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Hyperadrenocorticism in Dogs: Impact on Reproduction and Diagnostic Insights from Ultrasonography

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Abstract

Canine Cushing's syndrome, also known as hyperadrenocorticism (HAC), is one of the most prevalent endocrinopathies observed in dogs, characterized by elevated cortisol levels. The majority of cases are associated with pituitary tumors, leading to excessive production of corticotrophin (ACTH), thereby stimulating the adrenal glands to secrete cortisol. Clinical manifestations arise from the rise in cortisol concentration and encompass diabetes mellitus, polyuria, and polydipsia. Additionally, prolonged administration of glucocorticoids (iatrogenic) can also contribute to the development of Cushing's syndrome. The surplus cortisol resulting from this condition not only impacts the affected dog's health but also exerts adverse effects on various endocrine systems, leading to anestrus, infertility, premature labor, and high fetal mortality in canines. Therefore, a comprehensive understanding of these reproductive implications is essential to manage this syndrome effectively. The diagnosis of canine hyperadrenocorticism can be done by patient history, clinical signs, specific endocrine tests, and ultrasonography. Despite its significance, knowledge regarding the reproductive implications associated with Cushing's syndrome remains limited. Hence, this review aims to provide a thorough examination of the changes and challenges related to hyperadrenocorticism in canines, with a particular focus on its impact on the reproductive system. By shedding light on this aspect, the review intends to contribute valuable insights to the existing scientific literature and promote better management of this complex syndrome in dogs.

Keywords: Cushing Syndrome, Dog, Diagnosis, Ultrasound, Infertility.

INTRODUCTION

Canine Cushing's syndrome is a prevalent endocrine disorder characterized by chronic and pathological overproduction of cortisol, affecting approximately 1-2 per 1000 dogs annually (Willeberg *et al*., 1982). This condition predominantly affects middle-aged and older dogs and can arise from either pituitary or adrenal origins (O'Neill *et al*., 2016). Etiological factors include pituitary tumors, adrenal dysfunction, or iatrogenic glucocorticoid administration (Drazner, 1987a; Behrend *et al*., 2010). Clinical signs associated with elevated cortisol levels encompass hyperglycemia, polyuria, polydipsia, depression, hypertension, central obesity, hepatomegaly, dyspnea, hyperpigmentation and calcinosis cutis (Behrend *et al*., 2013). These classical combinations of signs are commonly observed in smaller breeds, particularly miniature Poodles, Boxers, and Dachshunds (Dunn, 1997). The high levels of cortisol can suppress pituitary hormones (LH and FSH), leading to disruptions in normal reproductive function (Dubey *et al*., 1985). Consequently, reproductive implications may include infertility, anestrus, and complications during pregnancy. Diagnosis of Canine Cushing's syndrome relies on a comprehensive evaluation, involving patient history, clinical signs, specific endocrine tests, and imaging techniques (Bennaim *et al*., 2019b). Early and accurate diagnosis enables timely initiation of appropriate treatment, which is essential in managing disease progression and preventing further complications. Overall, understanding Canine Cushing's syndrome is crucial for recognizing its clinical manifestations, especially its impact on the reproductive system, and facilitating effective diagnosis and management of affected dogs.

Pathophysiology and Diagnosis

Cushing's disease, also known as hyperadrenocorticism, can arise from two primary sources: pituitary-dependent hyperadrenocorticism, involving an ACTH-producing pituitary tumor, or adrenal-dependent hyperadrenocorticism, caused by an adenoma of the adrenal cortex (Drazner, 1987a). The majority of Cushing's disease cases in dogs are associated with pituitary-dependent hyperadrenocorticism, wherein a pituitary tumor overproduces ACTH. This excessive production of ACTH leads to bilateral adrenocortical hyperplasia, an abnormal increase in the size and activity of the adrenal cortex. Consequently, the adrenal glands become stimulated to hypersecrete cortisol, a vital glucocorticoid hormone (Miyachi, 2000). Cortisol plays crucial roles in various physiological processes, including metabolism, immune response, and stress regulation (Thau *et al*., 2022). However, elevated cortisol levels can disrupt normal metabolic functions and interfere with other endocrine activities (Raff and Carroll, 2015). Alternatively, Cushing's disease can also develop from long-term administration of synthetic glucocorticoids, which can disrupt the balance of the hypothalamic-pituitary-adrenal (HPA) axis, leading to the suppression of both hypothalamic corticotropin-releasing hormone (CRH) and pituitary ACTH secretion (Galac *et al*., 2010a). The pathophysiological effects of Cushing's disease include various clinical signs and potential complications, such as hyperglycemia, polyuria, polydipsia, lethargy, skin hyperpigmentation, and increased susceptibility to infections (Behrend *et al*., 2013).

