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Review article

Emerging Biomarkers in Canine Glaucoma: Insights into Clinical, Genetic, Oxidative, and Inflammatory Pathways

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Abstract: Canine glaucoma is a complex ocular disorder characterized by the progressive loss of retinal ganglion cells (RGCs) and specific optic nerve damage, often resulting in permanent blindness in affected dogs. Recent advancements highlight the importance of various biomarkers in understanding the development and progression of canine glaucoma, particularly in relation to clinical signs, genetics, oxidative stress, and inflammatory pathways. An imbalance between aqueous humor production and drainage significantly affects intraocular pressure (IOP), a key factor in managing glaucoma. Oxidative stress has emerged as a key contributor to RGC degeneration in canine glaucoma, mirroring findings in human studies, where it is implicated in glaucomatous neurodegeneration. The interaction between oxidative stress and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) in the aqueous humor reflects a complex biomarker network with potential diagnostic and therapeutic value. The identification of genetic biomarkers, including enzyme and protein variants, also indicates a move toward molecular methods for evaluating glaucoma risk across different dog breeds. Understanding these interconnected factors offers valuable insights into novel treatments and preventive measures, including genetic screening, oxidative stress monitoring, anti-inflammatory and neuroprotective therapies. Continued biomarker research is essential for improving clinical outcomes in canine glaucoma and may also offer translational relevance to human glaucomatous diseases, thereby broadening future therapeutic possibilities.

Keywords: canine glaucoma; clinical biomarker; genetic biomarker; inflammation biomarker; oxidative stress biomarker.

1. Introduction

Canine glaucoma is a complex eye condition mainly marked by increased intraocular pressure (IOP), which leads to the gradual loss of retinal ganglion cells (RGCs) and vision problems [1]. Glaucoma has become a leading cause of blindness in dogs, highlighting the need for better understanding and treatment of the disease. The prevalence of canine glaucoma varies across studies and populations. A study conducted at the University of Zurich between 1995 and 2009 found that secondary glaucoma accounted for only 3.6% of all new canine ophthalmology cases examined, highlighting its relative rarity within that specific population. In contrast, another study from California reported a higher prevalence of 6.9% for secondary glaucoma cases [2]. Such discrepancies may be attributed to differences in geographic or clinical settings and the effectiveness of managing underlying conditions that predispose dogs to secondary glaucoma. Diagnosing and managing canine glaucoma heavily depends on finding biomarkers, essential signs of the disease, and its progression [3].

Glaucoma is particularly common in certain dog breeds, and studies show that genetic factors play a role in its occurrence [4]. Clinical biomarkers like IOP, retinal nerve fiber layer (RNFL) thickness, and changes in the optic nerve head (ONH) are key to assessing damage caused by glaucoma. Advanced tools such as optical coherence tomography (OCT) enable accurate measurement of the RNFL, helping with early detection and monitoring of the disease. Precise measurement of IOP and careful examination of

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the ONH are also central to understanding the structural changes linked to glaucoma [5]. Beyond clinical tests, research into genetic biomarkers has become more critical in veterinary eye care. Specific gene mutations, such as those in the myocilin gene, are associated with primary open-angle glaucoma across different breeds. Understanding these genetic factors not only helps identify vulnerable populations but also opens the door to gene therapy treatments [6].

Oxidative stress is increasingly seen as a key part of how glaucoma develops. Higher levels of oxidative stress markers, such as malondialdehyde (MDA), show cellular damage within the retina and contribute to RGC death. The relationship between oxidative stress and high IOP suggests that therapies aimed at reducing oxidative damage could protect retinal tissue and help maintain vision in affected dogs [7]. Inflammation is recognized as a significant factor in glaucoma progression. Increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), are found in glaucomatous eyes and further damage the retina [8].

