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Utility of vitamin D serum evaluation and supplementation in dogs and cats' medical routine: a review

Utilidade da avaliação sérica e suplementação com vitamina D na clínica de cães e gatos: uma revisão

Utilidad de la evaluación serica y suplementación con vitamina D en clínica para perros y gatos: una revisión

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João da Cruz Filho
ORCID: https://orcid.org/0000-0002-6217-5696
Universidade Federal de Sergipe, Brazil
E-mail: cruzfilhojoao@yahoo.com.br
Leandro Branco Rocha
ORCID: https://orcid.org/0000-0003-1009-2853
Universidade Federal de Sergipe, Brazil
E-mail: leobrv@yahoo.com.br
Alessandra de Santana
ORCID: https://orcid.org/0000-0001-5312-2747
Universidade Federal de Sergipe, Brazil
E-mail: alessandra.d.santana@gmail.com
Gabriel de Araújo Lobão
ORCID: https://orcid.org/0000-0001-7700-8965
Universidade Federal de Sergipe, Brazil
E-mail: mv.gabriellobao@gmail.com

Abstract
Vitamin D is traditionally known for its role in regulating calcium homeostasis and consequently maintaining bone integrity and health. However, more recently, it has been observed that it has a series of previously unknown non-canonical functions, such as maintenance of immunity and intestinal mucosa integrity. Furthermore, it has been shown to be associated with the progression or perpetuation of several diseases since its serum concentration is reduced during the course of the conditions. Therefore, we sought to investigate, through a literature review, the usefulness of serum vitamin D measurement in dogs and cats as a prognostic factor for different diseases, as well as the possible therapeutic effect of supplementing this vitamin in the correction of those illnesses. Vitamin D is in fact deficient in gastroenteric diseases, such as protein-losing enteropathy, infectious diseases, such as canine leishmaniasis, heart and kidney disease, among others. However, it is necessary to understand more properly about the physiological role of vitamin D in health, so that we can also understand it in disease. There are also too few data reports supporting supplementing this vitamin as main or adjuvant therapy in the treatment of any disease, but evidence points to the usefulness of vitamin D serum measurement as a prognostic predictor for dogs and cats.
Keywords: Vitamin D; Prognosis; Supplementation; Cholecalciferol.

Resumo
A vitamina D é tradicionalmente conhecida por seu papel na regulação da homeostase de cálcio e, consequentemente, manutenção da saúde óssea. No entanto, mais recentemente, têm-se observado que a mesma possui uma série de funções não-canônicas até então desconhecidas, desde sua participação na função do sistema imune até a manutenção da integridade da mucosa intestinal. Ademais, tem-se mostrado associada à progressão ou perpetuação de várias doenças, já que sua concentração sérica se encontra reduzida durante o quadro clínico destas. Por isso, buscamos investigar, por meio de revisão de literatura, a utilidade da mensuração sérica de vitamina D em cães e gatos como fator prognóstico de diferentes doenças sistêmicas, bem como o possível efeito terapêutico da suplementação desta vitamina na correção das enfermidades. De fato, a vitamina mostra-se deficiente em doenças gastroentéricas, como a enteropatia perdedora de proteínas, infecciosas, como a leishmaniose, cardiopatias e nefropatias, dentre outras. No entanto, é necessário que compreendamos mais o papel fisiológico da vitamina D na saúde, para que também o entendamos na doença. Também são escassos os dados que comprovem a utilidade da suplementação como terapia principal ou adjuvante no tratamento destas doenças, mas a mensuração sérica de vitamina D se mostra promissora como preditor prognóstico hospitalar para cães e gatos.
Palavras-chave: Vitamina D; Prognóstico; Suplementação**;** Colecalciferol.