Reproductive Implications

The exact mechanism underlying the reproductive disorders caused by Hyperadrenocorticism (HAC) in dogs is not fully understood; however, it is often inferred (Nelson, 1989). The condition is characterized by chronically elevated levels of cortisol, which can have significant effects on the reproductive system. One of the primary mechanisms involves the suppression of gonadotropin release through the hypothalamic-pituitary-gonadal axis. Cortisol inhibits the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus (Dubey, 1985; Saketos *et al*., 1993). GnRH is a key hormone responsible for stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. These hormones play essential roles in regulating follicular growth and ovulation in female dogs. The suppression of LH and FSH due to elevated cortisol levels can lead to disruptions in normal ovarian function. This may result in prolonged anestrus and infertility (Stephen *et al*., 2000). Excessive cortisol levels during pregnancy can lead to fetal complications, such as premature birth, hypoglycemia, and respiratory distress. However, additional research is required to fully understand and explore this correlation (Caimari *et al*., 2017). In males, excess cortisol can negatively impact the production of testosterone, a critical male sex hormone (Mac Adams *et al*., 1986). Reduced testosterone levels can lead to decreased libido, impaired sperm production, and potential fertility issues (De Palatis *et al*., 1978).

Overall, while the precise mechanisms are not fully known, the elevated cortisol levels in Hyperadrenocorticism are believed to disrupt the hypothalamic-pituitary-gonadal axis, leading to disturbances in reproductive hormones and functions. These disruptions can result in reproductive disorders, such as infertility and prolonged anestrus, in both female and male dogs affected by HAC. Further research is necessary to unravel the intricacies of this complex interaction and gain a more comprehensive understanding of the reproductive implications of Hyperadrenocorticism in dogs.

Diagnosis

Diagnosing Cushing's syndrome involves a comprehensive approach, employing various diagnostic tools and tests (Behrend *et al*., 2013; Bennaim *et al*., 2019b). The process begins with a thorough clinical evaluation, including history-taking and examination, to identify common signs associated with the condition, such as hyperglycemia, polyuria, polydipsia, lethargy, and skin hyperpigmentation. Blood tests, including Complete Blood Count (CBC) and serum biochemistry panel, are then conducted to assess the overall health status and detect any abnormalities indicative of Cushing's syndrome. Characteristic changes observed in CBC may include neutrophilic leukocytosis, while increased serum alkaline phosphatase, triglyceride concentration, and hyperglycemia (>250 mg/dl) can provide further clues (Feldman and Nelson, 2004). Measurement of cortisol levels in the blood is essential to confirm the presence of Cushing's syndrome, with elevated cortisol concentrations (usually 20-25 µg/dl) serving as a hallmark of the disorder. Additional evidence is obtained through the Urine Cortisol: Creatinine Ratio (UCCR), which assesses the level of cortisol excretion in the urine, but is not specific diagnostic test (Rijnberk *et al*., 1988). To evaluate the cortisol response, the Low-Dose Dexamethasone Suppression Test (LDDST) is performed. In Cushing's syndrome, cortisol levels fail to suppress as they typically would in healthy dogs (Frank *et al*., 2001). The Corticotropin Stimulation Test is also conducted to assess the adrenal glands' response to synthetic ACTH administration, revealing excessive cortisol production in dogs with Cushing's syndrome (Chapman *et al*., 2003).