The complex nature of canine glaucoma calls for a comprehensive approach that includes clinical, genetic, oxidative stress, and inflammatory biomarkers [9]. These insights could improve diagnosis and treatment efforts to prevent vision loss from this severe disease. A better understanding of these biomarkers can lead to more effective management and tailored therapies, ultimately preserving sight and enhancing quality of life for affected dogs. This all-encompassing strategy aims to improve diagnostics and develop better treatments to improve outcomes in veterinary ophthalmology.

2. Results and Discussion

2.1 Pathophysiology

The pathogenesis of glaucoma in canines, as in humans, is a multifactorial process characterized primarily by the progressive degeneration of RGCs and their axons, often triggered by elevated IOP. Canine glaucoma can be classified as primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), each exhibiting differences in clinical manifestations and underlying structural changes [10]. A significant aspect of canine primary glaucoma is its genetic component; certain breeds show a higher predisposition to this disease due to hereditary factors. For example, Beagles are recognized as a breed with documented anatomical predispositions related to glaucoma [5]. Such genetic factors can result in anatomical anomalies affecting the iridocorneal angle, facilitating the onset of elevated IOP and playing a crucial role in understanding the disease's pathophysiology [11].

Inflammation is another fundamental element contributing to the pathophysiology of canine glaucoma. Elevated levels of inflammatory cytokines, particularly interleukin-1β, have been correlated with an increased risk and progression of the disease [12]. Compromised vascular integrity in the uvea, a consequence of elevated IOP, can worsen the inflammatory response, potentially creating a pathological feedback loop that may hasten RGC degeneration [8]. Additionally, inflammation can affect medication compliance in affected dogs, as local adverse reactions to treatments can lead to discontinuation of necessary medications, further complicating management strategies [13]. Oxidative stress also plays a critical role in the etiology of glaucoma. Increased oxidative stress has been linked to excitotoxic damage of RGCs and is associated with elevated levels of glutamate and nitric oxide (NO), both of which predispose RGCs to degeneration [7]. The pathogenic effects of oxidative stress include mitochondrial dysfunction, which may impair energy metabolism in retinal cells, contributing to cumulative damage within the ocular microenvironment [14].

2.2. Clinical Biomarkers

Canine glaucoma is a complex ocular condition characterized by elevated IOP that negatively affects RGCs and the ONH. This progressive condition can result in severe vision impairment and blindness due to increased IOP and subsequent damage to the optic nerve and retinal structures [1].

2.2.1. Intraocular pressure (IOP)

Elevated IOP indicates a significant disruption of the homeostatic balance of aqueous humor dynamics, typically due to obstruction of drainage through the trabecular meshwork. Normally, IOP in dogs ranges between 10 to 25 mmHg, with elevations suggesting potential glaucomatous conditions [15]. The balance between aqueous humor production mainly regulates IOP in the ciliary body and its outflow through the trabecular meshwork and uveoscleral pathways [16]. Glaucoma occurs when there is an obstruction or functional impairment in these outflow pathways, leading to increased IOP, which can then cause optic nerve damage and vision loss [5].

The pathological mechanisms underlying glaucoma in canines encompass both mechanical and biochemical components. Elevated IOP induces stress within the ONH, characterised by deformation and potential ischaemia due to compromised blood flow [10]. Chronic IOP elevation can alter neuroretinal structures, leading to the gradual degeneration of RGCs. Specific biochemical pathways, such as excitotoxicity arising from neurotransmitter imbalances or neurotrophin deprivation, have been implicated in RGC death, independent of IOP levels [4]. This suggests that while IOP is a significant risk factor, other concurrent mechanisms also contribute to the overall pathology of canine glaucoma.

- RGCs

RGCs serve as crucial clinical biomarkers for canine glaucoma, primarily because they transmit visual information from the retina to the brain and are susceptible to elevated IOP. In canine glaucoma, similar to the human condition, elevated intraocular pressure is a significant risk factor that initiates a cascade of events, ultimately compromising retinal ganglion cell survival [3]. Due to their pivotal role in transmitting visual information, retinal ganglion cells have emerged as prime candidates for biomarker development. Monitoring RGC health and function could provide invaluable insights into glaucoma pathogenesis and facilitate the evaluation of novel therapeutic strategies. The progressive degeneration of retinal ganglion cells and the loss of their axons are characteristic of glaucoma [17].