Resumen
La vitamina D es tradicionalmente conocida por su papel en la regulación de la homeostasis del calcio y, en consecuencia, en el mantenimiento de la integridad y la salud de los huesos. Sin embargo, más recientemente se ha observado que tiene una serie de funciones no canónicas previamente desconocidas, desde su participación en la inmunidad al mantenimiento de la integridad de la mucosa intestinal. Además, se ha demostrado que está asociado con la progresión o perpetuación de varias enfermedades, ya que su concentración sérica se reduce durante el curso de la afección. Por ello, buscamos investigar, a través de una revisión de la literatura, la utilidad de la medición de vitamina D sérica en perros y gatos como factor pronóstico de diferentes enfermedades sistémicas, así como el posible efecto terapéutico de complementar esta vitamina en la corrección de enfermedades. De hecho, la vitamina es deficiente en enfermedades gastroentéricas, como la enteropatía perdedora de proteínas, enfermedades infecciosas, como la leishmaniasis canina, enfermedades cardíacas y renales, entre otras. Sin embargo, es necesario comprender más adecuadamente el papel fisiológico de la vitamina D en la salud, para que también podamos comprenderla en estado patológico. También hay pocos datos que apoyen la utilidad de la suplementación como terapia principal o adyuvante en el tratamiento de estas enfermedades, pero la evidencia apunta a la utilidad de esta medida como predictor pronóstico para perros y gatos.
Palabras clave: Vitamina D; Pronóstico; Suplementación; Colecalciferol.

1. Introduction

Vitamin D, also known as cholecalciferol, is an essential nutrient classically involved with calcium homeostasis (Chacar et al., 2020). Differently from most mammal species, dogs and cats cannot synthesize this vitamin through skin exposition to ultraviolet light, presumably because of the hyperactivity of 7-dehydrocholesterol-reductase, an enzyme responsible for converting cutaneous precursor of the vitamin back to a cholesterol molecule, turning this metabolic pathway ineffective (Weidner & Verbrugghe, 2017). Thereby, vitamin D in those species is obtained exclusively in their diet (Uhl, 2018).

Despite plenty is known about its canonic activity, it has recently been demonstrated that vitamin D has a larger protagonism than what we currently know, since its receptor is found in several non-skeletal tissues, highlighting its functions in different systems (Zafalon et al., 2020). Hyperexpression of vitamin D receptor (VDR) in skeletal muscle was able to promote activity of AKT signaling pathway, involved in protein synthesis activity (Bass et al., 2020). On the other hand, calcitriol was able to reduce in vitro TNF:IL-10 ratio in whole blood obtained from ill dogs, characterizing an anti-inflammatory status (Jaffey et al., 2018).

Low concentration of this vitamin has been associated with several diseases, including chronic and infectious illnesses (Corbee, 2020; Weidner & Verbrugghe, 2017). In humans, vitamin D deficiency has been related to obesity and type II diabetes (Bouillon et al., 2014), while in dogs and cats an association has been made with gastroenteric, cardiovascular and renal diseases (Allenspach et al., 2017; Kraus et al., 2014; Parker et al., 2020). Several diseases in companion animals also promote disturbances in vitamin D metabolism and therefore vitamin D status evaluation may be useful as a prognostic predictor (Weidner & Verbrugghe, 2017). Therefore, this article aims to review evidences pointing to the therapeutical benefit of vitamin D supplementation as well as its serum measurement as a prognostic predictor to different diseases in dogs and cats.

2. Methodology

This work constitutes a qualitative literature review (Snyder, 2019) aimed to research evidences that serum concentration of vitamin D may be related to progression, development or even perpetuation of several diseases in dogs and cats. Besides, it investigated proof that vitamin D supplementation may work as ancillary therapy to different ailments.

Used databases include “Google Scholar”, “Science Direct” e “SciELO”. The descriptors selected to the research were “vitamin D metabolism in dogs and cats”, “vitamin D in disease in dogs and cats”, “vitamin D supplementation in dogs and cats”, “vitamin D and cardiovascular disease in dogs and cats”, “vitamin D and leishmaniasis in dogs and cats”, among others. English-based papers were preferably utilized, as well as those published in the last ten years.

The articles whose titles or abstracts coincided with the aim of this work were analyzed for inclusion in the final manuscript. The first analyzes were made in publications that discussed the physiology of vitamin D in dogs and cats or literature reviews that addressed the relationship between vitamin D and disease in dogs and cats. In these works, a manual review was carried out in their references, in search for other articles eligible for this paper.