Imaging techniques, such as ultrasonography, provide valuable insights, distinguishing between pituitary-dependent and adrenal-dependent hyperadrenocorticism. Ultrasonography allows for a non-invasive and real-time assessment of organs affected

due to high cortisol concentration, providing valuable information about their size, shape, and internal structure structure (Bueno *et al.*, 2022; Martins *et al*., 2019). In dogs with Cushing's disease, the liver may appear enlarged and display irregular echotexture due to hepatomegaly (Fig. 1). The gallbladder can exhibit the presence of sludge or a mucocele, indicating potential biliary abnormalities (Fig. 2). Spleenomegaly may be evident with changes in echotexture (Fig. 3). Kidneys might show altered echogenicity or changes in size (Fig. 4). The urinary bladder may demonstrate thickening of its wall. Moreover, ultrasonography aids in visualizing the adrenal glands, which are central to the diagnosis of Cushing's disease. Adrenal-dependent hyperadrenocorticism can be identified by observing unilateral or bilateral adrenal gland enlargement, which may manifest as irregular shape and altered echogenicity (Fig. 5) (Bueno *et al*., 2022; Martins *et al*., 2019). For a more detailed assessment of the pituitary and adrenal glands, along with the detection of vascular invasion and metastases, CT or MRI scans are preferred (Galac *et al*., 2010a; Kooistra and Galac, 2012; Behrend *et al*., 2013).

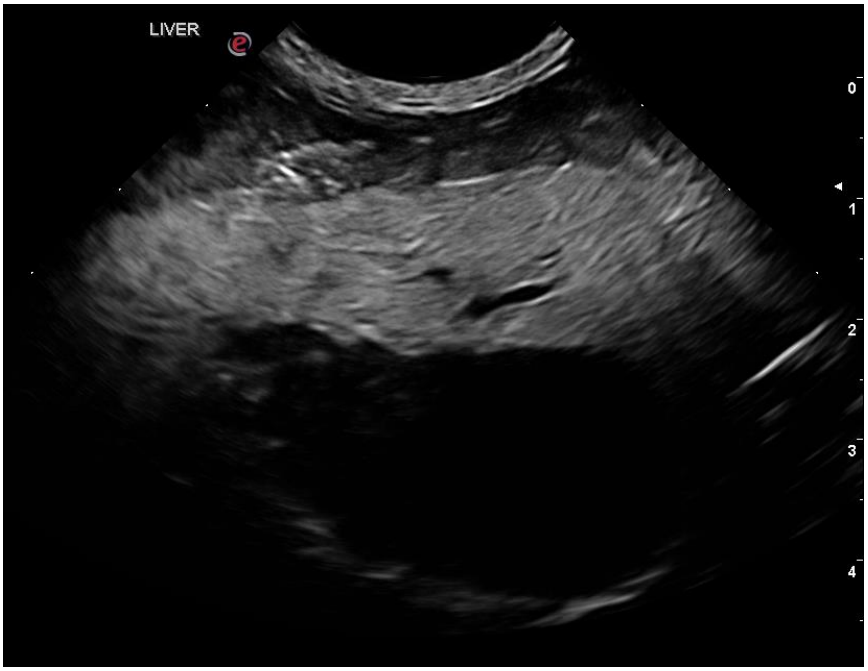

Figure 1: Enlarged liver with heterogeneous/coarse parenchyma, increased echogenicity and discrete hyperechoic focal zones

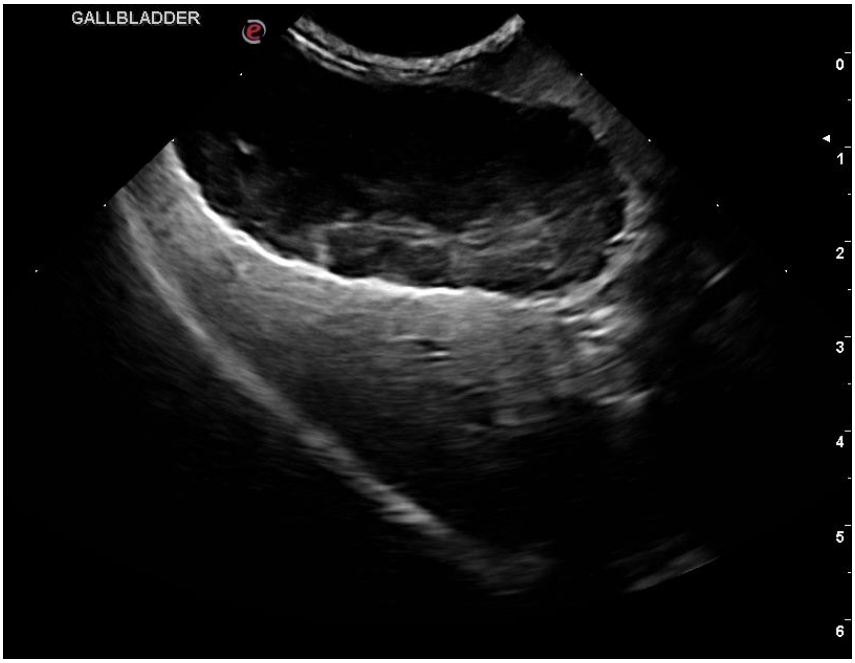

Figure 2: Well distended gall bladder with anechoic contents. The gall bladder has uniform wall and shows presence of multiple hyperechoic density suggestive of sludge in it

