DIAGNOSIS OF HYPERCORTISOLISM IN DOGS: A LITERATURE REVIEW

Diagnóstico de hipercortisolismo em cães: revisão de literatura

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Abstract

Hyperadrenocorticism (HAC), also known as hypercortisolism or Cushing's syndrome, is a common condition in dogs caused by the excessive production of cortisol, which is synthesized by the adrenal glands and performs various functions in the organism. Furthermore, HAC can be classified into three types: pituitary-dependent, which accounts for 80 to 85% of cases; adrenal-dependet, responsible for 15 to 20% of cases; and intragenic hyperadrenocorticism. This endocrinopathy is characterized by a slow and insidious progression and, in addition, it's noticed that the most frequent clinical signs include polydipsia, polyuria, hypertension and hypertensive retinopathy, polyphagia, abdominal distension, muscle alterations, lethargy, cutaneous alterations, persistent anestrus, testicular atrophy and neurological manifestations. Its diagnosis can be established through hormonal testing, associated with laboratorial and imaging exams. Therefore, knowledge about hyperadrenocorticism is essential to improve the dog's quality of life and to prevent complications, such as hypertension, and recurrent infections.

Keywords: Adrenal; clinical; cortisol; endocrinopathy.

Resumo

O hiperadrenocorticismo (HAC), também conhecido como hipercortisolismo ou síndrome de Cushing, é uma condição comum em cães causada pelo excesso de produção do cortisol, que é

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sintetizado pelas glândulas adrenais desempenhando diversas funções no organismo. Ademais, esta pode ser classificada em três tipos: hipófise dependente, representando 80 a 85% dos casos; adrenal dependente, sendo 15 a 20% e iatrogênico. Esta endocrinopatia apresenta característica de progressão lenta e insidiosa e, além disso, percebe-se que os sinais clínicos mais frequentes são polidipsia, poliúria, hipertensão arterial, retinopatia hipertensiva, polifagia, abaulamento abdominal, alterações musculares, letargia, alterações cutâneas, anestro persistente, atrofia testicular e manifestações neurológicas. Seu diagnóstico é realizado através de testes hormonais, associados a outros exames laboratoriais e de imagem. O conhecimento sobre o HAC é essencial para melhorar a qualidade de vida do cão e evitar outros tipos de complicações, como diabetes, hipertensão e infecções recorrentes.

Palavras-chave: Adrenal; clínica; cortisol; endocrinopatia.

Introduction

The adrenal glands, first described in 1563 in the book *Opuscula Anatomica* by Eustachius, only began to have their function defined in 1855 by Thomas Addison. Until 1732, they were considered hollow organs, when Winslow named them ''adrenals,'' referring to their position adjacent to the kidneys (González; Silva, 2017).

Currently, the adrenal glands are understood as small, paired retroperitoneal structures located craniodorsally to the kidneys and closely associated with major vessels such as the aorta and caudal vena cava, which traverse the abdominal cavity. Internally, they are composed of different histological groups responsible for producing various hormones, including androgens and estrogens, cortisol and aldosterone, as well as adrenaline and noradrenaline (Penninck; d'Anjou, 1991).

These organs are part of the endocrine system in animals and are therefore associated with various endocrinopathies with systemic effects. Hyperadrenocorticism (HAC), or hypercortisolism—also known as Cushing's syndrome—is one of the most common hormonal disorders in dogs, with its first reports dating back to around 1970; it also occasionally affects cats and horses. This syndrome was first described in humans by Harvey Cushing in 1910, who reported several patients with hypercorticism and basophilic tumors in the pituitary gland (González; Silva, 2017).

In HAC, the adrenal gland produces and secretes excessive amounts of cortisol. Cushing's disease may have different etiologies: the most common cause in dogs is pituitary-dependent (pituitary-dependent HAC [PDH]), accounting for 80–85% of cases; it may also be adrenal-dependent (adrenal-dependent HAC [ADH]), representing 15–20% of cases, or iatrogenic when the patient is undergoing prolonged glucocorticoid therapy (Benedito; Rossi; Camargo, 2017).

This endocrinopathy is relatively common in dogs, particularly affecting breeds such as poodles, dachshunds, small Terriers (Yorkshire, Jack Russell), Staffordshire Bull Terrier, beagles, and German Shepherds. PDH has a higher incidence in middle-aged dogs, ranging from two to sixteen years of age (Mooney; Peterson, 2015). In contrast, dogs with ADH tend to be older, between six and sixteen years, with a predisposition to the development of adrenal tumors, 65% of which occur in females (Mooney; Peterson, 2015). The present study aims to conduct a literature review on the diagnosis of hypercortisolism in dogs.

Anatomy and Histology

The adrenal glands are classified as primary endocrine organs, with their main function being the production of certain hormones. They are paired, elongated glands located near the

thoracolumbar junction of the dorsal abdomen and craniomedial to each kidney (Dyce; Sack; Wensing, 2019), with the left gland being more closely related to the abdominal aorta than to the kidney itself. They are often asymmetric and irregular, with size influenced by factors such as age, species, and gestation, and are larger in young animals, wild animals, and pregnant or lactating females. They are firm, solid structures surrounded by a fibrous capsule—more prominent than that of other endocrine organs (Evans; Lahunta, 2012)—which encloses the outer yellowish, striated cortex and the darker, more uniform inner medulla (Dyce; Sack; Wensing, 2019).

