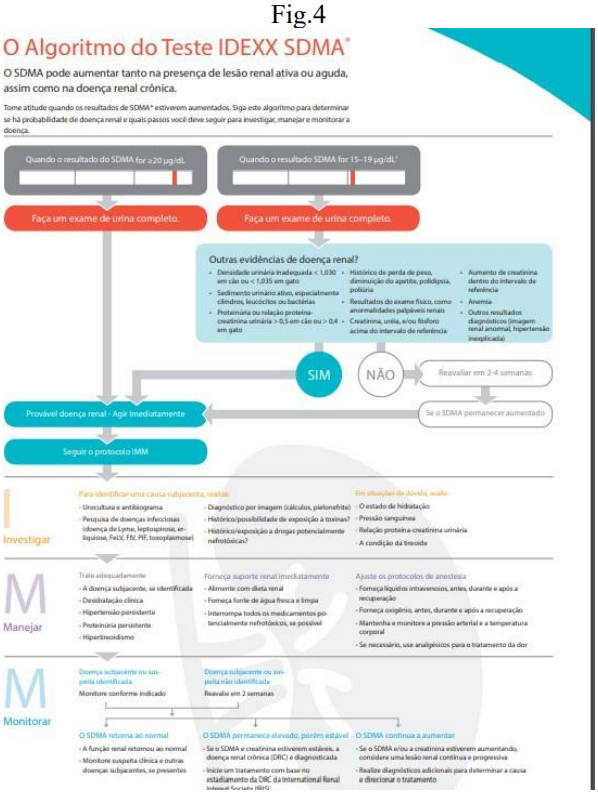
Serum creatinine concentration is not able to detect mild degrees of loss of renal function, due to its low sensitivity, making it unfeasible to measure it as an early diagnosis method, being feasible in patients with a reduction of 75% in GFR, indicating moderate to severe renal impairment (POLETTO,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

One of the aspects most highlighted as an advantage of SDMA compared to creatinine, one of the most important markers of renal function requested in the clinic, is the early detection of elevation in the face of the injury faced, according to Hall *et al.*, (2016b) the increase in SDMA possible in cases where there is a 25% loss of kidney function, making SDMA more reliable in cases of CKD, compared to creatinine, which only rises when there is a loss of approximately 75% of kidney function

In addition, Íris (2017) stated that the results of the SDMA test are more reliable for renal evaluation, and should therefore be evaluated before serum creatinine, however to classify Chronic Kidney Disease and analyze kidney function, the creatinine concentration rate is complementary to SDMA

When SDMA concentrations are increased, decreased renal function may be presumed as a result of AKI or CKD, or even both. Thus, it is essential to carry out a more in-depth research to elucidate the clinical condition in which the animal is, and to take the necessary measures **(Fig. 4)** (IDEXX, 2017).

Fig.4



Source; IDEXX (2017)

CONCLUSION

Through the work presented and the information collected, it is possible to affirm that, according to data in the literature, SDMA initially represented an interesting alternative for the early diagnosis of Chronic Kidney Disease, and can also be used to monitor the renal system due to the involvement of primary diseases that can affect this system. However, after some research, the need for further studies on its application was demonstrated. In addition, through the research carried out in this work, it was possible to verify the low applicability of it in the routine of the participating veterinarians, and the main justifications can be raised: the high cost, animals presenting themselves in an advanced stage of CKD, making early diagnosis impossible, and finally, restriction of authorization by the owners to perform the exam. It is worth mentioning that this research was a pioneering work, where it aimed to evaluate the applicability of SDMA in the routine of veterinarians, and future investigations and research are necessary for a greater understanding of the opinion, acceptance and application of it in the veterinary clinical routine.

