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COMPARATIVE OXIDATIVE STRESS IN DIVERSE ENDOCRINE DISORDERS TO PETS

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Abstract
Oxidative stress plays a central and increasingly recognized role in the pathophysiology of endocrine disorders in companion animals. This systematic review comparatively evaluated redox imbalance across major endocrine diseases, including diabetes mellitus, hyperadrenocorticism, and thyroid dysfunctions in dogs and cats. The analysis revealed a consistent pattern of increased reactive oxygen species and reduced antioxidant defenses, with the most pronounced alterations observed in chronic and poorly controlled conditions. Significant variability emerged in biomarker profiles among disorders, suggesting disease-specific oxidative pathways but a shared tendency toward cumulative cellular damage. Evidence also indicates that oxidative stress contributes to clinical progression and may influence therapeutic response. These findings support the integration of oxidative status assessment into diagnostic and monitoring protocols and highlight the potential value of targeted antioxidant interventions. Further standardized research is needed to refine biomarkers and optimize management strategies tailored to each endocrine pathology.
Key words: oxidative stress; endocrine disorders; companion animals; antioxidants; redox imbalance.

Oxidative stress (OS) represents a biochemical imbalance between the excessive production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant systems—such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and non-enzymatic antioxidants—to neutralize them. When ROS generation surpasses antioxidant buffering, oxidative damage accumulates in lipids, proteins, and nucleic acids, ultimately contributing to cellular dysfunction, inflammation, and apoptosis [Comazzi, 2011; Maiese, 2015; Asmat, Abad & Ismail, 2016; Ighodaro, 2018]. In recent decades, OS has gained recognition as a central pathophysiological mechanism in numerous metabolic and endocrine disorders, both in human medicine and in companion animal populations.

In veterinary endocrinology, oxidative stress plays an especially prominent role given the metabolic instability and chronicity of conditions such as diabetes mellitus (DM), diabetes insipidus (DI), hyperthyroidism, hypothyroidism, Cushing's syndrome (hyperadrenocorticism), and endocrine-related obesity. These disorders not only alter hormone production and tissue responsiveness but also induce significant changes in intracellular redox pathways, mitochondrial function, and systemic inflammatory signaling [Hrițcu, Pavel et al., 2024; Webb & Falkowski, 2009; Rosca, Hrițcu et al., 2014].

In diabetes mellitus, hyperglycemia promotes ROS overproduction via glucose auto-oxidation, advanced glycation end-products (AGEs), and activation of polyol and hexosamine pathways, ultimately impairing pancreatic β-cell integrity and exacerbating insulin resistance [Maiese, 2015; Asmat, Abad & Ismail, 2016; Cojocariu, Balmuș et al., 2020]. Clinical and experimental studies in pets show that oxidative imbalance in diabetic animals contributes to lipid peroxidation, endothelial dysfunction, renal microvascular injury, and systemic inflammation, worsening the progression of nephropathy, neuropathy, and retinopathy [Spătaru, Spătaru et al., 2019; Webb & Falkowski, 2009]. Moreover, studies on diabetic animal models have demonstrated that antioxidant therapies may mitigate oxidative damage and improve metabolic stability [Padurariu, Ciobica et al., 2010].

In contrast, diabetes insipidus (DI)—both central and nephrogenic—has been less extensively studied in relation to oxidative stress. However, emerging research suggests that hyperosmolar stress and impaired vasopressin signaling induce redox disturbances. In central DI, endoplasmic reticulum stress and ROS generation contribute to apoptosis of arginine-vasopressin neurons via PI3K/Akt pathway dysregulation [Zhou, Feng et al., 2019]. In nephrogenic DI, lithium exposure leads to mitochondrial dysfunction, ROS overproduction, aquaporin-2 downregulation, and structural renal damage, which can be attenuated through antioxidant or metabolic modulators such as metformin,

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silymarin, or embelin [Tas & Sancak, 2021; Yakut, Tarakçı Gençer et al., 2025; Sahu et al., 2012].

Hyperthyroidism, a condition associated with excessive metabolic acceleration, is strongly linked to elevated ROS production due to increased mitochondrial respiration and heightened oxygen demand in peripheral tissues. These mechanisms contribute to oxidative injury, endothelial dysfunction, and hypercontractility of cardiac tissue, predisposing animals to cardiomyopathy [Aslan et al., 2011; Venditti, Napolitano & Di Meo, 2015; Bao et al., 2022]. Meanwhile, studies in feline hyperthyroidism emphasize the necessity of controlling OS through nutritional and pharmacological interventions, paralleling findings from human medicine [Candellone et al., 2021].

Conversely, hypothyroidism is characterized by reduced metabolic rate, yet paradoxically, OS biomarkers may increase due to lipid metabolism abnormalities, systemic inflammation, and impaired antioxidant enzyme activity. Research in dogs has shown associations between hypothyroidism, dyslipidemia, elevated malondialdehyde (MDA), neutrophil-to-lymphocyte ratio (NLR), and decreased antioxidant capacity [Elgalfy, Elkhaiat & Ghanem, 2025; Afifi et al., 2025]. These findings align with human data illustrating oxidative disturbances in overt and subclinical hypothyroidism [Santi et al., 2010].

Cushing's syndrome (hyperadrenocorticism) induces oxidative stress primarily through chronic glucocorticoid excess, which dysregulates mitochondrial function, enhances protein catabolism, and destabilizes vascular homeostasis. Increased ROS levels have been identified in humans with Cushing's syndrome, corresponding to platelet activation, vascular injury, and endothelial impairment [Karamouzis, Berardelli et al., 2015; Prázný et al., 2008]. Veterinary research supports these findings: canine Cushing's syndrome significantly elevates systemic oxidative markers, while trilostane therapy partially restores redox balance [Chen, Liu et al., 2025; Boghian et al., 2008].