The RGCs are a crucial link between the retina and the brain, relaying visual information essential for sight; their deterioration is a hallmark of glaucoma. This degeneration often appears as thinning of the RNFL, which correlates with the loss of RGC axons. The RNFL thinning can precede RGC soma loss, suggesting that RNFL thickness monitoring can serve as an early marker of glaucoma progression. Additionally, quantitative assessments such as OCT offer methods to evaluate structural changes in the retina that reflect RGC status [18].

- ONH

The ONH plays a critical role in understanding glaucoma pathophysiology in canines, primarily through its relationship with IOP and RGC health. In dogs, glaucomatous changes at the ONH can manifest as alterations in its appearance, reflecting possible functional deficiencies earlier than conventional visual assessments can detect [1]. Normal conditions at the ONH include a defined optic disc morphology, typical blood supply, and integrity of the nerve fibre layers. However, in glaucomatous conditions, mechanical stress from elevated IOP causes optic nerve degeneration, leading to changes in the ONH, such as cupping, increased disc pallor, and changes in shape due to nerve fibre loss. Histopathological studies have shown that ongoing inflammation, characterised by the infiltration of neutrophils and the presence of elevated pro-inflammatory cytokines like TNF-α, can correlate with changes in ocular structures and may exacerbate degenerative processes in glaucomatous eyes [13].

Abnormal conditions at the ONH in glaucomatous dogs may result from the breakdown of the blood-retinal barrier and subsequent inflammation. This inflammation can arise from increased IOP, which mechanically disrupts normal tissue architecture, and immune-mediated processes that further exacerbate damage. Such mechanisms highlight the significance of ONH assessment, as early identification of changes can influence the clinical management of canine glaucoma [19].

2.3. Genetic Biomarkers

Given its heritable nature across breeds, canine glaucoma, which is primarily genetic, presents an intriguing field of study. Emerging evidence indicates several genetic biomarkers that can aid in understanding the underlying mechanisms contributing to this ocular condition [6].

- ADAMTS10

ADAMTS10 is part of a family of metalloproteinases crucial in remodeling the extracellular matrix (ECM) in ocular tissues. Mutations in the ADAMTS10 gene have been implicated in primary glaucoma in certain breeds, such as the Basset Hound. These mutations can impair ECM turnover, disrupting normal ocular structure and function. As a result, alterations in the trabecular meshwork can hinder aqueous humor drainage, raising IOP and ultimately contributing to optic nerve damage [5].

- ADAMTS17

Like ADAMTS10, the ADAMTS17 gene encodes a protein involved in ECM remodeling. Genetic variations in ADAMTS17 have been linked to hereditary glaucoma, particularly in breeds such as the Petit Basset Griffon Vendéen (PBGV). The dysfunction arising from ADAMTS17 mutations leads to structural changes

in the eye, which can increase IOP by obstructing aqueous humor outflow pathways. This not only increases the risk of developing glaucoma but also instigates progressive optic nerve damage [11]. The MYOC gene is perhaps the best-known genetic marker for glaucoma, as it has been extensively studied in both canines and humans. The MYOC gene has been extensively studied in breeds like the Beagle and Labrador Retriever. Mutations in MYOC disrupt normal protein folding and function, leading to the accumulation of abnormal myocilin protein in the trabecular meshwork and increased resistance to aqueous humor outflow. This condition raises IOP and promotes the death of RGCs, leading to irreversible optic nerve damage typical of glaucomatous conditions [4].