They maintain close anatomical relationships with major vessels, such as the aorta on the left and the vena cava on the right, adhering to them when the kidneys shift from their usual positions. Their vascularization is extensive, consisting of small branches arising from the aorta and the renal, lumbar, phrenicoabdominal, and cranial mesenteric arteries. Blood then flows through the central vein, where emissary vessels pass through the hilum to enter the caudal vena cava or one of its tributaries, reaching target cells (Dyce; Sack; Wensing, 2019). The hilum is the region through which veins and arteries exit and enter the organ; it is also where the medulla—completely surrounded by the cortex—approaches the external surface (Evans; Lahunta, 2012).

Regarding innervation, the cortex contains few slender nerves connected to the hypothalamus for tissue regulation. In contrast, the medulla is richly innervated by preganglionic sympathetic fibers connected to medullary cells, which function as postganglionic sympathetic neurons (Dyce; Sack; Wensing, 2019).

Primarily, the adrenal glands consist of two tissues with distinct functions and structures: an inner medulla, an outer cortex, and a connective capsule surrounding them. Overall, their products influence the organism's response to acute or chronic stress. The medullary portion is composed of modified sympathetic neurons that synthesize adrenaline and noradrenaline, storing them in granules. The adrenal cortex, in turn, is enclosed by a dense collagenous connective tissue capsule with an arteriolar plexus that ensures blood supply to both portions of the gland (Eurel; Frappier, 2012). In this region, approximately 30 steroid hormones are synthesized and secreted, the most important being cortisol, a glucocorticoid, and aldosterone, a mineralocorticoid (Marco, 2015). These compounds are essential for mineral homeostasis regulated by the kidneys and play a key role in carbohydrate metabolism (Evans; Lahunta, 2012).

Subsequently, the cortical region can be divided into several zones, each secreting different hormones, all derived from cholesterol (Reece *et al*., 2017). These zones are the zona glomerulosa, zona fasciculata, an intermediate zone, and finally the zona reticularis, which is the innermost layer (González; Silva, 2017), as shown in Figure 1. The zona glomerulosa is responsible for producing mineralocorticoid steroid hormones that regulate electrolyte balance. The zona fasciculata, the largest cortical layer, produces glucocorticoids, which are involved in glucose metabolism and stress response, such as cortisol and corticosterone. The zona reticularis is responsible for the production of androgens and glucocorticoids (Eurel; Frappier, 2012).

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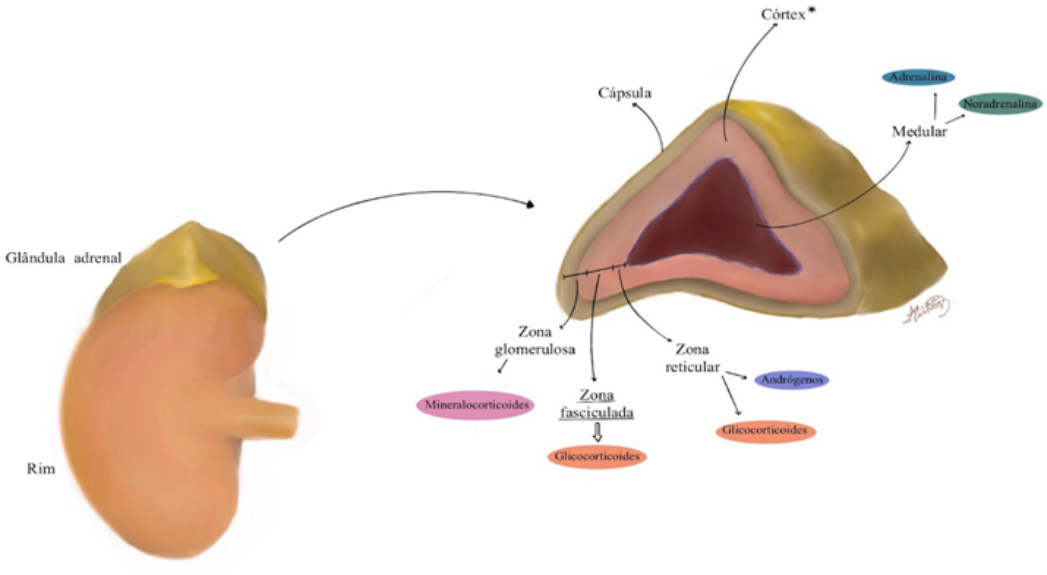
Figure 1 – Anatomy of the kidney and adrenal gland (zones and hormones produced)



Source: Adapted from Campos-Rodríguez *et al.* (2013).

Physiology and biochemistry of cortisol

Cortisol is the primary glucocorticoid produced and secreted by the zona fasciculata of the adrenal gland and, to a lesser extent, by the zona reticularis. Its synthesis and secretion occur through the hypothalamic–pituitary–adrenal (HPA) axis, regulated by negative feedback exerted by circulating cortisol levels. In this cascade, hypothalamic neurons first secrete corticotropin-releasing hormone (CRH), which reaches the adenohypophysis and acts on corticotrophic basophilic cells, stimulating the production of adrenocorticotropic hormone (ACTH) (Reece *et al*., 2017) (Figure 2).