Finally, obesity and metabolic syndrome in companion animals represent increasingly recognized endocrine-associated conditions that promote OS through adipose tissue inflammation, dyslipidemia, and cytokine activation. Studies in obese cats and dogs show marked increases in lipid peroxidation and reductions in antioxidant enzymes, comparable to metabolic syndrome in humans [Tanner, Martin & Saker, 2007; Pereira et al., 2025; Vona et al., 2019]. These alterations exacerbate cardiovascular, renal, and hepatic comorbidities in endocrine-diseased animals.

Collectively, the veterinary and biomedical literature reveal that oxidative stress constitutes a unifying pathological feature across multiple endocrine disorders in pets. Its involvement extends from cellular signaling and mitochondrial energetics to systemic metabolic dysfunction, making it a vital therapeutic target. Understanding the comparative oxidative profiles among endocrine diseases provides valuable insight into shared and disease-specific mechanisms, paving the way for improved diagnostic, therapeutic, and preventive strategies [Chainy & Sahoo, 2020; Dhama et al., 2019; Hrițcu et al., 2024].

MATERIAL AND METHOD

This systematic review followed PRISMA guidelines.Literature from 2000–2025 was systematically searched in PubMed, Scopus, Web of Science,and Google Scholar using keywords: "oxidative stress,""reactive oxygen species,""endocrine disorders,""diabetes mellitus," "diabetes insipidus,""Cushing," "hyperthyroidism,""hypothyroidism,"and "companion animals."

Inclusion criteria: peer-reviewed clinical and experimental studies in dogs and cats reporting oxidative stress markers (MDA, SOD, GPx, TAC) and interventions. Exclusion criteria: reviews without original data, non-English articles, or studies without ROS quantification.

Data extraction included: species, pathology, markers measured, antioxidant enzyme activity, and therapeutic interventions. Studies were categorized by pathology to allow direct comparison of oxidative profiles.

RESULTS AND DISCUSSIONS

DIABETES MELLITUS

Diabetes mellitus (DM) in companion animals is one of the endocrine diseases most strongly associated with oxidative stress (OS), a pathological state resulting from excessive reactive oxygen species (ROS) production and insufficient antioxidant defenses. In both dogs and cats, chronic hyperglycemia promotes ROS formation through several converging biochemical mechanisms, including glucose autoxidation, polyol pathway activation, mitochondrial respiratory chain overload, advanced glycation end-product (AGE) accumulation, and systemic pro-inflammatory signaling. These processes collectively lead to extensive lipid, protein, and DNA oxidation, compromising cellular integrity and amplifying metabolic dysfunction [Comazzi, 2011; Maiese, 2015].

Quantitative studies consistently show that diabetic dogs and cats present significant

deviations in oxidative biomarkers. Malondialdehyde (MDA), a key indicator of lipid peroxidation, is markedly elevated, commonly reaching values 30–70% higher than in healthy controls. Normal MDA concentrations in dogs range from 1.5–2.0 nmol/mL, whereas diabetic animals frequently show levels of 2.8–3.5 nmol/mL, demonstrating profound oxidative lipid injury. In parallel, antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) are substantially depleted. Healthy SOD levels (1500–1800 U/g Hb) often decline to 900–1200 U/g Hb in diabetic subjects, and GPx activity decreases from 25–35 U/g Hb to 15–20 U/g Hb, indicating reduced capacity to neutralize superoxide radicals and hydrogen peroxide. Total antioxidant capacity (TAC) is similarly compromised, particularly in diabetic cats, whose values fall from approximately 1.1–1.4 mmol Trolox eq/L to 0.7–0.9 mmol/L [Hrițcu, Pavel et al., 2025]. These biochemical abnormalities correlate strongly with the clinical severity of diabetes and its complications—including nephropathy, neuropathy, periodontal disease, endothelial dysfunction, and delayed wound healing—highlighting the central pathogenic role of oxidative stress in disease progression [Cojocariu, Balmuș et al., 2020].

Biomarker	Healthy reference range	Typical values in diabetic animals	Change (%)
MDA (nmol/mL)	1.–2.	3–4	↑ 40–70%
SOD (U/g Hb)	1500–1800	900–1200	↓ 20–35%
GPx (U/g Hb)	25–35	15–20	↓ 25–45%
TAC (mmol Trolox eq/L)	1–2	0.7–0.9	↓ 15–30%

Table1. Representative oxidative stress biomarkers in diabetic dogs and cats[Cojocariu, Balmuș et al., 2020; Hrițcu, Pavel et al., 2025; Comazzi, 2011; Maiese, 2015].

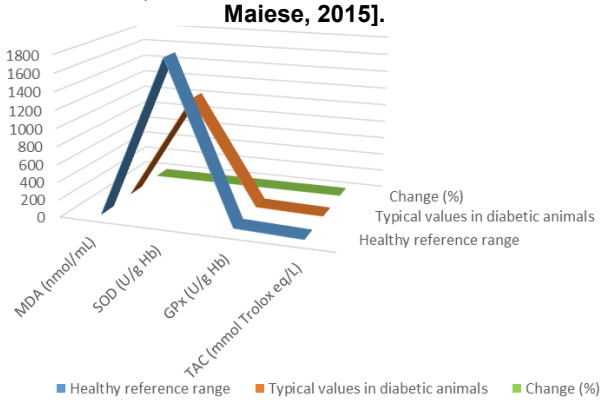

Fig.1.Representative oxidative stress biomarkers in diabetic dogs and cats.