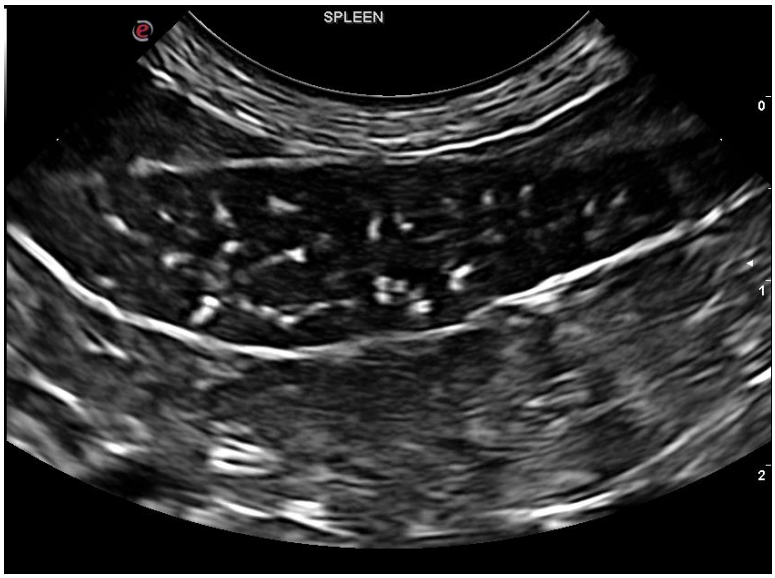

Figure 3: Enlarged spleen with coarse parenchyma. A roughly circular hyperechoic density seen in the body of the spleen

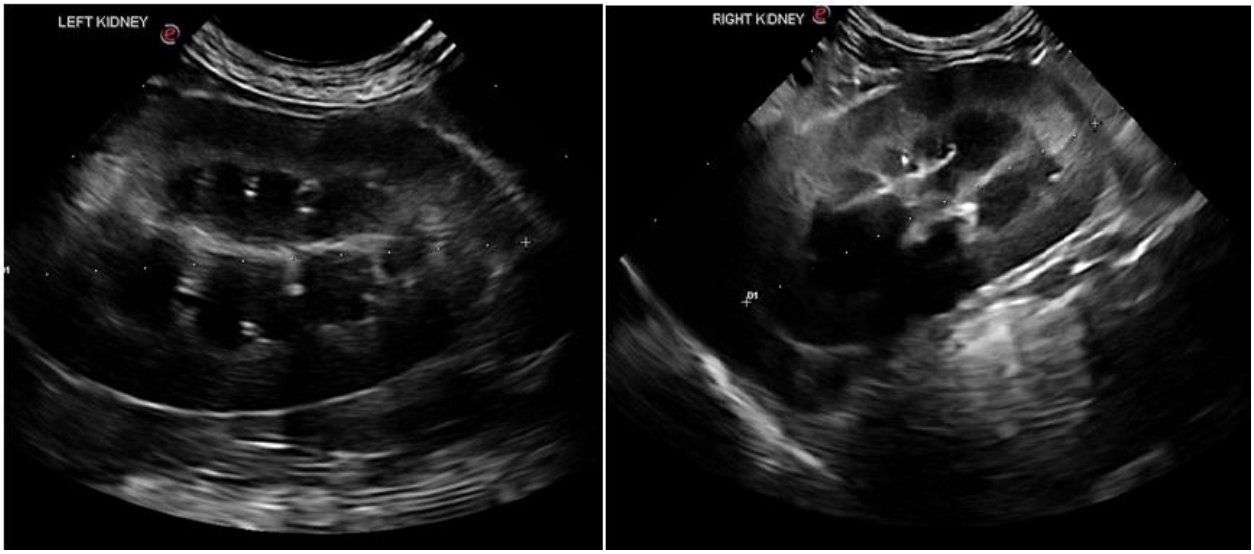

Figure 4: left kidney shows precipitation of hyperechoic density at the cortico-medullary juncyion (CMJ). The right kidney cortex shows thickening and fibrosis, the CMJ shows precipitation of hyperechoic density at the CMJ