Subsequently, via the bloodstream, ACTH reaches the adrenal gland, where it binds to surface receptors in the zona fasciculata and stimulates enzymatic activity, leading to the release of isocaproaldehyde and pregnenolone. This process results in the formation of progesterone, which is associated with aldosterone synthesis, or initiates the cortisol pathway—culminating in the production and secretion of cortisol into the bloodstream (González; Silva, 2017). This steroid hormone then reaches its target cells through circulation and influences their metabolism. Finally, when its blood concentration becomes elevated, it exerts negative feedback on the hypothalamus, inhibiting the secretion of CRH and, consequently, ACTH (Reece *et al*., 2017).

Cortisol exerts multiple metabolic effects by inducing the transcription of specific enzymes and inhibiting genes involved in DNA synthesis. This glucocorticoid is particularly relevant during stress, which may be internal—resulting from chronic pain and infections—or external, such as stressful situations including environmental changes and significant temperature fluctuations (González; Silva, 2017).

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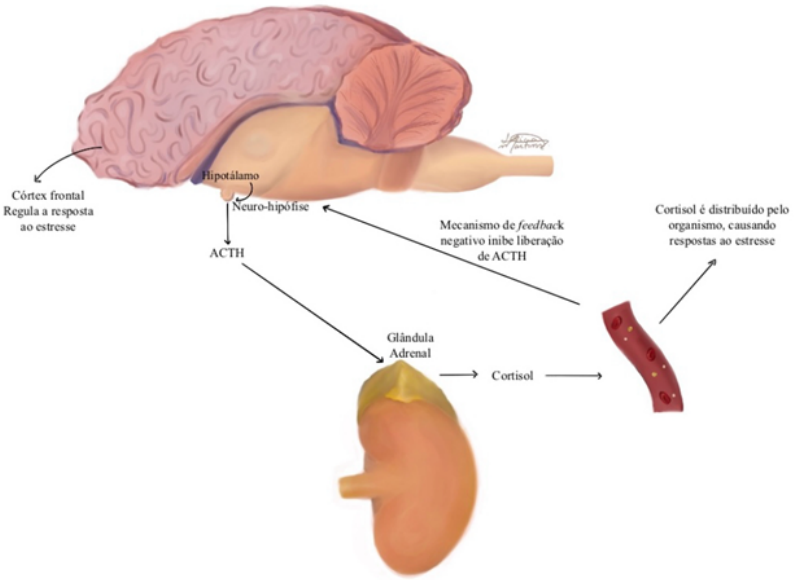
Figure 2 – Hypothalamic–pituitary–adrenal axis in cortisol release



Source: Adapted from Campos-Rodríguez *et al.* (2013).

During stress, cortisol stimulates enzymes involved in gluconeogenesis, increasing blood glucose levels to supply the brain and muscles, resulting in hyperglycemia and, potentially, glycosuria. This occurs due to the glucocorticoid's effect on glucagon and epinephrine, which stimulate glycogenolysis, gluconeogenesis, and glycogenesis, while inhibiting peripheral glucose utilization. This metabolic state is sustained by inhibitory effects on insulin, promoting lipolysis and muscle catabolism. These increases in serum glucose, lipids, and amino acids represent an adaptive mechanism that ensures substrate availability for the brain and muscles and supports gluconeogenesis, redirecting resources from peripheral tissues and local growth processes (Reece *et al.*, 2017).

Moreover, cortisol exhibits immunosuppressive activity at high concentrations, as it inhibits the synthesis of inflammatory prostaglandins derived from pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Thus, it exerts anti-inflammatory and antiallergic effects and is widely used in clinical practice in cases of severe tissue damage, acting through multiple mechanisms to suppress immune responses. Additionally, it inhibits cellular growth and wound healing by reducing fibroblast proliferation and connective tissue formation (González; Silva, 2017).

Cortisol may also display mineralocorticoid activity, as it can bind to aldosterone receptors. It may produce psychoneural effects, initially causing euphoria and increased appetite, followed by depression. It also affects fluid balance by increasing diuresis through vasopressin inhibition, leading to polyuria and polydipsia with effective water loss in urine. Prolonged cortisol secretion may result in atrophy of the zona fasciculata and thymus, lymphopenia, and reduced bone matrix (Reece *et al.*, 2017).

Clinical manifestations and pathophysiology

This endocrinopathy may develop insidiously, with slow progression, and may present intermittent characteristics with recurrent episodes. To further complicate prognosis, caregivers often delay recognizing clinical manifestations, as these signs are

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frequently misinterpreted as normal aging processes in pets. The clinical presentation is diverse and directly related to elevated cortisol levels (Jesus, 2019).

The most frequent clinical signs include polydipsia, polyuria, systemic arterial hypertension, hypertensive retinopathy, polyphagia, abdominal distension, muscle alterations, lethargy, dermatological changes, persistent anestrus, testicular atrophy, and neurological manifestations. Large-breed dogs tend to exhibit fewer characteristic signs in the short term compared to small-breed dogs (Mooney; Peterson, 2015).