3. Results and Discussion

Exclusively obtained from food intake, vitamin D is absorbed and transported along with a vitamin D-binding protein (VDBP) through the circulation to the liver, where it undergoes a first hydroxylation reaction carried out by a 25-hydroxylase and it is converted to calcidiol (25(OH)D). 25(OH)D travels to the proximal tubules in the kidneys, where it is again hydroxylated by an 1α-hydroxylase to calcitriol (1,25(OH)2D), the hormonal biologically active form of vitamin D, which acts through cytoplasmic receptors. When activated, vitamin D receptors promote regulation of gene and consequently protein transcription, allowing vitamin D to exert its biological functions (Parker et al., 2017). Calcitriol promotes intestinal calcium absorption through the expression of membrane channels in enterocytes, followed by its intracellular transport. The mechanism is similar in the distal tubules of nephrons, where it promotes calcium reabsorption. The hydroxylation reaction that activates vitamin D is also targeted by parathyroid hormone (PTH), which promotes osteoclastogenesis aiming an increase in the circulating calcium (Chacar et al., 2020).

In humans, the recommended serum concentration varies by age group, according to the Endocrine Society (Holick et al., 2011). In dogs and cats, the term deficient is adopted for a 25(OH)D concentration less than 25 ng/mL, insufficient when between 25 and 100 ng/mL or sufficient when at or above 100 ng/mL (Selting et al., 2016; Sharp et al., 2015). However, the physiological role of vitamin D in dogs and cats, as well as in the pathogenesis of any disease is not fully known (Mellanby, 2016).

Beyond its canonic function, vitamin D is important in the maintenance of intestinal health, being able to promote integrity of the mucosal barrier through expression of occlusion proteins, which significantly reduced the deleterious effects of experimental colitis induced in mice (Kong et al., 2008). On the other hand, hyperexpression of VDR in skeletal muscle promoted the activity of major markers involved in protein synthesis leading to the development of muscle hypertrophy (Bass et al., 2020).

Due to the relationship between vitamin D and different organs regarding its metabolism, pathological disorders may cause changes in the serum concentration of this vitamin or its metabolites, such as 25(OH)D, which is more frequently used for estimating vitamin D status due to its stability and half-life in blood (Parker et al., 2017; Weidner & Verbrugghe, 2017).

A retrospective study carried out with dogs diagnosed with protein-losing enteropathy proved that the disease is accompanied with vitamin D deficiency which was more pronounced in patients with a worst clinical status, demonstrating its usability as a prognostic predictor (Allenspach et al., 2017). This deficiency could be a consequence of the hypoalbuminemia frequently diagnosed alongside this disorder, since the vitamin being fat-soluble requires its binding protein to circulate in the bloodstream (Zafalon, et al., 2020). However, other studies carried out in dogs and cats with different enteropathies, such as inflammatory bowel disease also demonstrated hypovitaminosis D associated with the diseases without correlation with serum albumin concentration (Gow et al., 2011; Lalor et al., 2012). Thus, although these parameters are interrelated, serum albumin and vitamin D levels seem to be independent prognostic markers in gastrointestinal tract diseases (Titmarsh et al., 2015).

Since vitamin D is obtained only through diet, it must be considered that different disorders capable of inducing anorexia, poor digestion or malabsorption may interfere with its circulating quantity (Titmarsh et al., 2015). In fact, the level of appetite in dogs with inflammatory bowel disease was correlated with the concentration of vitamin D. Patients with moderate to severely depressed levels experienced greater vitamin deficiency (Gow et al., 2011).