- COL12A

The COL12A gene encodes collagen type XII, a critical component of the ocular ECM, and has been linked to glaucoma in breeds such as the Shih Tzu. Mutations in this gene can lead to weaknesses in the collagen fibers that provide structural support to the eye. This abnormality may disrupt the normal biomechanics of the eye, leading to elevated IOP through impaired drainage and contributing to glaucoma development. Abnormal collagen organization has been associated with increased resistance in aqueous humor outflow, further compounding the IOP changes that induce optic nerve damage [20].

- RAB22A

RAB22A plays a significant role in intracellular trafficking, influencing vesicle transport in ocular tissues that are associated with an increased risk of glaucoma in breeds such as the Staffordshire Bull Terrier. Dysregulation of this gene can lead to abnormal cellular responses in the trabecular meshwork, disrupting the normal processes of aqueous humor outflow. This disruption can lead to increased IOP as the flow of fluid through the ocular drainage system is obstructed, consequently heightening the risk of glaucomatous degeneration in the optic nerve [11].

- NEB

The NEB gene encodes nebulin, which is significant for the structural integrity of various connective tissues in breeds such as the Eurasier. Variants in NEB may alter the mechanical properties of the sclera and other ocular structures, thereby altering the eye's response to IOP fluctuations. These abnormalities can increase the susceptibility to glaucomatous changes by affecting how the ocular tissues withstand elevated pressures, ultimately leading to further optic nerve degeneration [1].

- SRBD1

The SRBD1 gene, which is associated with RNA processing, has been shown to be significantly associated with glaucoma in certain breeds, including the Shiba Inu. Specific polymorphisms in SRBD1 were associated with increased susceptibility to the disease. This gene's involvement suggests a genetic mechanism where metabolic or regulatory dysfunctions can amplify apoptotic pathways in RGCs, facilitating progressive optic nerve damage characteristic of glaucoma [21].

2.4. Oxidative Stress Biomarkers

Oxidative stress significantly contributes to the pathogenesis of canine glaucoma, as evidenced by various biomarkers indicating oxidative damage and the stress response.

- MDA

MDA is a significant biomarker of oxidative stress that provides insight into the underlying mechanisms of canine glaucoma. Elevated levels of MDA reflect lipid peroxidation, a process in which reactive species interact with cellular membrane lipids, leading to potential damage to retinal and other ocular tissues [22]. In glaucoma, MDA serves as a crucial indicator of oxidative damage that can contribute to the disease's pathophysiology. Oxidative stress in the eye occurs when the production of reactive oxygen species (ROS) exceeds the eye's antioxidant defense mechanisms. Under normal conditions, antioxidants such as glutathione (GSH) and various enzymes help mitigate oxidative damage. However, increased IOP can induce cellular stress in conditions such as glaucoma, leading to elevated ROS levels that trigger lipid peroxidation.

MDA, a byproduct of lipid peroxidation, serves as a sensitive marker of oxidative damage in the retina and other ocular tissues [23]. The cellular environment rapidly becomes hostile when dogs develop glaucomatous conditions, often due to impaired aqueous humor drainage or elevated intraocular pressure. Elevated levels of MDA indicate significant membrane damage and contribute to further inflammation and cell death within the retina, adversely affecting RGCs, which are crucial for visual function [7]. This chain of events underscores MDA's role not only as a marker but also as a contributor to degenerative processes that

lead to vision loss. Specifically, elevated MDA levels in the aqueous humor of dogs with glaucoma may also indicate an underlying inflammatory response driven by oxidative stress, further contributing to ongoing damage to the optic nerve head and subsequent degeneration of the visual pathway. Enhanced lipid peroxidation, as evidenced by elevated MDA levels, indicates that the retina struggles to cope with oxidative stress due to diminished antioxidant defenses, ultimately leading to cellular apoptosis and vision impairment [24].