Regarding these signs, systemic arterial hypertension (SAH) may occur due to the glucocorticoids themselves, which can exert mineralocorticoid activity by binding to these receptors due to hormonal similarity, or it may result from excessive activation of the renin–angiotensin–aldosterone system (RAAS), typically triggered in hypotensive states. Through this mechanism, angiotensin II increases blood pressure via vasoconstriction and stimulation of the thirst center through enhanced vasopressin production, while aldosterone—secreted by the adrenal gland—increases sodium and water reabsorption in the proximal convoluted tubule. However, excess cortisol leads to inhibition or rapid inactivation of antidiuretic hormone in the renal tubules, preventing water reabsorption and resulting instead in polyuria and secondary polydipsia, with urine output exceeding 50 mL/kg/day and water intake surpassing 100 mL/kg/day, respectively (Fiegenbaum, 2013). Consequently, SAH is associated with complications such as blindness, pulmonary thromboembolism, glomerulonephropathy, proteinuria, ventricular hypertrophy, congestive heart failure, cerebral edema, and hypertensive encephalopathy (Leal, 2008).

Moreover, insatiable polyphagia results from the direct action of glucocorticoids on the central nervous system and may or may not be associated with the weight gain observed in many patients. It has been reported that this steroid reduces metabolic rates and suppresses insulin as part of its physiological role during stress to ensure substrate availability; however, with excessive cortisol levels, there is marked fat redistribution, particularly to the dorsal and abdominal regions, giving the dog a "pot-bellied" or "tabletop" appearance. This abdominal distension results from lipid redistribution, hepatomegaly, and atrophy and weakness of the abdominal musculature (Mooney; Peterson, 2015).

Myopathy, or muscle atrophy, initially affects the abdominal region, limbs, vertebral column, and eventually the cranial temporal region. It is caused by the catabolism of myofibrillar proteins and the inhibitory action of insulin, which is responsible for protein and lipid synthesis. Pseudomyotonia, defined as persistent muscle contraction even after cessation of the stimulus, is associated with sarcolemmal hyperexcitability characterized by delayed hyperpolarization, likely due to alterations in sodium and chloride channels. This condition is noticeable after physical activity and repeated contractions of a muscle fiber group following percussion, leading to progressive muscle stiffness (Fernández; Bernardini, 2010).

Regarding dermatological changes, cortisol directly affects hair quality and growth, resulting in dull, dry coats and bilateral symmetrical alopecia. This hormonally induced hair loss is not typically associated with pruritus unless secondary pyoderma develops, which is common due to immunosuppression. The condition progresses slowly, initially affecting the trunk, flanks, and perineal region, and later the abdomen. Additionally, excessive steroid levels inhibit epidermal mitosis, fibroblast proliferation and migration, and lead to collagen atrophy—particularly type III collagen—resulting in thinner skin. Combined with abdominal distension and vascular alterations, this leads to telangiectasia. Furthermore, affected dogs may develop seborrhea due to sebaceous gland atrophy, comedones due to follicular degeneration, cutaneous calcinosis, and hyperpigmentation associated with the

chronicity of the disease, as well as melanocyte stimulation in paraneoplastic syndromes (Fiegenbaum, 2013).

Concerning reproductive manifestations, both persistent anestrus and testicular atrophy occur due to the exaggerated negative feedback effect on the pituitary gland, leading to suppression of gonadotropic hormones, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These changes may also indicate the duration of the disease (Mooney; Peterson, 2015).

Pituitary-Dependent Hyperadrenocorticism (PDH)

The most frequent cause of PDH is a pituitary alteration, either due to an inappropriate endogenous secretion of adrenocorticotropic hormone (ACTH) or increased primary or secondary production of ACTH associated with neoplasms (Jesus, 2019).

Initially, it has been suggested that this excessive and spontaneous ACTH secretion may occur due to several factors: a primary failure in cortisol negative feedback, allowing continued CRH release; diffuse hyperplasia of corticotrophic cells in the anterior pituitary; or excessive stimulation of these cells. Nevertheless, the specific etiology of this form of HAC remains unknown (Mooney; Peterson, 2015).

Secondarily, pituitary carcinomas are the most common cause of PDH, particularly tumors arising from corticotrophic cells in the distal and intermediate lobes, which are the most frequently reported in dogs. These tumors can be classified by size as microadenomas (less than 1 cm) or macroadenomas (greater than 1 cm), the latter accounting for approximately 10–15% of cases (Mooney; Peterson, 2015). As they grow, both types may compress brain structures and exert mass effects. Generally, microadenomas do not compress the brain parenchyma—except in small breeds—whereas macroadenomas, which typically grow slowly, often compress the hypothalamus and thalamus. Affected patients may or may not present clinical signs related to tumor growth, including ataxia, altered mental status, absence of menace response, circling behavior, visual deficits, and even seizures (Fernández; Bernardini, 2010).

These neoplasms characterize a paraneoplastic syndrome by secreting ACTH autonomously, independent of regulatory feedback mechanisms (whether negative or positive) and without reliance on ACTH-releasing hormone (Reece *et al*., 2017; Goff, 2017). Consequently, neoplastic cells induce excessive cortisol production and secretion by the adrenal glands, leading to PDH. Chronic secretion of CRH and/or ACTH results in bilateral adrenal hyperplasia (Silva; Drumond; Coelho, 2022).

Adrenal-Dependent Hyperadrenocorticism (HAD)

ADH, the second most common cause, results from neoplastic formations within the adrenal gland itself. These tumors may be bilateral or unilateral. The latter, in addition to being more frequent, lead to hypertrophy of the affected gland and significant cortical atrophy of the contralateral gland. These tumors may be classified as benign or malignant (Jesus, 2019).