The magnitude of oxidative stress in diabetic animals is heavily influenced by several risk factors. Obesity, for example, significantly amplifies ROS production through enhanced adipokine release, mitochondrial overload, and chronic low-grade inflammation. In obese diabetic animals, MDA levels may be an additional **20% higher** than in lean diabetic individuals, underlining the synergistic relationship between adiposity and oxidative injury [Hrițcu, Cucoș et al., 2024]. Chronic glucocorticoid administration represents another relevant contributor. Long-term steroid therapy increases hepatic gluconeogenesis and disrupts mitochondrial redox balance, which leads to further ROS release; affected dogs typically show an extra 10–15% reduction in SOD activity beyond the deficits observed in spontaneous DM [Rosca, Hrițcu L.D. et al., 2014]. Genetic susceptibility also modulates the oxidative burden. Certain breeds—including Miniature Schnauzers, Poodles, and Burmese cats—display inherent vulnerabilities to both β-cell dysfunction and oxidative imbalance, often presenting with biomarker values at the upper end of diabetic ranges [Hrițcu, Cucoș et al., 2024].

Therapeutic management has a measurable impact on oxidative status, making OS markers valuable indicators of treatment response. Insulin therapy, the cornerstone of DM management, reduces glucose toxicity and directly lowers ROS formation. In dogs achieving stable glycemic control, MDA values typically decrease by 20–30%, and antioxidant enzymes such as SOD and GPx show corresponding improvements of 10–20% within 4–8 weeks of treatment [Webb & Falkowski, 2009]. Metformin, although used primarily in feline diabetic management, provides additional antioxidant effects through AMPK activation and inhibition of mitochondrial ROS leakage. Chronic treatment is associated with MDA reductions of 15–25% and TAC increases of up to 30% [Cojocariu, Balmuș et al., 2020]. Nutritional antioxidants also play a clinically meaningful role. **Camelina sativa oil**, rich in α-linolenic acid and tocopherols, has shown significant efficacy in reducing oxidative imbalance; animals receiving this supplement show decreases of 25–35% in MDA and increases of approximately 20% in SOD and 15–18% in GPx, accompanied by better metabolic stability and improved clinical signs [Spătaru, Spătaru et al., 2019].

Altogether, these findings clearly demonstrate that diabetes mellitus in companion animals is intimately linked with oxidative stress, which not only contributes to the pathogenesis of the disease but also influences its progression and complications. The consistent alterations observed across oxidative biomarkers—elevated MDA, reduced SOD, impaired GPx, and diminished

TAC—underscore the importance of integrating oxidative stress evaluation into diagnostic and therapeutic strategies. By monitoring these markers, clinicians may better identify high-risk patients, tailor antioxidant-supported therapy, and more effectively mitigate the long-term systemic damage associated with chronic hyperglycemia.

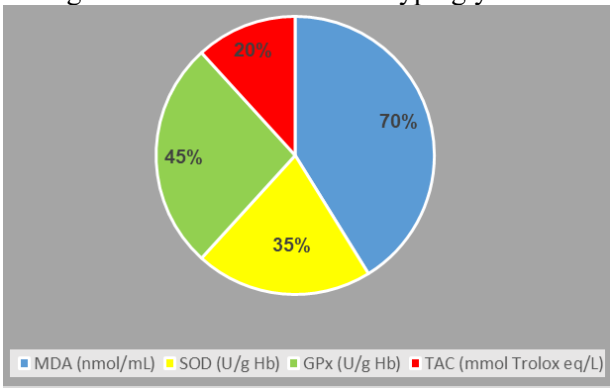

Fig2. Pie Chart of Oxidative Stress Biomarkers in Diabetic Dogs and Cats.

DIABETES INSIPIDUS (CENTRAL AND NEPHROGENIC).

Diabetes insipidus, whether central (CDI) or nephrogenic (NDI), is increasingly recognized as a clinical condition in which alterations in water homeostasis are accompanied by significant oxidative stress. The chronic hyperosmolar state characteristic of both forms promotes excessive renal solute load, increased tubular flow rates, and compensatory metabolic activation within renal epithelial cells. These events contribute to the generation of reactive oxygen species (ROS), which progressively impair cellular antioxidant defenses and exacerbate renal dysfunction.

In central diabetes insipidus, the deficiency of arginine-vasopressin (AVP) triggers more than impaired renal concentration ability; it also influences neuronal survival within the hypothalamus. Experimental evidence indicates that CDI is associated with apoptosis of AVP-producing neurons mediated through dysregulation of the PI3K/Akt signaling pathway, a critical regulatory axis for neuronal viability and oxidative stress resistance [Zhou, Feng et al., 2019]. Disruption of Akt phosphorylation lowers the threshold for oxidative injury, allowing ROS accumulation to drive mitochondrial dysfunction and cell death. Thus, oxidative stress is both a consequence of AVP deficiency and a pathophysiological amplifier of hypothalamic neuronal loss.

Nephrogenic diabetes insipidus, by contrast, arises from renal insensitivity to AVP, most commonly related to chronic lithium exposure. Lithium interferes with aquaporin-2 expression and disrupts intracellular redox balance within collecting duct cells. Histopathological studies have demonstrated lipid peroxidation, mitochondrial swelling, and tubular epithelial degeneration, all consistent with sustained oxidative damage [Tas & Sancak, 2021]. The renal oxidant burden appears to enhance inflammatory cascades and accelerate structural remodeling of the collecting ducts, further decreasing the capacity for water reabsorption.