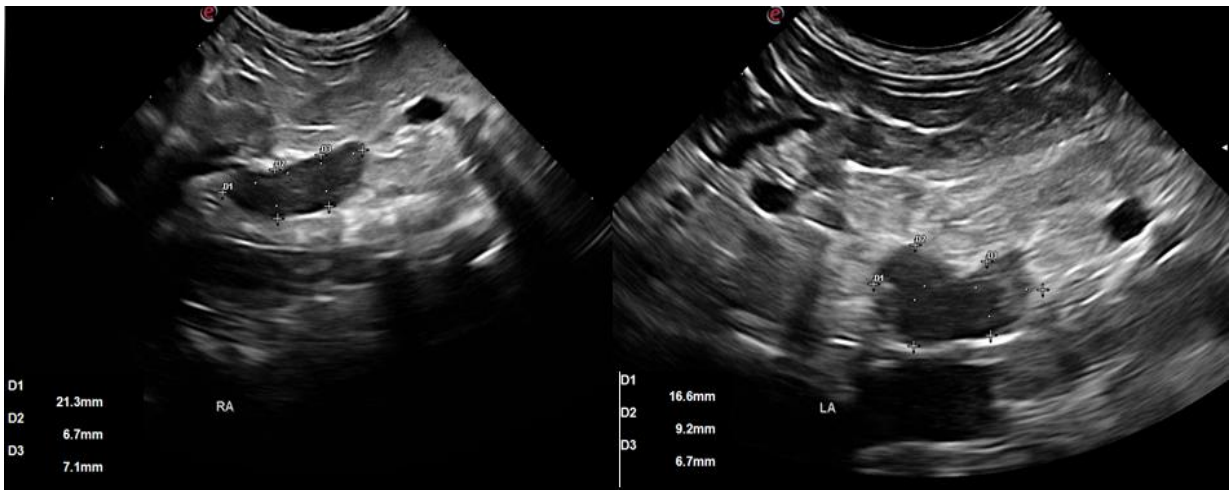

Figure 5: Both the adrenal glands are enlarged (Left-1.6x0.92; Right-2.13x6.7 cm in diameter)

DISCUSSION

Cushing's disease, or hyperadrenocorticism, is a prevalent endocrine disorder in dogs characterized by excessive cortisol production. It results from ACTH-producing pituitary tumors (pituitary-dependent hyperadrenocorticism) or adrenal adenomas (adrenal-dependent hyperadrenocorticism), disrupting hormonal balance and causing clinical signs. While the exact reproductive implications are not fully understood, disruptions in the hypothalamic-pituitary-gonadal axis are believed to play a role. Diagnosis involves clinical evaluation for common signs like polyuria, polydipsia, lethargy, dyspnea, dilated abdomen, and skin hyperpigmentation. Blood tests, including CBC and serum biochemistry, reveal characteristic changes like neutrophilic leukocytosis and elevated alkaline phosphatase. Cortisol level measurements and the Urine Cortisol:Creatinine Ratio confirm Cushing's disease. The Low-Dose Dexamethasone Suppression Test and Corticotropin Stimulation Test aid in differential diagnosis. Ultrasonography plays a crucial role in diagnosis, differentiating between pituitary and adrenal forms. It detects changes in organs like the liver, gallbladder, spleen, kidneys, urinary bladder, and adrenal glands due to excess cortisol. Advanced imaging techniques like CT or MRI are recommended for in-depth assessment of the pituitary gland, improving diagnostic accuracy and treatment planning.

CONCLUSION

Cushing's disease in dogs is a complex endocrine disorder affecting the normal metabolism and other endocrine functions. A comprehensive diagnostic approach involving clinical evaluation, blood tests, hormonal assessments, and imaging techniques is essential for accurate diagnosis and effective management of affected dogs. Further research in this area will contribute to a deeper understanding of the reproductive implications of Cushing's disease and facilitate improved treatment strategies for affected canines**.**

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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