Benign neoplasms, such as adenomas, are generally small, well circumscribed, and exhibit low metastatic potential, and may be partially calcified. In contrast, malignant tumors, such as carcinomas, are associated with metastases to the liver, lungs, and kidneys due to the anatomical relationship of the right adrenal gland with the phrenicoabdominal veins,

caudal vena cava, and lymphatic circulation. These tumors are larger and more aggressive, often presenting necrotic and hemorrhagic features due to their high vascularization, and may also exhibit calcifications with some frequency. Adenomas and carcinomas occur in similar proportions in dogs (Mooney; Peterson, 2015).

Adrenal tumors are autonomous, functional, and independent of regulatory control mechanisms, secreting excessive cortisol without pituitary dependence. As a result, serum ACTH levels remain low, while cortisol levels increase independently of feedback regulation (Silva; Drumond; Coelho, 2022). It is noteworthy that, sporadically, these neoplastic cells may also secrete excessive mineralocorticoids or androgens (Reece *et al*., 2017).

Iatrogenic Hyperadrenocorticism

This condition occurs due to excessive administration of cortisol, either through prolonged veterinary prescription or improper use by animal caregivers, often intended to manage immune-mediated or allergic diseases. Such medication suppresses endogenous glucocorticoid production; therefore, if exogenous hormone administration is abruptly discontinued, the dog may be unable to restore endogenous production, leading to hypoadrenocorticism (Leal, 2008) due to bilateral adrenocortical atrophy (Silva; Drumond; Coelho, 2022).

Diagnosis

The diagnosis of HAC is established through hormonal testing, as baseline cortisol measurement alone is insufficient, given that this hormone may be elevated in response to stress. Correlation with clinical signs, imaging findings, and laboratory alterations is essential to support the diagnosis, as manifestations are diverse and vary in intensity (Leal, 2008). Accordingly, Table 1 provides a guideline for approaching the diagnosis of a dog suspected of having HAC.

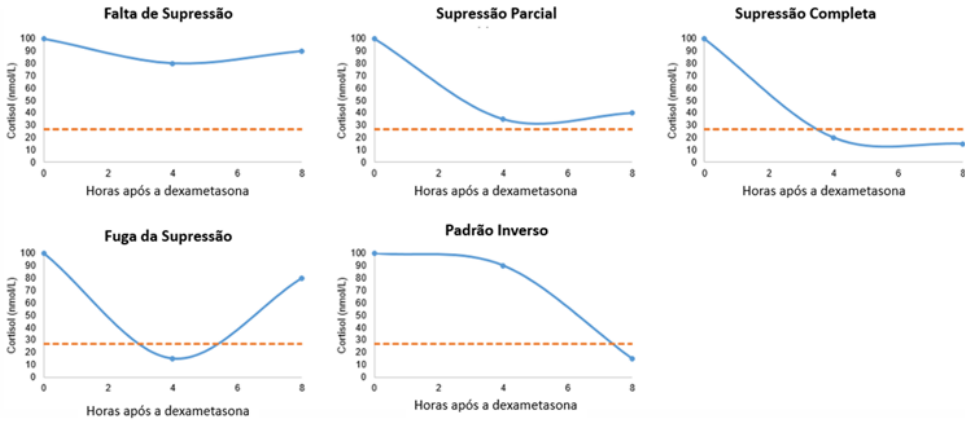
The low-dose dexamethasone suppression test (LDDST) is a screening endocrine test with high sensitivity for evaluating the hypothalamic–pituitary axis. It is performed by collecting a baseline plasma sample in the morning, followed by intravenous administration of dexamethasone at a dose of 0.01 mg/kg, with subsequent sample collection at four and eight hours post-administration. In negative results, dexamethasone suppresses cortisol release by directly inhibiting ACTH secretion, with both values below 1.4 µg/dL (Xella, 2010). In positive cases, results may show persistent elevation—characteristic of adrenocortical tumors that secrete cortisol independently of ACTH—or an initial decrease followed by an increase, indicative of PDH due to relative pituitary resistance to cortisol negative feedback. However, this test may be influenced by factors such as anticonvulsant medications, stress from bathing, hospitalization, or concurrent diseases (Ettinger; Feldman, 2004).

In 2013, the American College of Veterinary Internal Medicine (ACVIM) published a consensus statement on the diagnosis of spontaneous HAC in dogs (Behrend *et al*., 2013), in which the LDDST was recommended as the screening test of choice, along with a recommendation to reassess cutoff values.