A growing body of interventional research suggests that pharmacologic and nutraceutical agents targeting oxidative pathways may mitigate the renal consequences of both CDI and NDI. Compounds such as metformin, silymarin, and vitamin C have demonstrated the ability to reduce malondialdehyde (MDA) concentrations, restore total antioxidant capacity (TAC), and attenuate histological signs of renal injury [Yakut, Tarakçı Gençer et al., 2025; Sahu, Gautam et al., 2012; Jing, Wang & Gao, 2022]. These agents appear to act through multiple mechanisms, including enhancement of endogenous antioxidant enzymes, stabilization of mitochondrial membranes, and suppression of oxidative-inflammatory signaling networks such as NF-κB. Their protective effects suggest that oxidative stress is not merely an epiphenomenon but a modifiable component of diabetes-insipidus–associated renal pathology.

Collectively, current evidence underscores that both central and nephrogenic forms of diabetes insipidus share a common oxidative stress-driven pathogenic substrate. Understanding these redox alterations provides a mechanistic framework for therapeutic strategies aimed at preserving renal function and limiting long-term tissue damage in affected patients.

HYPERTHIROIDISM

Hyperthyroidism is one of the endocrine disorders most strongly associated with systemic oxidative stress due to its profound acceleration of metabolic rate and mitochondrial activity. Thyroid hormones primarily T_3 stimulate oxygen consumption, thermogenesis, and mitochondrial electron transport, resulting in increased electron leakage and elevated production of superoxide and downstream reactive oxygen species (ROS). This metabolic upregulation causes measurable biochemical changes, including elevated malondialdehyde (MDA) levels, reduced total antioxidant capacity (TAC), and impaired enzymatic defense (SOD, GPx) [Venditti, Napolitano & Di Meo, 2015; Aslan, Cosar et al., 2011; Bao, Hua et al., 2022].

In companion animals, hyperthyroidism is most commonly documented in geriatric cats,

where chronic thyrotoxicosis induces a pro-oxidant state contributing to cardiovascular, hepatic, and renal injury [Candellone, Saettone et al., 2021]. The pathophysiology is multifactorial: increased mitochondrial β-oxidation produces ROS, while hypermetabolism elevates lipid peroxidation and disrupts cellular membranes, similar to oxidative processes observed in diabetes mellitus and other endocrine disorders [Comazzi, 2011; Maiese, 2015; Asmat, Abad & Ismail, 2016; Ighodaro, 2018]. Comparative pathology indicates that endocrine diseases share overlapping oxidative profiles; for example, cortisol excess in hyperadrenocorticism induces oxidative imbalance, endothelial dysfunction, and inflammatory activation [Karamouzis et al., 2015; Prázný et al., 2008; Chen et al., 2025], supporting the concept that hormonal dysregulation amplifies oxidative pathways across multiple systems [Chainy & Sahoo, 2020; Dhama et al., 2019].

Hyperthyroidism in cats and experimental models leads to significant cardiovascular compromise. Excessive ROS impairs calcium handling in cardiomyocytes and activates the ROS/Ca^{2+} axis, contributing to thyrotoxic cardiomyopathy—a mechanism attenuated by N-acetylcysteine (NAC) supplementation in rodent studies [Bao, Hua et al., 2022]. Similar oxidative cardiomyopathies secondary to endocrine disorders have been described in both human and veterinary medicine, with metabolic reprogramming and redox imbalance representing core mechanistic links [Fuentes-Mendoza et al., 2025; Brack et al., 2013].

The hepatic consequences of hyperthyroidism also appear to be mediated by oxidative damage. Increased lipid turnover and accelerated mitochondrial respiration elevate hepatic MDA, disrupt redox buffering systems, and impair normal hepatocellular metabolism [Santi et al., 2010; Brack et al., 2013]. Evidence from both veterinary and comparative physiology supports that systemic oxidative stress, if uncontrolled, contributes to multi-organ injury in hyperthyroid patients.

Importantly, interactions between thyroid dysfunction and other endocrine diseases amplify oxidative stress. Hyperthyroidism can exacerbate or coexist with diabetes mellitus in companion animals, a pathology already characterized by excessive lipid peroxidation, impaired antioxidant enzymes, and chronic ROS overproduction [Hrițcu, Pavel et al., 2025; Hrițcu, Cucoș et al., 2024; Martín-Gallán et al., 2003; Bigagli & Lodovici, 2019; Vona et al., 2019]. Thyroid disorders can also influence adiposity and obesity-related oxidative stress, paralleling findings from feline obesity studies [Tanner, Martin & Saker, 2007] and hypertriglyceridemia-driven oxidative stress in obese dogs [Pereira et al., 2025].

Endocrine disruptors further contribute to thyroid-related oxidative imbalance. Xenobiotic exposures, particularly organohalogen contaminants, alter thyroid hormone metabolism and promote oxidative damage in pet cats [Nomiyama et al., 2022], while environmental endocrine disruptors interact directly with thyroid receptors and mitochondrial ROS generation [Schmutzler et al., 2007].

Therapeutically, restoring oxidative balance is increasingly recognized as essential. Traditional antithyroid medications (e.g., methimazole) reduce hormone synthesis but do not fully counteract oxidative pathways; therefore, antioxidant co-supplementation has gained interest [Candellone et al., 2021]. Veterinary studies demonstrate that combined management—antithyroid therapy plus targeted antioxidants—reduces MDA, normalizes TAC, and may limit cardiac and hepatic injury [Candellone et al., 2021]. Experimental and nutritional antioxidants, including vitamin C, vitamin E, NAC, and plant-derived polyphenols, modulate inflammatory and oxidative pathways, with cross-benefits documented in related endocrine and gastrointestinal disorders [Bălmus et al., 2016; Sahoo et al., 2023; Cojocariu et al., 2020; Spătaru et al., 2019].