- Nitrated Tyrosines (NT)

NTs are significant markers of oxidative stress associated with various ocular diseases, including canine glaucoma. NT form when reactive nitrogen species (RNS), such as peroxynitrite ($ONOO^-$), modify tyrosine residues in proteins, leading to cellular damage. This modification has been studied as a biomarker in glaucoma due to its implications for RGC health, which are particularly susceptible to oxidative stress. In canine glaucoma, elevated IOP increases ROS and RNS production, including NO, in retinal tissues. When NO reacts with superoxide anions (O_2^-), $ONOO^-$ forms, which can subsequently lead to the nitration of tyrosine residues in proteins, resulting in NT accumulation [22]. NT indicates ongoing oxidative damage to cellular proteins, impairing their normal functions. This nitration can disrupt crucial cellular signaling pathways, leading to protein misfolding or dysfunction and ultimately promoting apoptosis in RGCs. Since RGCs are integral to the transmission of visual information, their degeneration significantly contributes to vision loss in dogs affected by glaucoma [25].

- GSH

GSH is a tripeptide made up of glutamine, cysteine, and glycine, and it exists in high concentrations in retinal tissues. Its primary role is as a cellular antioxidant, neutralizing free radicals and ROS produced during metabolic processes and environmental stressors. In canine glaucoma, GSH levels can become severely altered. Studies have shown that dogs with glaucoma often exhibit significantly reduced GSH levels, adversely affecting their ability to cope with oxidative stress [7]. This reduction indicates abnormal conditions, reflecting an overwhelmed antioxidant defense system under continuous oxidative assault. When GSH levels decline, the retina becomes increasingly vulnerable to oxidative stress, which can lead to RGC degeneration. The decrease in GSH levels is associated with elevated markers of oxidative damage. Compromised GSH levels and their subsequent inability to neutralize excess ROS can lead to cellular apoptosis. This cellular stress is known to drive RGC death, further worsening the visual impairment associated with glaucoma [25].

- Advanced Glycation End-products (AGEs)

AGEs form through non-enzymatic glycation. In this reaction, reducing sugars react with proteins, lipids, or nucleic acids, resulting in structural and functional alterations in these macromolecules. In canines suffering from glaucoma, oxidative stress intensifies due to elevated IOP and subsequent tissue damage in the eye. This mechanism involves excessive ROS production, which can enhance the formation of AGEs through glycation. Elevated levels of AGEs in the aqueous humor and ocular tissues correlate with oxidative stress markers, indicating significant oxidative damage within the eye. The accumulation of AGEs can worsen oxidative stress, creating a feedback loop that further promotes degeneration of RGCs and aggravates glaucoma [8]. Glycation-induced modifications of proteins impair their function, including those essential for maintaining ocular pressure and aqueous humor dynamics. This impairment can lead to chronic elevation of IOP, further deteriorating glaucoma conditions. The AGEs have promoted apoptosis among RGCs. The binding of AGEs to RAGE activates signaling pathways that can lead to neuroinflammation and cell death. Such effects contribute to the progressive loss of vision observed in dogs with glaucoma, underscoring the importance of AGEs in the disease's progression [14].

- Total Antioxidant Capacity (TAC)

TAC is a critical biomarker of oxidative stress and is particularly significant in canine glaucoma. TAC reflects the overall ability of the eye's tissues, including the retina and aqueous humor, to counteract oxidative damage from ROS. The TAC represents the combined effects of various antioxidants in the ocular environment, including enzymes (such as superoxide dismutase, catalase, and glutathione peroxidase (GPX)) and non-enzymatic antioxidants (such as ascorbic acid and alpha-tocopherol). A delicate balance exists between ROS production and antioxidant defenses in a healthy ocular environment, facilitating normal physiological function. However, under oxidative stress conditions, such as those encountered in glaucoma, antioxidant defenses may become insufficient [8]. In canine glaucoma, elevated IOP results in increased ROS production. This oxidative stress can surpass local antioxidant defenses, including TAC, leading to damage

to RGCs and other ocular structures. A reduction in TAC indicates a diminished capacity to neutralize ROS effectively [24]. A significant decline in TAC has been associated with increased oxidative damage markers, such as MDA and protein oxidation products. In glaucomatous dogs, low TAC levels indicate an inability to protect retinal cells from ROS-mediated damage, leading to cell apoptosis and neurodegeneration. Studies indicate that decreased TAC levels are connected to the progression of RGC loss in glaucomatous conditions. The compromised antioxidant defense critically limits the retina's ability to recover from oxidative damage, thereby accelerating a pathophysiological decline in visual function [21].