Behrend *et al.* (2013) also strongly recommended additional endocrine testing for dogs presenting an ''inverse'' pattern in the LDDST, defined as a cortisol concentration > 27.59 nmol/L (>1 µg/dL) four hours after dexamethasone administration (t4) and < 27.59 nmol/L (<1 µg/dL) at eight hours (t8). This pattern was traditionally interpreted as negative; however,

Mueller *et al*. (2006) were the first to describe it in five dogs with pituitary-dependent hyperadrenocorticism (PDH). The authors hypothesized that this might represent a novel form of HAC, although the same pattern was also identified in two of 29 dogs initially suspected, but later ruled out, for HAC. A subsequent study investigated five different LDDST patterns and their respective positive predictive values (PPV) for HAC diagnosis. These patterns were defined as: complete suppression (t4 and t8 < 27.59 nmol/L [<1 µg/dL]); no suppression (t4 and t8 > 27.59 nmol/L [>1 µg/dL] and > 50% of baseline [t0]); partial suppression (t4 and/or t8 > 27.59 nmol/L [>1 µg/dL], but < 50% of t0); escape (t4 < 27.59 nmol/L [<1 µg/dL] and t8 > 27.59 nmol/L [>1 µg/dL]); and inverse (t4 > 27.59 nmol/L [>1 µg/dL] and t8 < 27.59 nmol/L [<1 µg/dL]), as illustrated in Figure 3.

Figure 3 – Patterns observed during the suppression test



Source: Adapted from Zeugswetter *et al*. (2021).

The ''inverse'' and ''escape'' patterns showed very low PPVs, raising concerns that these patterns may not be compatible with a diagnosis of HAC. However, the ''escape'' pattern is currently considered a classic and common presentation of HAC (Mueller *et al*., 2006).

Additionally, an increasing pattern, defined as a >50% rise in cortisol concentrations between any time points, has been considered potentially useful for differentiating pituitary-dependent hyperadrenocorticism (PDH) from adrenal tumor–associated hyperadrenocorticism (ATH) (Mueller *et al*., 2006).

The sensitivity of the low-dose dexamethasone suppression test (LDDST) across different studies ranges from 85% to 97% (Feldman, 1983; Reusch; Feldman, 1991; Mueller *et al*., 2006; Bennaim *et al*., 2018; Zeugswetter *et al*., 2021; Lim *et al*., 2023).

The currently accepted cutoff for diagnosing hypercortisolism—based on serum cortisol concentration eight hours after LDDST (>39 nmol/L)—was established over 30 years ago using the mean ±3 standard deviations from a cohort of 22 healthy dogs in a study employing radioimmunoassay, a methodology no longer widely available (Feldman, 1983). Most commercial laboratories currently use a competitive chemiluminescent immunoassay (Immulite 2000®, Siemens Healthcare Ltd, Los Angeles, CA), which has not been fully validated for LDDST in dogs. Due to this methodological shift, Behrend *et al*. (2013) recommend reestablishing new eight-hour cutoff values for assays performed by chemiluminescence. In a 2023 prospective study evaluating LDDST in 30 healthy control dogs and 27 dogs diagnosed with hypercortisolism—confirmed by treatment response—serum cortisol concentrations

measured using a chemiluminescent assay yielded diagnostic cutoffs comparable to those originally reported using radioimmunoassay (Lim *et al*., 2023).

According to diagnostic guidelines for dogs with HAC (Behrend *et al*., 2013), in animals presenting ''partial suppression,'' ''escape from suppression,'' or ''inverse patterns'' in the LDDST, but exhibiting clinical signs consistent with HAC, the LDDST may be repeated or an ACTH stimulation test may be performed, as it has higher specificity. This test involves collecting samples before and one to two hours after administration of natural or synthetic ACTH. A positive result for HAC is indicated by cortisol levels above 24 µg/dL, reflecting an exaggerated adrenal response to stimulation (Ettinger; Feldman, 2004). This screening test can also identify iatrogenic HAC, which cannot be distinguished by other methods, as cortisol concentrations are typically lower than or equal to physiological levels (5–17 µg/dL). However, values between normal and positive (18–24 µg/dL) fall within a gray zone, where it is uncertain whether HAC, chronic stress, or concurrent disease is present (Bugbee *et al*., 2023).

Abdominal ultrasonography is a widely used imaging modality for evaluating adrenal glands in Veterinary Medicine and can assist in differentiating types of hypercortisolism. Typically, the size of the caudal pole of the adrenal gland is used to compare healthy and affected patients (Table 1), although any morphological alteration should be considered (Melián *et al*., 2021). This imaging approach can identify adrenal tumors, invasion of the caudal vena cava, compression of adjacent organs, and associated hepatic metastases. Furthermore, symmetry in gland size may indicate the underlying cause of the syndrome: unilateral enlargement with contralateral reduction suggests ADH, whereas bilateral enlargement is indicative of PDH, due to the influence of ACTH on both glands. However, diagnosis based solely on imaging findings is not recommended, as other differential diagnoses must be considered, including cysts, myelolipoma, hemorrhage, nonfunctional primary tumors, pheochromocytoma, metastatic tumors, or granulomas (Ettinger; Feldman, 2004).

Table 1 – Caudal pole thickness of the adrenal gland in 86 healthy patients and 91 patients with HAC

Variable (mm)		>2,5 – 5 Kg	>5 – 10 Kg	>10 – 20 Kg	>20 – 40 Kg
Healthy patients	**Left caudal pole thickness**	4,1 (3,7 – 4,4)	4,3 (3,8 – 4,6)	5,0 (4,5 – 5,5)	5,7 (5,3 -6,3)
	Right caudal pole thickness	3,9 (3,2 – 4,4)	4,2 (3,9 – 5,0)	4,7 (4,2 -5,7)	6,3 (5,9 – 6,9)
Patients with HAC	**Left caudal pole thickness**	7,2 (6,0 – 8,0)	7,5 (6,2 – 8,7)	7,3 (6,3 – 9,8)	6,9 (4,2 – 7,8)
	Right caudal pole thickness	6,1 (5,5 – 8,7)	7,3 (6,2 – 9,3)	7,0 (6,9 – 8,5)	8,3 (5,6 – 12,5)

Source: Melián *et al*. (2021).