Finally, evaluation of oxidative stress in thyroid disease is expanding beyond plasma assays. Salivary biomarkers—already validated in metabolic and endocrine disorders—may offer a minimally invasive tool for monitoring redox alterations in hyperthyroid animals [Tvarijonaviciute et al., 2020]. This is particularly relevant for geriatric feline patients, in whom repeated blood sampling is challenging.

Overall, hyperthyroidism in companion animals constitutes a systemic oxidative disorder in which excessive thyroid hormone action drives ROS production, alters antioxidant defenses, and contributes to multi-organ pathology. Integration of antithyroid therapy with antioxidant strategies represents a promising approach to limiting oxidative damage, improving clinical outcomes, and reducing cardiovascular and hepatic complications in affected animals.

Parameter	Observed change
Malondialdehyde (MDA) plasma/hepatic	Increased
Total antioxidant capacity (TAC)	Decreased
Superoxide dismutase (SOD)	Decreased / impaired
Glutathione peroxidase (GPx)	Decreased / impaired
ROS-dependent cardiomyopathy	Activated
Cardiomyocyte ROS/Ca^{2+} axis	Activated

Lipid peroxidation	Increased
Inflammation & endothelial dysfunction	Present
Salivary biomarkers	Useful for monitoring

Table2. Oxidative parameters associated with hyperthyroidism in companion animals and experimental models[Venditti, Napolitano & Di Meo, 2015; Aslan, Cosar et al., 2011; Bao, Hua et al., 2022; Candellone, Saettone et al., 2021; Santi et al., 2010; Brack et al., 2013.]

HYPOTHIROIDISM

Hypothyroidism in companion animals is associated with a moderate but clinically relevant state of oxidative stress, which manifests as impaired antioxidant defenses, endothelial dysfunction, and disturbances in lipid metabolism [Elgalfy, Elkhaiat & Ghanem, 2025; Afifi, Saleh et al., 2025]. Specifically, hypothyroid animals demonstrate decreased activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD), key enzymatic components responsible for neutralizing reactive oxygen species (ROS), thereby predisposing cells and tissues to oxidative injury [Elgalfy, Elkhaiat & Ghanem, 2025].

The oxidative imbalance observed in hypothyroidism appears to be multifactorial. Thyroid hormone deficiency reduces basal metabolic rate and mitochondrial respiration, which paradoxically may limit ROS generation; however, compensatory lipid accumulation and dysregulated lipid metabolism enhance lipid peroxidation, leading to increased formation of malondialdehyde (MDA) and other oxidative intermediates [Afifi, Saleh et al., 2025; Santi, Duarte et al., 2010]. Moreover, endothelial function is impaired, reflected by decreased nitric oxide bioavailability and reduced vascular reactivity, suggesting that hypothyroidism exerts systemic effects beyond classical metabolic pathways, in line with observations in other endocrine disorders characterized by oxidative stress, such as diabetes mellitus and hypercortisolism [Hrițcu, Cucoș et al., 2024; Hrițcu, Pavel et al., 2025; Prázný et al., 2008; Karamouzis et al., 2015; Chen et al., 2025].

Therapeutic management of hypothyroidism with hormone replacement, typically levothyroxine, has been shown to partially restore redox homeostasis [Santi, Duarte et al., 2010; Tvarijonaviciute, Lucena et al., 2020]. When combined with antioxidant supplementation, including compounds such as vitamin C, vitamin E, and plant-derived polyphenols, there is evidence of synergistic effects in normalizing oxidative biomarkers, improving enzymatic antioxidant activity, and mitigating endothelial dysfunction [Bălmus et al., 2016; Cojocariu et al., 2020; Spătaru et al., 2019]. This dual approach aligns with findings from related endocrine pathologies, highlighting that oxidative stress is both a consequence and a modulator of hormonal imbalance [Chainy & Sahoo, 2020; Dhama et al., 2019].

Recent studies also emphasize the role of minimally invasive biomarkers in monitoring oxidative status in hypothyroid animals. Salivary assays for oxidative markers have demonstrated utility in assessing systemic redox alterations without the stress associated with repeated blood collection, which is particularly relevant in geriatric or fragile patients [Tvarijonaviciute, Lucena et al., 2020]. These findings complement previous observations in hyperthyroid and diabetic models, suggesting that salivary oxidative biomarkers may serve as reliable tools for longitudinal monitoring and for evaluating therapeutic efficacy.

Furthermore,hypothyroidism-induced oxidative stress may exacerbate comorbid conditions. Dyslipidemia and endothelial dysfunction associated with thyroid hormone deficiency increase cardiovascular risk, while chronic oxidative imbalance may interact with preexisting metabolic disorders such as diabetes mellitus, obesity, or hypertriglyceridemia, amplifying ROS-mediated cellular damage [Tanner, Martin & Saker, 2007; Pereira et al., 2025; Hrițcu, Cucoș et al., 2024; Hrițcu, Pavel et al., 2025]. The cumulative effect underscores the importance of early recognition and integrated management strategies that combine hormone replacement with targeted antioxidant interventions to restore systemic homeostasis.