REFERENCES

1. Agopian, R. G., et al. (2016). Estudo morfométrico de rins em felinos domésticos (Felis catus). *Pesquisa Veterinária Brasileira*, 36, 329-338. Disponível em https://www.scielo.br/j/pvb/a/kZzrCtTkMNz37qxTLHjHdPg/?lang=pt

2. Alcantara, S. M., et al. (2019). Carcinoma simples tubular mamário em *Rattus Novergicus*. *Brazilian Journal of Development*, 5(12), 31761-31778.

3. Berford, M. T., & Richard, S. (2005). Arginine methylation: an emerging regulator of protein function. *Molecular Cell*, 18(2), 263-272.

4. Bichard, J. S. (2003). *Manual Saunders – Clínica de Pequenos Animais* (2ª ed.). São Paulo: Rocca.

5. Boag, A. K., et al. (2007). Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine. *Veterinary Record*, 161(21), 711-715.

6. Borges, D. F. (2022). Doença do trato urinário inferior em felino com contaminação secundaria por *E. Coli*.

7. Braff, J., Obare, E., Yerramilli, M., Elliott, J., & Yerramilli, M. (2014). Relationship between serum symmetric dimethylarginine concentration and glomerular filtration rate in cats. *Journal of Veterinary Internal Medicine*, 28(6), 1699-1701.

8. Brown, S. A. (2015). Symmetric dimethylarginine (SDMA): new biomarker of renal function in cats and dogs. *International Renal Interest Society* (IRIS).

9. Buresova, E., Stock, E., Paepe, D., Daminet, S., Stammeleer, L., Vandermeulen, E., Smets, P., Duchateau, L., & Lefebvre, H. P. (2019). Assessment of symmetric dimethylarginine as a biomarker of renal function in hyperthyroid cats treated with radioiodine. *Journal of Veterinary Internal Medicine*, 33(2), 516-552.

10. Carvalho, M. B. (2020). *Semiologia Veterinária. A arte do Diagnóstico* (4ª ed., pp. 1132-1179). Rio de Janeiro: Editora Roca.

11. Chew, D. J., DiBartola, S. P., & Schenck, P. A. (2012). *Urologia e Nefrologia do Cão e do Gato* (2ª ed., pp. 145-148). Rio de Janeiro: Elsevier.

12. Crivellenti, L. Z., Alvarenga, A. W. O., Magalhães, L. F., & Silva, G. E. B. (2021). Tratado de nefrologia e urologia em cães e gatos. In L. Z. Crivellenti & L. Giovaninni (Eds.), *Histopatologia do sistema urinário* (pp. 13-19). São Paulo: MedVep.

13. Crivellenti, L. Z., & Crivellenti, S. B. (2015). *Casos de Rotina em medicina veterinária de pequenos animais* (2ª ed.). São Paulo: MedVet.

14. D'Almeida, A. T. (2023). Relatório final do estágio curricular obrigatório do curso de medicina veterinária, realizado junto à clínica de felinos ClinFel em Campinas (SP) e à clínica veterinária Mundo Animal em São Carlos (SP). Caso de interesse: Síndrome da Hiperestesia Felina.

15. Del Barrio, M. A. M. (2019). Doença Renal Crônica Felina (DRC). Revisão Técnica. Boehringer Ingelheim.

16. Dittrich, L. T., & Piazzolo, M. (2023). Linfoma com infiltração renal em felino: Relato de caso. *Pubvet*, 17(03), e1352-e1352.

17. El-Khoury, J. E., et al. (2011). A simple and fast liquid chromatography-tandem mass spectroscopy method for the measurement of underivatized L-arginine, symmetric dimethylarginine and asymmetric dimethylarginine and establishment of reference ranges. *Analytical Bioanalytical Chemistry*, 402(2), 771-779.

18. Fachini, G. F., et al. (2023). Doença Renal Crônica associada ao bem-estar e enriquecimento ambiental direcionada aos Felinos Domésticos (*Felis catus*) - Revisão de Literatura.