In hematological evaluation, red blood cell counts are typically within normal limits; however, glucocorticoids may stimulate the production of myeloid precursors in the bone marrow, leading to moderate polycythemia—particularly in females—and thrombocytosis. The leukogram is characterized by a stress response, presenting leukocytosis with neutrophilia and

monocytosis due to the anti-inflammatory effects of glucocorticoids, which inhibit neutrophil diapedesis and prevent normal cellular migration out of circulation, resulting in their retention in the bloodstream. Eosinopenia may also occur due to sequestration in the bone marrow, along with lymphopenia, as lymphocytes are redistributed from the bloodstream to secondary lymphoid organs. Additionally, glucocorticoids exert a toxic effect that promotes lympholysis (Ettinger; Feldman, 2004).

In biochemical analysis of patients with HAC, several alterations may be observed. Increased serum glucose concentrations due to hepatic gluconeogenesis, combined with insulin inhibition, may lead to the development of diabetes mellitus and diabetic ketoacidosis (Caragelasco, 2013). Hepatopathy may also be identified through elevated markers of liver injury, such as alanine aminotransferase (ALT) and serum alkaline phosphatase (ALP), resulting from processes including hepatic lysis, hepatitis, altered hepatic blood flow, and glycogen-related vacuolization. However, it is important to note that these biochemical changes are not definitive for distinguishing primary from secondary liver injury associated with HAC. Additionally, elevations in ALP are more common and generally more pronounced than those in ALT. Finally, a rare increase in pancreatic enzymes—amylase and lipase—may occur due to polyphagia, potentially leading to acute pancreatitis (Leal, 2008).

Calcium and phosphorus are absorbed in the gastrointestinal tract under the influence of vitamin D, while parathyroid hormone (PTH) promotes the storage of these cations in bone (Meuten, 2014). Patients with HAC present hypocalcemia, which may be associated with secondary adrenal hyperparathyroidism induced by glucocorticoids—leading to increased PTH levels and alterations in vitamin D biotransformation, resulting in greater urinary calcium excretion and reduced intestinal absorption (Leal, 2008). Due to low serum calcium concentrations, affected animals may exhibit tachycardia, tremors, tetany, muscle fasciculations, and seizures. In addition, dogs with Cushing's syndrome may develop hyperphosphatemia due to increased glomerular filtration rate and reduced phosphate reabsorption by tubular cells. Consequently, bone weakening may occur, characterized by osteoporosis, spontaneous fractures, and soft tissue calcifications, arising from mechanisms not yet fully understood (Meuten, 2014).

Sodium is absorbed in the intestine and potassium throughout the gastrointestinal tract, both being excreted by the kidneys. Aldosterone stimulates sodium reabsorption, preventing excessive water loss, while promoting active potassium excretion. As previously discussed, the similarity between mineralocorticoids and glucocorticoids allows cortisol to exert aldosterone-like effects; thus, patients with HAC excrete more potassium and retain more sodium. However, due to rapid inhibition of antidiuretic hormone (ADH) by glucocorticoids, water reabsorption does not occur proportionally, leading to hypernatremia associated with polyuria. This increase in serum sodium predisposes to hypertension, which is linked to several clinical manifestations previously discussed. Additionally, patients may develop hypokalemia—a common disorder in critically ill animals—which may also be associated with diabetic ketoacidosis and adrenal tumors. In such cases, clinical signs include muscle weakness and skeletal muscle paralysis (notably ventroflexion of the neck), alterations in smooth muscle function, cardiac arrhythmias, and reduced cardiac output (Bohn, 2014).

Patients with Cushing's syndrome may also exhibit increased serum cholesterol and triglyceride concentrations, exceeding 80% of reference values, due to dysregulation of lipid metabolism and induction of lipolysis (Caragelasco, 2013). Although this laboratory alteration is present in approximately 90% of HAC cases (Leal, 2008), it is not considered specific to this condition; therefore, its interpretation should be used as part of the differential diagnostic process (Xella, 2010).

Animals with HAC also show decreased secretion of thyroid-stimulating hormone (TSH), and the condition may alter TSH binding to plasma proteins, impairing the conversion of T4 to T3 and leading to reduced serum T3 levels. This may result in clinical manifestations similar to hypothyroidism (Ettinger; Feldman, 2004).