Pancreatitis is a multifactorial disease that affects dogs and a deficiency in enzyme secretion into the duodenum impairs the absorption of lipid components, including fat-soluble vitamins (Barko & Williams, 2018; Barnes et al., 2020). Consequently, the acute crisis of pancreatitis in dogs might be associated with vitamin D deficiency, which in turn is positively correlated with a decrease in circulating ionic calcium and a high concentration of C-reactive protein, a marker of acute inflammation. In addition, dogs that died from acute pancreatitis were found to be more deficient than those that survived the crisis, indicating a role for this vitamin as a prognostic marker during pancreatitis (Kim et al., 2017). In cats with cholestatic disease, serum concentration of vitamin D was identical when compared to felines sick from different systemic causes (Kibler et al., 2020).

In the human epithelial tissue, vitamin D is capable of supporting innate immunity, and participates in differentiation and proliferation of keratinocytes, demonstrating its importance for skin health. Furthermore, its deficiency seems to be associated with the pathophysiology of allergic disorders such as atopic dermatitis (Kovalik et al., 2012; Umar et al., 2018). Traditionally, canine atopic disease is treated with protocols based on the use of corticosteroids in an immunosuppressive dose. When measuring severity degree index for atopic dermatitis clinical signs at day 0 and six weeks after treatment of 20 dogs with prednisolone, it was noted that atopic patients did not have significantly lower concentrations of vitamin D compared to healthy dogs. However, those animals who showed more intense clinical improvement had a higher concentration of 25(OH)D prior to treatment compared to the ones that did not achieve such an effective therapeutic response (Kovalik et al., 2012).

Supplementation of atopic dogs with cholecalciferol (300UI/kg/day) for 84 days resulted in a significant reduction in their pruritus index and they ended up the study with an increase of up to 250% in circulating 25(OH)D when compared to the beginning of the study. However, supplementation with paracalcitol (vitamin D receptor agonist) was unable to bring about improvement, but rapidly caused the development of short-term adverse effects (Klinger et al., 2018). In dogs with autoimmune disease, including juvenile cellulitis, vitamin D deficiency was also observed being associated with a shorter survival time (Mick et al., 2019).

Through its genomic and non-genomic actions, calcitriol has shown anti-neoplastic potential as seen, for example, in its protective effect against DNA damage caused by ultraviolet light, inhibiting the growth of cells from malignant melanoma and regulating signaling pathways involved in the proliferation of different cell lines (Feldman et al., 2014). Furthermore, studies have suggested that vitamin D is able to regulate the entire oncogenic process, from its initiation to cell metastasis, since it exerts control over the processes of differentiation, proliferation, cell death and autophagy, among others (Jeon & Shin, 2018).

Canine C2 cells for mast cell tumors incubated in the presence of calcitriol in increasing concentrations (0.1nM to 6.25mM) showed lower viability in a concentration-dependent manner. When calcitriol was added together with chemotherapy drugs used in clinical routine (lomustine, vinblastine, imatinib or toceranib), it was able to potentiate their effect, significantly reducing the viability of neoplastic cells when compared to those incubated with the chemotherapeutics alone (Malone et al., 2010). Vitamin D also showed in vitro synergism with the anti-neoplastic effects of cisplatin in different tumoral cell lines, but the clinical significance of this finding needs to be further demonstrated, as the intravenous application of calcitriol in different doses among with cisplatin did not result in clinical improvement of patients (Rassnick et al., 2008).

Calcitriol was also tried as monotherapy for the treatment of canine mast cell tumors, at doses of 1.5 or 2.25µg/kg, resulting in a short-period total (n=1/10) or partial (n=3/10) remission of the tumors in some individuals. But the nodules relapsed within a short period of time and most patients developed adverse effects such as vomiting, anorexia, azotemia and hypercalcemia. Thus, the assessment of the therapeutic efficacy of calcitriol as a chemotherapy agent requires further studies (Malone et al., 2010). Labrador Retriever dogs with mast cell tumors also had vitamin D deficiency when compared to healthy patients. However, such deficiency did not appear to have been induced by food intake deficit, as there was no significant

difference in vitamin D intake between the two groups (Wakshlag et al., 2011).

Vitamin D also contributes to the function of the immune system, promoting the maturation of circulating monocytes and the production of an antimicrobial peptide, cathelicidin (Medrano et al., 2018). Besides, VDR is also present in most immune cells lines such as monocytes, macrophages, T and B lymph cells, dendritic cells and natural killer (Nagpal et al., 2005).