- Superoxide Dismutase (SOD)

SOD is a critical enzyme in the antioxidant defense system that catalyzes the dismutation of superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2) and molecular oxygen. In glaucoma, elevated IOP leads to increased ROS production, including superoxide radicals. The accumulation of these radicals is harmful to retinal cells. SOD mitigates this risk by converting superoxide into the less harmful hydrogen peroxide, which can be further detoxified by other antioxidant enzymes like catalase (CAT) and GPX [14]. Studies have shown that dogs with glaucoma often exhibit reduced SOD activity in the aqueous humor and retinal tissues. This decrease limits the capacity to neutralize superoxide radicals effectively, leading to increased oxidative damage. The reduced activity may correlate with disease severity, suggesting that antioxidant defense is compromised in glaucomatous dogs. A reduced level of SOD activity can lead to increased oxidative stress, as excess superoxide radicals are not adequately converted to hydrogen peroxide. This imbalance can lead to a cascade of cellular damage, including lipid peroxidation, protein oxidation, and ultimately apoptosis of RGCs. Elevated markers of oxidative damage, such as MDA, may be observed alongside reduced SOD activity, further substantiating the association with glaucoma [25].

- CAT

CAT primarily converts H_2O_2, a potentially harmful byproduct of cellular metabolism and oxidative stress, into water and oxygen. This reaction helps mitigate oxidative damage within cells, especially in organs such as the eye, where oxidative stress can lead to severe complications like RGC death. In canine glaucoma, elevated IOP leads to increased ROS production, resulting in increased hydrogen peroxide accumulation. CAT efficiently neutralizes H_2O_2, preventing oxidative damage to retinal cells. By maintaining low H_2O_2 levels, CAT protects the retina's delicate cellular structures from oxidative stress-induced apoptosis. Studies have reported that dogs with glaucoma exhibit reduced CAT activity in ocular tissues, elevated IOP, and markers of oxidative stress. A decrease in CAT activity compromises the eye's ability to handle elevated hydrogen peroxide levels, leading to increased oxidative damage and cellular apoptosis, particularly in RGCs. This decline in CAT activity is often associated with the severity of glaucoma, as higher rates of oxidative damage correlate with lower CAT activity [26].

- GPX

GPX is an enzyme that catalyzes the reduction of H_2O_2 and organic hydroperoxides by utilizing GSH as a substrate, resulting in the generation of oxidized glutathione (GSSG) and water. In canine glaucoma, increased IOP correlates with increased ROS production and oxidative stress, leading to hydrogen peroxide accumulation. GPX helps detoxify H_2O_2, protecting RGCs and other ocular tissues from oxidative damage. By effectively reducing H_2O_2 levels, GPX plays a crucial role in preventing cell death and preserving retinal function. Studies have shown that dogs diagnosed with glaucoma exhibit significantly reduced GPX activity in ocular tissues and in the aqueous humor. This reduction correlates with elevated oxidative stress markers, indicating compromised antioxidant defense and potentially exacerbating retinal damage and RGC apoptosis. Low GPX activity may parallel increased markers of oxidative damage, such as MDA, further underscoring its association with glaucoma severity [23].

2.5. Inflammation Biomarkers

Canine glaucoma is a complex disease that presents significant challenges in veterinary ophthalmology, with inflammation playing a key role in the disease's progression. Growing evidence indicates that inflammatory mediators and oxidative stress markers are crucial indicators of the disease's underlying mechanisms. Understanding these markers not only aids in diagnosing glaucoma but also improves our knowledge of the fundamental processes involved, including the interaction between oxidative stress and inflammation.