19. Feitor, B. D., et al. (2021). Biomarcadores de doença renal crónica e a sua relação com um instrumento de qualidade de vida nos gatos (Dissertação de Mestrado). Disponível em https://recil.ensinolusofona.pt/bitstream/10437/12659/1/VF_DURA%cc%83O_Ba%cc%81rbara_MIMV_2021_1de1.pdf

20. Fettman, M. J., & Rebar, A. (2006). Avaliação Laboratorial da Função Renal. In M. A. Thrall et al. *Hematologia e Bioquímica Clínica Veterinária* (pp. 285-310). São Paulo: Roca.

21. Finch, N., & Heien, R. (2017). Early detection of chronic kidney disease. In J. Elliott, G. F. Grauer, & J. L. Westropp (Eds.), *BSAVA Manual of Canine and Feline Nephrology and Urology* (3rd ed., pp. 130-142). Gloucester, UK: British Small Animal Veterinary Association.

22. Garcia, F. F., et al. (2011). Avaliação laboratorial da função renal de cães e gatos.

23. Goldstein, R. E. (2005). Feline chronic renal failure – Why do urinalysis? *Proceedings of North American Veterinary Conference*, 532-533.

24. Gultekin, G., et al. (2023). Níveis de arginina, dimetilarginina simétrica e assimétrica na leishmaniose canina. *Patogênese Microbiana*, 178, 106085. Disponível em https://www.sciencedirect.com/science/article/abs/pii/S0882401023001183

25. Gusso, A. B., & Da Cunha Mazutti, M. L. (2021). Doença renal crônica em gatos: A importância dos estadiamentos e do diagnóstico precoce: Revisão de literatura. *Arquivos Brasileiros de Medicina Veterinária FAG*, 4(1). Disponível em https://themaetscientia.fag.edu.br/index.php/ABMVFAG/article/view/400/495

26. Hagiwara, M. K. (2014). *Cunningham tratado de fisiologia veterinária* (Revisão Técnica). Rio de Janeiro: Elsevier.

27. Hall, J. A., Yeramilli, M., Obare, E., Yerramilli, M., & Jewell, D. E. (2014a). Comparison of serum symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine*, 28(6), 1676-1683.

28. Hall, J. A., et al. (2014b). Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein foods enriched with fish oil, L-carnitine, and medium-chain triglycerides. *Veterinary Journal*, 202(3), 588-596.

29. Hall, J. A., et al. (2015). Relationship between lean body mass and serum renal biomarkers in healthy dogs. *Journal of Veterinary Internal Medicine*, 29(3), 808-814.

30. Hall, J. A., et al. (2016). Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. *Journal of Veterinary Internal Medicine*, 30(3), 794–802.

31. Hall, J. A., et al. (2016a). Positive impact of nutritional interventions on serum symmetric dimethylarginine and creatinine concentrations in client-owned geriatric cats. *PLOS ONE*, 1-14.

32. Hall, J. A., et al. (2016b). Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. *Journal of Veterinary Internal Medicine*, 30(3), 794-802.

33. Hardy, L. (2023). A dimetilarginina simétrica é superior à creatinina na avaliação da taxa de filtração glomerular em gatos com doença renal? *Evidência Veterinária*, 8(4). Disponível em https://veterinaryevidence.org/index.php/ve/article/view/661

34. Hokamp, J. A., & Nabity, M. B. (2016). Renal biomarkers in domestic species. *Veterinary Clinical Pathology*, 45(1), 28-56.

35. IDEXX. (2016). *SDMA impacts how veterinarians diagnose and manage kidney disease in dogs and cats*. Disponível em https://www.idexx.com.br/files/sdma-data-white-paper.pdf

36. IDEXX. (2017). *O Algoritmo do Teste IDEXX SDMA®*. Disponível em https://www.idexx.com.br/pt-br/veterinary/reference-laboratories/sdma/interpreting-your-sdma-results/

37. IDEXX. (2019). *Perguntas frequentes sobre SDMA*. Disponível em https://www.idexx.com.br/ptbr/veterinary/reference-laboratories/sdma/sdma-faqs/