Both animals and humans have a vitamin D deficiency during the course of some infectious diseases (Abrishami et al., 2021; Dvir et al., 2019; Lalor et al., 2012; Vescini et al., 2011). It was observed that dogs suffering from canine distemper had a mean concentration of 25(OH)D that ranged between 20 and 40ng/mL, a value considered insufficient. All animals were supplemented with cholecalciferol (1000UI/kg), but they only reached sufficient levels around the 90th day post treatment, when a mean serum value of 140 to 160ng/mL was obtained. Despite that, vitamin D supplementation was unable to modify speed, rhythm and distribution of myoclonus associated with the disease after 120 days (Dóro & Amaral, 2021; Selting et al., 2016).

The presence of clinical signs in canine leishmaniasis was also related to low serum concentration of vitamin D found in positive symptomatic patients. The asymptomatic positive group, however, showed no difference compared to symptomatic or negative patients. In addition to the clinicopathological score, antibody titers and circulating parasite load were also higher in vitamin-deficient animals (Rodriguez-Cortes et al., 2017). Nevertheless, conflicting results have been observed regarding the association of vitamin D and its receptor with infection by Leishmania sp. In contrast to previous studies, dogs diagnosed with leishmaniasis obtained from a zoonoses center (São Paulo, Brazil) presented vitamin A and zinc deficiency, but a higher plasma concentration of 25(OH)D compared to the control group. In vitro leukocyte supplementation with calcitriol was able to reduce parasite load, as well as increase the production of reactive oxygen species and nitric oxide, both substances involved in the parasite elimination process (Hernandez et al., 2021). Vitamin D has been shown to reduce the production of inflammatory cytokines in Th1 and Th17 lymph cells, whose activity is related to the growth control of *Leishmania infantum* (Rodriguez-Cortes et al., 2017). On the other hand, VDR expression was associated with inhibition of the leishmanicidal activity of macrophages, as VDR-knockout mice showed greater resistance to infection by *Leishmania major* (Ehrchen et al., 2007). The incubation of macrophages with vitamin D reduced parasitic growth in the cells contaminated by *Leishmania amazonenses* (Machado et al., 2020), whereas mice treated every 48h for 12 weeks with calcitriol showed a drastic reduction in skin lesions caused by infection with Leishmania sp. (Ramos-Martínez et al., 2013).

The vitamin also demonstrates cardioprotective activity, since VDR-knockout mice are predisposed to the development of cardiac hypertrophy and hyperactivity of the renin-angiotensin-aldosterone system, which in long term participates in the pathogenesis of systemic hypertension (Bouillon et al., 2014; Xiang et al., 2005). In dogs with heart disease (degenerative valve disease or dilated cardiomyopathy), the concentration of 25(OH)D was statistically lower than in healthy patients (100 ± 44nmol / L vs. 123 ± 42nmol / L) and was associated with a higher risk for clinical manifestation of congestive heart failure or sudden death, demonstrating that vitamin D deficiency is a predisposing factor, risk factor and prognostic marker for heart failure in dogs (Kraus et al., 2014).

Degenerative valve disease in dogs can be classified into different stages. Patients who benefit from treatment are classified in stages B2, C or D, while stages A and B1 include respectively patients who are predisposed to disease or even already have it but without hemodynamic complications or evidence on imaging diagnostic exams (Keene et al., 2019). It was observed as from stage B2, there was a significant deficit in the serum concentration of 25(OH)D when compared to the control group which consisted of patients staged B1 (mean 33.2 nmol/L vs. mean 52 .5 nmol/L). This deficiency was even more marked in dogs in a more advanced stage, that is C/D (mean 13.1nmol/L vs. mean 52.5nmol/L) (Osuga et al., 2015).

Usually, 25(OH)D measurement is used as an estimate of the serum vitamin D concentration (Parker et al., 2017).