Chart 1 – Approach to the diagnosis of suspected canine HAC

Stages	Group 1 Classic Signs of HAC	Grupo 2 Clinicopathological Abnormalities Without Clinical Signs	Group 3 Clinical Signs Without Abnormalities	Group 4 Patients That May Have HAC
Clinical Presentation	The clinical presentation and findings will be consistent with HAC.	*Through anamnesis, assess potential clinical signs and determine whether there has been exposure to corticosteroids; * If the identified clinical signs are compatible with HAC, follow Group 1; * If no clinical signs are identified, follow Group 2.	Through anamnesis, determine whether there is potential exposure to	During the clinical examination, assess the presented signs and the underlying cause of the acute disease.
Next Steps	*Perform a low-dose dexamethasone suppression test; *If positive: consider performing additional tests to differentiate PDH from ADH in order to treat the patient accordingly; *If negative: perform an adrenocorticotropic hormone stimulation test; *If both tests are negative, consult a specialist.	*Repeat the tests to confirm clinicopathological abnormalities; *Consider other differential diagnoses if abnormalities are present; *Endocrine testing is not necessary; *Urinary cortisol analysis may be performed to rule out HAC if deemed necessary by the clinician or the owner.	*If there is a strong suspicion of HAC, perform a specific endocrine test. *If there is no strong suspicion of HAC or if the condition is not confirmed, consider other differential diagnoses.	*Wait two to four weeks before performing another endocrine test, while monitoring the resolution of the disease. *If the acute condition appears unlikely to resolve without treating HAC, consider referring the case to a specialist.

Source: Bugbee *et al*. (2023).

Regarding urinalysis, it is important to note that cortisol reduces water reabsorption in the proximal convoluted tubule, resulting in polyuria and hyposthenuria, with urine specific gravity below 1.008. Patients may present glycosuria in cases of diabetes mellitus secondary to HAC (Xella, 2010). This, combined with immunosuppression and muscle deficits, predisposes to urinary tract infections (UTIs). Consequently, dogs may also develop crystalluria more easily, due to increased calcium excretion as well as associated UTIs and immunosuppression. This may manifest as urinary crystals, active sediment (erythrocytes, leukocytes, and bacteria), and inactive sediment (Leal, 2008).

Urinalysis may also reveal pathological proteinuria, which can arise from several mechanisms, including increased glomerular filtration rate leading to enhanced permeability of the glomerular membrane and passage of high-molecular-weight proteins; decreased tubular protein reabsorption; glomerular damage due to hypertension and immunosuppression associated with HAC (Caragelasco, 2013); or, alternatively, urinary tract infections, characterizing post-renal proteinuria (Xella, 2010).

Radiographic examination is typically used only when ultrasonography is unavailable, although it may still assist clinical evaluation. In the abdominal region, increased fat deposition enhances image contrast, often allowing visualization of moderate to severe hepatomegaly and distension of the urinary bladder due to impaired complete urine elimination. In light of this, the adrenal mass constitutes the most significant finding; however, its identification may be less frequent, since not all masses present calcification. In the thoracic region, radiography may help identify pulmonary metastases and signs of infection related to immunosuppression through evaluation of lung parenchyma. Calcification of tracheal rings and osteoporosis are also commonly observed, although these findings are not specific to HAC (Ettinger; Feldman, 2004).

Computed tomography (CT) is an advanced diagnostic imaging modality in which the animal remains anesthetized for approximately 30 minutes to two hours to complete image acquisition, offering greater sensitivity than abdominal radiography (Ettinger; Feldman, 2004). In the abdominal region, CT successfully identifies adrenal enlargement with a normal contralateral gland in ADH, or bilateral enlargement in PDH, as also observed on ultrasonography, in addition to enabling assessment of metastatic lesions (Leitão, 2011). Regarding pituitary evaluation, approximately 50% of tumors are small and confined within the gland, making visualization difficult, whereas around 40% of tumors without central nervous system manifestations may still be detected on CT (Ettinger; Feldman, 2004).

Magnetic resonance imaging (MRI) is an imaging technique focused on soft tissue evaluation, although it is less commonly available in routine veterinary practice (Leitão, 2011). The procedure requires sedation, with additional doses administered every 15 minutes, allowing intubation and reducing respiratory motion, thereby improving image quality. Gadolinium DTPA is a contrast agent that enhances visualization of masses following administration (Ettinger; Feldman, 2004). Pituitary tumors measuring up to 10 mm are easily visualized and typically do not present central nervous system signs, whereas larger tumors that expand dorsally beyond the sella turcica—without causing bone destruction—generally produce neurological signs and are more readily identified due to their size and morphological alterations (Leitão, 2011).

In this context, these complementary examinations contribute to multiple stages of HAC identification and should be indicated according to the diagnostic objective and clinical stage of the disease. The low-dose dexamethasone suppression test (LDDST) is widely used as a screening tool due to its high sensitivity, enabling higher detection rates among affected patients. However, it has lower specificity, as factors such as stress, concurrent diseases, hospitalization, and certain medications may interfere with results. Conversely, the ACTH stimulation test has higher specificity and is used for diagnostic confirmation and identification of the iatrogenic form, as it directly evaluates adrenal gland function and hormonal response.

Furthermore, additional laboratory and imaging tests support both diagnostic and therapeutic approaches, as they help identify secondary systemic alterations and differentiate potential etiologies. Therefore, the definitive diagnosis of HAC is best established through integration of clinical examination

and identification of signs, combined with appropriate screening via hormonal testing, laboratory analyses, and imaging assessments.

Final considerations

In summary, hyperadrenocorticism in dogs has a high prevalence in veterinary clinical practice, making accurate recognition and diagnosis of this endocrine disorder essential. Understanding the normal mechanisms of the hypothalamic–pituitary–adrenal axis and the physiological functions of cortisol is fundamental for interpreting the clinical manifestations of the disease. Additionally, laboratory and imaging examinations play a critical role in achieving a definitive diagnosis. &

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