38. International Renal Interest Society (IRIS). (2015). *Treatment recommendations for CKD in cats*. Disponível em http://www.iris-kidney.com/pdf/002-5559-001-iris-website-treatment-recommendation-pdfs-cats_070116-final.pdf

39. International Renal Interest Society (IRIS). (2016). *Diagnosing, staging, and treating chronic kidney disease in dog and cats*. Disponível em https://ca.idexx.com/files/irisbooklet-guidelines-ca-en.pdf

40. International Renal Interest Society (IRIS). (2017). *IRIS Staging of CKD (modified 2017)*. Disponível em http://www.iris-kidney.com/pdf/IRIS_2017_Staging_of_CKD_09May18.pdf

41. IRIS. (2023). *Estadiamento Iris da DRC*. Reino Unido. Disponível em http://www.iris-kidney.com/guidelines/staging.html

42. Jepson, R. E., et al. (2008). Plasma asymmetric dimethylarginine, symmetric dimethylarginine. *Journal of Veterinary Internal Medicine*, 22(2), 317-324.

43. Kielstein, J. T., et al. (2006). Symmetric dimethylarginine (SDMA) as endogenous marker of renal function - A meta-analysis. *Nephrology Dialysis Transplantation*, 21(9), 2446–2451.

44. Kogika, M. M., Waki, M. F., & Martorelli, C. R. (2015). Doença Renal Crônica. In M. M. Jericó, M. M. Kogika, & J. P. A. Neto (Eds.), *Tratado de Medicina Interna de Cães e Gatos* (1ª ed.). Rio de Janeiro: Roca.

45. König, H. E., Maierl, J., & Liebich, H. G. (2016). Systema urinarium. In H. E. König & H. G. Liebich (Eds.), *Veterinary anatomy of domestic mammals* (6th ed., pp. 399-412). São Paulo, Brasil: Artmed.

46. König, H. E., & Liebich, H. G. (2021). *Anatomia dos animais domésticos: Texto e atlas colorido* (7ª ed.). Editora Artmed.

47. Langston, C. E., & Eatroff, A. (2020). Chronic kidney disease, overt (symptomatic). In L. A. Cohn & E. Côté (Eds.), *Côté's Clinical Veterinary Advisor: Dogs and cats* (4th ed., pp. 169-171). St. Louis, Missouri: Elsevier.

48. Langhor, R., Kieler, I. N., Koch, J., Christiansen, L. B., & Jessen, L. R. (2018). Dimetilarginina simétrica em gatos com cardiomiopatia hipertrófica e diabetes mellitus. *Jornal de Medicina Interna Veterinária*, 32, 57–63. https://doi.org/10.1111/jvim.14902

49. Lourenço, P. P., & Albuquerque, K. D. (2019). O uso da dimetilarginina simétrica (SDMA) no diagnóstico e estadiamento da doença renal crônica em felinos: Revisão de literatura. *Revista de Educação Continuada em Medicina Veterinária e Zootecnia do CRMV-SP*, 17(2), 24-33. Disponível em: https://revistamvez-crmvsp.com.br/index.php/recmvz/article/view/37918

50. Mack, R. M., Hegarty, E., McCrann, D. J., Michael, H. T., & Grauer, G. F. (2021). Avaliação longitudinal da dimetilarginina simétrica e concordância de biomarcadores renais em cães e gatos. *Revista Veterinária*, 276, 105732. https://doi.org/10.1016/j.tvjl.2021.105732

51. Maniaki, E., & Finch, N. (2018). Chronic kidney disease in cats and dogs: Managing proteinuria. *In Practice*, 40(7), 266-280.

52. Marcuz, L. W., & Bruch, D. (2022). Doença renal crônica em felinos: Revisão de literatura. *Anais do EVINCI-UniBrasil*, 8(1), 326-334. Disponível em: https://portaldeperiodicos.unibrasil.com.br/index.php/anaisevinci/article/view/6445

53. Marques, B. A. S., et al. (2020). Sertolioma em cão associado a criptorquidismo: Relato de caso. *Revista de Educação Continuada em Medicina Veterinária e Zootecnia do CRMV-SP*, 18(2), e37990.