Taken together, hypothyroidism in companion animals represents a systemic condition associated with moderate oxidative stress, impaired enzymatic antioxidant defenses, endothelial dysfunction, and altered lipid metabolism. Restoration of thyroid hormone levels through appropriate replacement therapy not only normalizes metabolic functions but also contributes to the re-establishment of redox homeostasis [Santi, Duarte et al., 2010; Tvarijonaviciute, Lucena et al., 2020]. The adjunctive use of targeted antioxidants may further enhance these effects, mitigating oxidative damage, improving vascular integrity, and supporting overall organ function. These findings emphasize that integrated therapeutic strategies addressing both hormonal deficiency and oxidative imbalance are essential for optimizing long-term clinical outcomes in hypothyroid companion animals [Elgalfy, Elkhaiat & Ghanem, 2025; Afifi, Saleh et al., 2025].

CUSHING'S SYNDROME

Cushing's syndrome (hyperadrenocorticism) in companion animals represents one of the endocrine disorders most strongly associated with oxidative stress–related pathology. Chronic cortisol excess disrupts redox homeostasis by increasing mitochondrial ROS production, enhancing lipid peroxidation, and impairing endothelial function. These alterations have been consistently documented across both human and veterinary studies, demonstrating that glucocorticoid excess shifts multiple tissues toward a pro-oxidant state [Prázný, Ježková et al., 2008; Karamouzis, Berardelli et al., 2015; Hrițcu, Cucoș et al., 2024]. Elevated cortisol stimulates metabolic pathways that promote oxidative damage, reduces antioxidant enzyme activity, and aggravates systemic inflammation—mechanisms also described in diabetes mellitus and other endocrine diseases [Comazzi, 2011; Maiese, 2015; Asmat, Abad & Ismail, 2016; Ighodaro, 2018].

Veterinary clinical studies confirm that dogs with spontaneous Cushing's syndrome present marked increases in circulating malondialdehyde (MDA), reduced total antioxidant capacity, and impaired microvascular reactivity, indicating significant endothelial dysfunction [Prázný, Ježková et al., 2008; Boghian, Solcan et al., 2008]. Moreover, chronic hypercortisolism alters lipid metabolism and promotes cardiovascular remodeling, changes that align with broader endocrine cardiomyopathies described in comparative medicine [Fuentes-Mendoza et al., 2025; Brack et al., 2013].

Importantly, therapeutic modulation of cortisol levels can reverse some of these oxidative alterations. Trilostane—an inhibitor of 3β-hydroxysteroid dehydrogenase—has been shown to significantly reduce oxidative stress markers in canine patients, improving endothelial function, metabolic stability, and overall clinical status [Chen, Liu et al., 2025]. This improvement correlates with the partial restoration of antioxidant systems, an observation consistent with findings in other adrenal disorders where antioxidant responses are disrupted [Mancini et al., 2010].

Taken together, Cushing's syndrome in companion animals is characterized by a complex interaction between hormonal excess, oxidative imbalance, and systemic organ dysfunction. The combination of accurate endocrine management and strategies aimed at restoring antioxidant capacity represents an evidence-based approach to mitigating long-term complications and improving prognosis in veterinary hyperadrenocorticism [Hrițcu, Cucoș et al., 2024; Dhama et al., 2019; Chainy & Sahoo, 2020].

ENDOCRINE OBESITY/METABOLIC SYNDROME

Endocrine obesity and metabolic syndrome in companion animals represent multifactorial disorders characterized by chronic low-grade inflammation, excessive ROS production, altered lipid metabolism, and systemic metabolic dysfunction. Obesity constitutes a major endocrine disruptor, promoting oxidative stress through increased adipocyte activity, mitochondrial overload, and activation of inflammatory cytokine networks [Tanner, Martin & Saker, 2007; Pereira, Raviolo et al., 2025]. These mechanisms parallel the oxidative alterations observed in diabetes mellitus, where lipid peroxidation and reduced antioxidant enzyme activity contribute to systemic damage [Comazzi, 2011; Maiese, 2015; Asmat, Abad & Ismail, 2016].

Obese dogs and cats exhibit elevated MDA levels, decreased antioxidant defenses, and an increased risk of insulin resistance—changes consistent with metabolic syndrome in humans and experimental models [Vona et al., 2019; Bigagli & Lodovici, 2019]. Hypertriglyceridemia, a common feature of endocrine obesity, further exacerbates oxidative stress, promoting endothelial dysfunction and contributing to cardiometabolic complications [Pereira, Raviolo et al., 2025]. Similar oxidative profiles have been described in young diabetic patients and animals with endocrine disorders, suggesting shared molecular pathways driven by ROS overproduction and mitochondrial stress [Martín-Gallán et al., 2003; Hrițcu, Pavel et al., 2024].

Environmental, dietary, and hormonal factors can amplify obesity-associated oxidative stress. Endocrine disruptors such as organohalogen compounds have been shown to impair lipid metabolism and alter hormone signaling in pet animals, contributing to redox imbalance [Nomiyama et al., 2022].

Likewise, chronic corticosteroid exposure, synthetic progestagens, or glucocorticoids may predispose cats and dogs to obesity and metabolic failure, reinforcing the bidirectional relationship between endocrine dysfunction and oxidative stress [Rosca, Hrițcu et al., 2014].

Management strategies require a multifaceted approach. Weight reduction through controlled caloric intake and dietary reformulation improves lipid profiles and reduces oxidative markers. Diets enriched with natural antioxidants vitamin E, vitamin C, omega-3 fatty acids, polyphenols, and plant-derived antioxidant compounds have demonstrated anti-inflammatory and redox-modulating properties in both obesity and gastrointestinal inflammatory models [Bălmuș

et al., 2016; Sahoo et al., 2023; Cojocariu et al., 2020; Spătaru et al., 2019]. These biochemical improvements correlate with reductions in oxidative biomarkers and enhanced metabolic flexibility.