However, it has recently been proven that unlike other species, felines have a considerable circulating concentration of another vitamin D metabolite called C-3, a calcidiol alpha epimer (Sprinkle et al., 2018). Therefore, it is suggested that the sum of vitamin D (i.e., sum of calcidiol plus C-3 serum concentrations) may be a more accurate parameter for estimating vitamin D status in cats. In addition, the sum was negatively related to the age of cats, indicating there is less production or circulation of vitamin D in older patients (Ware et al., 2020).

In cats with heart disease, the sum of vitamin D was significantly lower compared to healthy cats, but when standardized for age, the result became non-significant, indicating that the low circulating vitamin D may coincide with the older age that is observed in cats with heart disease. Nevertheless, the sum of vitamin D was positively correlated with survival time and fractional shortening (an indicator of systolic function), corroborating the action of vitamin D on cardiovascular function (Ware et al., 2020).

Vitamin D also appears to aid renal cell growth and differentiation post injury as well as diminishing glomerulosclerosis, renal interstitial fibrosis and proteinuria, suggesting a great importance in the control of chronic kidney disease (Andress, 2007). In Wistar rats, experimental kidney injury induced by monosodium glutamate was successfully reversed in the group of animals supplemented with vitamin D (12 µg/kg/day, 3x/week, from the 21st to the 90th day of life) associated with the practice of swimming for the entire supplementation period (Zanuzo et al., 2020).

In long term, chronic kidney disease may predispose an individual to a series of secondary disorders, aggravating the patient's clinical condition and the already present renal injury. Proteinuria induces or worsens glomerular damage, while systemic arterial hypertension results from renin-angiotensin-aldosterone system dysfunction (Kobori et al., 2007; Wu et al., 2020). Along with the kidneys, parathyroid gland and vitamin D accurately regulate the balance of circulating calcium. During hypocalcemia, parathyroid hormone is responsible for stimulating the conversion of calcidiol into its active form, calcitriol, in the kidneys, in order to reestablish circulating calcium. However, as the kidney disease progresses, the gland is no longer able to compensate for excessive calciuria, resuting in a secondary renal hyperparathyroidism, which results in bone fragility due to excess calcium reabsorbed from its matrix (Chacar et al., 2020).

The progression of kidney disease in cats is negatively correlated with calcitriol concentration, that is, the more advanced the disease, the lower the vitamin concentration (Barber & Elliott, 1998). However, supplementation with calcitriol was ineffective in reversing secondary hyperparathyroidism. The serum concentration of parathyroid hormone remained unchanged when observing the two points of the study, before and after supplementation. There was also no statistical correlation between serum vitamin D concentration and total calcium (Hostutler et al., 2006).

In dogs, the concentration of calcitriol was significantly lower than that of the control group from stage III of kidney disease (Cortadellas et al., 2010). Supplementation with 25(OH)D (30 or 60µg/animal/day) continuously or intermittently in nephropathic dogs was able to increase the mean serum concentration of 25(OH)D by 470% and calcitriol mean serum concentration by 94% until the 84th day of therapy, without signs of toxicity. However, no beneficial effects of this supplementation on disease progression or manifestation of clinical signs were noted until the end of the work (Parker et al., 2020).

4. Final Considerations

Although it is classically known for its role in mineral metabolism, the range for non-canonical actions of vitamin D remains wide open in both humans and animals, as literature has increasingly demonstrated. It is important that we know epidemiological data regarding vitamin D status in our local populations of dogs and cats, in order to investigate if these are not already in need of this vitamin even while healthy, since even though living in a tropical country, sun exposure is not an important factor for vitamin D synthesis in these species.

Vitamin D has been proven as a prognostic predictor in several diseases, since it is found deficient in those. Nevertheless, very few authors have already approached the benefits of supplementing this vitamin alongside conventional therapeutics. Therefore, it is necessary to improve our knowledge regarding biology of vitamin D in dogs and cats both in physiological and pathological situations, so that we can better understand the relationship between low vitamin D and sickness and, doing so, better approach the correction of vitamin D status in disease and explore the benefits of doing it.

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