54. Medeiros, I. A., et al. (2023). Doença renal policística (DRP) em felino doméstico: Relato de caso.

55. Moraillon, R., et al. (2013). *Manual Elsevier de medicina veterinária*. Elsevier Brasil. Disponível em: https://www.ufrb.edu.br/ccaab/images/AEPE/Divulga%C3%A7%C3%A3o/LIVROS/Manual_Elsevier_de_Veterin%C3%A1ria_Diagn%C3%B3stico_e_Tratamento_de_C%C3%A3es_Gatos_e_Animais_Ex%C3%B3ticos_-_7%C2%AA_Edi%C3%A7%C3%A3o_-_Robert_Moraillon_-_2013-compactado.pdf

56. Nabity, M. B., et al. (2015). Symmetric dimethylarginine assay validation, stability, and evaluation as a marker for the early detection of chronic kidney disease in dogs. *Journal of Veterinary Internal Medicine*, 29(4), 1036-1044.

57. Nhanharelli, J. P. (2018). Avaliação da eficácia da terapia com células-tronco renais, oriundas do metanéfro de gato doméstico, no tratamento da doença renal crônica em felinos (Dissertação de mestrado, Universidade de São Paulo). São Paulo.

58. Oliveira, G. B. M. de, Teixeira, K. C., Franco, D. Q. de S., & Varzim, F. L. S. B. (2020). Uso do biomarcador renal dimetilarginina simétrica no diagnóstico precoce da insuficiência renal crônica em cães e gatos. *Revista de Educação Continuada em Medicina Veterinária e Zootecnia do CRMV-SP*, 18(3). Disponível em: https://www.revistamvez-crmvsp.com.br/index.php/recmvz/article/view/38106

59. Oravec, L. B. V., et al. (2021). Doença renal crônica em felino de 4 meses de idade: Relato de caso.

60. Paiva, T. R. P. (2018). Marcadores precoces de lesão renal em cães e gatos domésticos: Revisão de literatura.

61. Palumbo, M. I. P., Machado, L. H. A. de, & Romão, F. G. (2011). Manejo da insuficiência renal aguda em cães e gatos. *Arquivos de Ciências Veterinárias e Zootecnia da UNIPAR*, 14(1), 73-76. Disponível em: file:///C:/Users/Usuario/Downloads/3747-11992-1-PB-3.pdf

62. Paz, G. de M., et al. (2016). Nefrologia em medicina felina. *Cadernos Técnicos de Veterinária e Zootecnia*, nº 82. Disponível em: https://www.vet.ufmg.br/ARQUIVOS/FCK/file/editora/caderno%20tecnico%2082%20medicina%20de%20felino.pdf

63. Pedersen, L. G. (2006). Body size, but neither age nor asymptomatic mitral regurgitation, influences plasma concentrations of dimethylarginines in dogs. *Journal of Veterinary Internal Medicine*, 80, 336–342.

64. Pelander, L., Häggström, J., Larsson, A., Syme, H., Elliott, J., Heine, R., & Ljungvall, I. (2019). Comparison of the diagnostic value of symmetric dimethylarginine, cystatin C, and creatinine for detection of decreased glomerular filtration rate in dogs. *Journal of Veterinary Internal Medicine*, 33(1), 630-639.

65. Peterson, M. E., Castellano, C. A., & Rishniw, M. (2016). Evaluation of body weight, body condition, and muscle condition in cats with hyperthyroidism. *Journal of Veterinary Internal Medicine*, 30(6), 1780–1789.

66. Peterson, M. E., Varela, F. V., Rishniw, M., & Polzin, D. J. (2018). Evaluation of serum symmetric dimethylarginine concentration as a marker for masked chronic kidney disease in cats with hyperthyroidism. *Journal of Veterinary Internal Medicine*, 32(1), 295–304.