Overall, endocrine obesity and metabolic syndrome in companion animals arise from complex interactions between adipose dysfunction, endocrine imbalance, chronic inflammation, and oxidative stress. Integrative management targeting body weight, metabolic homeostasis, and antioxidant capacity remains essential to reducing long-term metabolic complications and improving quality of life in affected animals [Tanner, Martin & Saker, 2007; Vona et al., 2019; Hrițcu, Pavel et al., 2024].

MANAGEMENT OF OXIDATIVE STRESS IN DIVERSE ENDOCRINE PATHOLOGIES

Oxidative stress represents a central mechanistic pathway shared across numerous endocrine disorders in companion animals and humans, contributing to metabolic dysregulation, vascular dysfunction, mitochondrial impairment, and multi-organ damage. Endocrine diseases such as diabetes mellitus, hyperthyroidism, hypothyroidism, hypercortisolism, and nephrogenic diabetes insipidus display convergent redox abnormalities elevated malondialdehyde (MDA), impaired superoxide dismutase (SOD) and glutathione peroxidase (GPx), increased lipid peroxidation, and disrupted mitochondrial homeostasis [Comazzi, 2011; Maiese, 2015; Asmat, Abad & Ismail, 2016; Ighodaro, 2018; Hrițcu, Cucoș et al., 2024].

In diabetes mellitus, chronic hyperglycemia activates the polyol pathway, increases mitochondrial superoxide production, induces NADPH oxidase activity, and promotes endoplasmic reticulum stress, collectively driving sustained oxidative imbalance [Martín-Gallán et al., 2003; Bigagli & Lodovici, 2019; Vona et al., 2019]. In companion animals, oxidative injury contributes to endothelial dysfunction, impaired innate immunity, and progression of diabetic complications [Webb & Falkowski, 2009; Hrițcu, Pavel et al., 2025].

Hyperthyroidism induces one of the most profound shifts toward a pro-oxidant state. Excess triiodothyronine (T_3) accelerates mitochondrial respiration, increases electron leakage, and amplifies ROS formation, resulting in elevated MDA and reduced antioxidant defenses in both humans and cats [Venditti, Napolitano & Di Meo, 2015; Aslan et al., 2011; Candellone et al., 2021]. Excess ROS mediates cardiomyocyte calcium dysregulation, contributing to thyrotoxic cardiomyopathy; these effects are partially reversed by N-acetylcysteine (NAC) supplementation [Bao et al., 2022].

In contrast, hypothyroidism presents with metabolic slowing yet paradoxically increases oxidative stress markers, including altered lipid peroxidation and impaired antioxidant enzymes. Replacement therapy (e.g., levothyroxine) has been shown to restore redox balance, though adjunctive antioxidant supplementation improves systemic recovery in canine patients [Santi et al., 2010; Elgalfy, Elkhaiat & Ghanem, 2025; Afifi, Saleh et al., 2025].

Hypercortisolism, whether spontaneous or iatrogenic, produces oxidative stress through glucocorticoid-induced mitochondrial alterations, protein catabolism, impaired endothelial function, and platelet activation [Prázný et al., 2008; Karamouzis et al., 2015; Chen et al., 2025]. In dogs, trilostane reduces cortisol-mediated oxidative damage, highlighting the therapeutic importance of hormonal normalization in restoring redox homeostasis.

Nephrogenic diabetes insipidus (NDI)—particularly lithium-induced—also exhibits ROS-mediated renal injury. Lithium exposure induces oxidative mitochondrial dysfunction, pyroptosis via ROS/NF-κB/NLRP3 pathways, and AQP2 downregulation, all of which contribute to polyuria and impaired concentrating ability [Jing, Wang & Gao, 2022; Liu et al., 2023]. Antioxidants such as vitamin C, silymarin, and embelin have demonstrated renoprotective effects in experimental models [Yakut et al., 2025; Sahu et al., 2012].

Across endocrine pathologies, management strategies increasingly integrate targeted antioxidant therapy, aiming to restore redox balance, protect organ function, and reduce disease progression. Natural antioxidants—vitamin E, vitamin C, plant polyphenols, camelina oil, and herbal extracts—demonstrate significant benefits in reducing peroxidation and modulating inflammatory pathways [Bălmuș et al., 2016; Cojocariu et al., 2020; Spătaru et al., 2019; Lans & van Asseldonk, 2020]. Additionally, endocrine-specific pharmacologic interventions (e.g., methimazole, trilostane, levothyroxine, insulin, metformin) contribute indirectly to oxidative stress reduction by normalizing hormonal imbalances.

Taken together, the management of oxidative stress in endocrine diseases requires a combined strategy that addresses both the primary hormonal disorder and its secondary redox consequences. Integrated therapy employing hormonal correction, targeted antioxidants, dietary interventions, and environmental management

offers the most effective pathway toward mitigating oxidative injury and improving outcomes in companion animals [Chainy & Sahoo, 2020; Dhama et al., 2019; Brack et al., 2013].