67. Pet Support. (2023). Medicina veterinária: Doença renal crônica em cães e gatos: causas, sintomas e tratamentos. Disponível em: https://www.petsupport.com.br/blog/insuficiencia-renal-em-caes-e-gatos/

68. Polzin, D. J. (2016). Chronic kidney disease. In S. J. Ettinger, E. C. Feldman, & E. Côté (Eds.), *Textbook of veterinary internal medicine* (8th ed., pp. 4693-4734). St. Louis: Elsevier.

69. Polzin, D. J. (2011). Chronic kidney disease in small animals. *Veterinary Clinics of North America: Small Animal Practice*, 41(1), 15-30.

70. Reece, W. O. (2008). *Anatomia funcional e fisiologia dos animais domésticos*. Editora Roca.

71. Reece, W. O. (2017). *Dukes – Fisiologia dos animais domésticos* (13th ed., pp. 361-437). Editora Guanabara.

72. Relford, R., Robertson, J., & Clements, C. (2016). Symmetric dimethylarginine improving the diagnosis and staging of chronic kidney disease in small animals. *Veterinary Clinics of North America: Small Animal Practice*, 46(6), 941-960.

73. Sargent, H. J., Elliott, J., & Jepson, R. E. (2021). A nova era dos biomarcadores renais: O SDMA resolve todos os nossos problemas? *Jornal de Prática de Pequenos Animais*, 62(2), 71–81. https://doi.org/10.1111/jsap.13

74. Schwedhelm, E., & Böger, R. (2011). The role of asymmetric and symmetric dimethylarginines in renal disease. *Nature Reviews – Nephrology*, 7(5), 275-285.

75. Silva, L. S. (2018). Doença renal crônica em felino: Relato de caso (Trabalho de Conclusão de Curso). Disponível em: https://repository.ufrpe.br/bitstream/123456789/1547/1/tcc_luceliasan%27anasilva.pdf

76. Souza, R. M. B. (2022). A percepção social quanto às áreas de atuação e importância do profissional médico veterinário na saúde pública.

77. Tatematsu, S., et al. (2007). Role of nitric oxide-producing and -degrading pathways in coronary endothelial dysfunction in chronic kidney disease. *Journal of the American Society of Nephrology*, 18(3), 741–749.

78. Tain, V.-L., & Hsu, C.-N. (2017). Dimetilargininas tóxicas: Dimetilarginina assimétrica (ADMA) e dimetilarginina simétrica (SDMA). *Toxinas*, 9(3), 92.

79. Tozzetti, D. S., Ângelo, G., & Lot, R. F. E. (2009). Insuficiência renal crônica em cães e gatos: Revisão de literatura. *Revista Científica Eletrônica de Medicina Veterinária*, 6. Disponível em: http://faef.revista.inf.br/imagens_arquivos/arquivos_destaque/gCnyC9arzn0rVwc_2013-6-21-11-46-38.pdf

80. Thrall, M. A., et al. (2015). *Hematologia e bioquímica clínica veterinária* (2nd ed.). Rio de Janeiro: Guanabara Koogan.

81. Vieira, A. N. L. S. (2022). Biomarcadores de lesão renal no diagnóstico precoce e monitoração da lesão renal aguda na erliquiose monocítica canina. Disponível em: https://repositorio.unesp.br/items/2fc69fa3-96f1-4513-9df6-a283fbe5292e

82. Vilela, L. S., et al. (2022). Implicação da glomerulonefrite na fisiologia renal de cães e gatos: Uma revisão de literatura. *Revista de Educação Continuada em Medicina Veterinária e Zootecnia do CRMV-SP*, 20(1).

83. Watson, A. D. J., Lefebvre, H. P., & Elliott, J. (2015). Using urine specific gravity. *International Renal Interest Society (IRIS)*.