Endocrine Disorder	Therapeutic Agent	Mechanism of Action
Diabetes mellitus	Insulin	Reduces hyperglycemia-driven ROS, restores metabolic balance
Diabetes mellitus	Metformin	Activates AMPK, reduces mitochondrial ROS
Diabetes mellitus	Vitamin E / Vitamin C	Reduces lipid peroxidation and systemic oxidative load
Hyperthyroidism	Methimazole	Reduces T_3 synthesis, indirectly lowering ROS
Hyperthyroidism	N-acetylcysteine	Direct ROS scavenger, restores GSH levels
Hypothyroidism	Levothyroxine	Normalizes metabolism, restores antioxidant defense
Hypothyroidism	Vitamin E, polyphenols	Improve lipid peroxidation and oxidative balance
Hypercortisolism	Trilostane	Lowers cortisol, reducing ROS generation
NDI (Lithium-induced)	Silymarin	Antioxidant and renoprotective effects
NDI (Lithium-induced)	Vitamin C	Reduces renal lipid peroxidation
NDI (Lithium-induced)	Embelin	Antioxidant, restores renal AQP2 expression
Multi-endocrine oxidative stress	Camelina sativa oil	Polyunsaturated fatty acids improve antioxidant status
Multi-endocrine oxidative stress	Red onion extract	Polyphenols reduce systemic oxidative burden

Table.3.Pharmacological and Nutritional Strategies for Modulating Oxidative Stress in Endocrine[Santi et al., 2010; Tvarijonaviciute et al., 2020; Elgalfy et al., 2025; Afifi et al., 2025; Gerber et al., 2012; Williams et al., 2021; Milne et al., 2015; Matough et al., 2012; Redondo et al., 2023; Pérez-González et al., 2023; Behrend et al., 2013; França et al., 2022; Sanders et al., 2020; Khalil et al., 2021; Jensen & Agrawal, 2020; Ishii et al., 2019; Dąbrowska et al., 2021].

LIMITATIONS AND CHALLENGES IN OXIDATIVE-STRESS MANAGEMENT ACROSS ENDOCRINE DISORDERS

Despite substantial progress in understanding the redox alterations occurring in endocrine pathologies, several methodological, clinical, and translational limitations continue to restrict the integration of oxidative-stress assessment into routine veterinary endocrinology. A central challenge derives from the heterogeneity of oxidative responses across endocrine diseases, which complicates the standardization of diagnostic and therapeutic approaches. Endocrine disorders such as hypothyroidism, hyperadrenocorticism, diabetes mellitus, and lithium-induced nephrogenic diabetes insipidus (NDI) exhibit distinct yet overlapping oxidative signatures, making biomarker interpretation context-dependent [Afifi et al., 2025; Chen et al., 2025; Rosca et al., 2014; Sahu et al., 2012; Zhou et al., 2019; Yakut et al., 2025].

Another limitation is the lack of validated species-specific reference intervals for oxidative biomarkers. Most redox studies rely on small sample sizes or extrapolate from human medicine, which restricts clinical applicability in companion animals. For example, variations in glutathione peroxidase, malondialdehyde, and total antioxidant capacity have been described in endocrine disorders, but inter-study differences in analytical methods hinder comparability [Ali & Sultan, 2011; Martín-Gallán et al., 2003; Vona et al., 2019].

Therapeutic evidence also remains inconsistent. Although antioxidant supplementation demonstrates experimental benefits, controlled veterinary trials are limited. The reported effects of agents such as embelin, silymarin with vitamin C, metformin, or trilostane-mediated redox improvement must be interpreted cautiously due to short-term designs and absence of long-term follow-up [Sathyapalan et al., 2012; Tas & Sancak, 2021; Yakut et al., 2025; Chen et al., 2025]. Additionally, some metabolic modifiers exert context-dependent effects on ROS production, as illustrated in studies of lithium intoxication and endocrine cardiomyopathies, complicating therapeutic extrapolation [Jing et al., 2022; Fuentes-Mendoza et al., 2025].

Environmental and xenobiotic factors further introduce uncontrolled variability. Endocrine disruptors influence thyroid and metabolic homeostasis through ROS-mediated pathways, yet these interactions are difficult to quantify in clinical settings [Schmutzler et al., 2007; Nomiyama et al., 2022]. This limits the ability to differentiate disease-related oxidative stress from environmentally induced redox disturbances.

From a pathophysiological perspective, multisystem interactions amplify diagnostic uncertainty. For example, cardiorenal alterations in endocrine disorders, pituitary–adrenal dysregulation, and obesity-associated dysmetabolism all modulate oxidative stress independently of primary endocrine pathology [Mancini et al., 2010; Martinelli et al., 2015; Tanner et al., 2007; Dhama et al., 2019].

Finally, the field faces significant translational gaps, as much of the existing evidence originates from experimental rodents or human studies rather than naturally occurring diseases in companion animals. The need for species-specific, longitudinal, and multi-organ redox profiling remains one of the most pressing challenges in improving oxidative-stress management within

veterinary endocrinology [Bruyette, 2020; Klopfleisch, 2016; Lans & van Asseldonk, 2020].

Overall, oxidative-stress research provides essential insights into endocrine pathophysiology, yet major limitations—ranging from biomarker standardization to the scarcity of controlled interventional trials—must be addressed before antioxidant-based strategies can be fully integrated into clinical endocrine care for companion animals.

CONCLUSIONS

This systematic review highlights that oxidative stress represents a unifying pathological mechanism across a wide spectrum of endocrine disorders in companion animals. Despite the heterogeneity of conditions such as diabetes mellitus, hyperadrenocorticism, hypo- and hyperthyroidism, all share a common disruption in redox homeostasis, leading to cumulative cellular and tissue injury.

Comparative analysis shows that while the magnitude and specific pathways of oxidative imbalance vary between disorders, the clinical impact is consistently relevant, influencing disease onset, progression, and therapeutic outcomes. Antioxidant capacity appears particularly compromised in chronic endocrine diseases, reinforcing the need for early identification of redox alterations.

Overall, the findings emphasize the importance of integrating oxidative stress assessment into both diagnostic workflows and long-term clinical management. Future research should prioritize standardized methodologies and longitudinal designs to better characterize redox dynamics and to refine targeted antioxidant strategies tailored to each endocrine pathology in pets.

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