- Cytokines and Interleukin

Cytokines and interleukins act as critical mediators of inflammation in canine glaucoma, offering insight into the underlying pathophysiological mechanisms and facilitating potential therapeutic interventions. In canine glaucoma, elevated levels of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α, have been documented. These cytokines play a pivotal role in recruiting inflammatory cells, including neutrophils and macrophages, to the injury site, thereby worsening the inflammatory response. Dysregulation of these cytokines can lead to sustained inflammation, which is associated with RGC degeneration in glaucoma. Elevated IL-6 levels, for example, have been linked to increased RNFL loss, indicating its potential as a biomarker for disease severity [19]. The mechanism of cytokine involvement includes the activation of retinal microglia and other innate immune cells, which release inflammatory mediators contributing to neurodegeneration. As inflammatory cytokines trigger signaling pathways that induce apoptosis in RGCs, their persistent presence can lead to chronic damage. For instance, IL-1 stimulates MMP production, which contributes to pathological remodeling of the extracellular matrix in the trabecular meshwork, thereby affecting aqueous humor outflow and raising IOP. This interaction between elevated IOP, abnormal cytokine signaling, and inflammation creates a vicious cycle that progressively exacerbates glaucomatous changes in the affected eye [8].

- Matrix metalloproteinases (MMPs)

MMPs play a significant role as biomarkers of inflammation in canine glaucoma, linking inflammation to the neurodegenerative processes that characterize this disease. Glaucoma is associated with neuronal degeneration, particularly in RGCs, a hallmark of the condition [27]. In canine glaucoma, elevated pro-inflammatory proteins, such as MMPs and cytokines, in the aqueous humor have been associated with increased IOP and subsequent RGC damage. MMP-9, a critical ECM remodeling enzyme, is upregulated by elevated IOP and has been shown to contribute to RGC death via oxidative stress and inflammation. Identifying such proteomic markers in the aqueous humor allows for the distinction between normal and glaucomatous states, thus serving diagnostic and prognostic purposes [12]. The mechanisms by which MMPs contribute to neuroinflammation in canine glaucoma can be elucidated through several key pathways. For instance, the activation of microglial cells and astrocytes in response to RGC injury leads to the release of MMPs, facilitating the degradation of the extracellular matrix, thereby influencing both inflammation and neuronal survival [19]. Additionally, canine primary glaucoma is associated with an inflammatory response characterized by increased expression of inflammatory markers, such as MCP-1 and TNF-α. This response has been observed to correlate with the severity of neurodegeneration and increased MMP activity, supporting the hypothesis that these molecules serve as mediators of ocular inflammatory responses [13].

Clinically, the relevance of MMPs as biomarkers extends to their potential for use in diagnostic and therapeutic strategies for glaucoma management. Their quantifiable presence in ocular tissues, such as the aqueous humor, enables the monitoring of disease progression and therapeutic response. Furthermore, anti-inflammatory treatments, including corticosteroids, may have beneficial effects in modulating the inflammatory environment and potentially reducing MMP-triggered damage within the ocular environment, highlighting the therapeutic implications of targeting MMPs [27].

- Glial Biomarkers

Glial biomarkers, such as myelin basic protein (MBP) and S100B, are crucial for understanding the neuroinflammatory processes linked to canine glaucoma. MBP is a structural protein in the myelin sheath surrounding nerve fibers. In canine glaucoma, elevated levels of MBP in the aqueous humor may indicate demyelination and glial disruption in response to neuronal apoptosis and degeneration. MBP can serve as a biomarker for neuroinflammation, suggesting an active inflammatory response in the optic nerve and retinal tissues. Protein S100B is a calcium-binding protein predominantly located in astrocytes and is associated with neuroinflammatory responses. Increased levels of S100B in the cerebrospinal fluid and peripheral areas have been correlated with various neurodegenerative diseases, including glaucoma [21]. In dogs with primary glaucoma, elevated S100B levels in the retina and aqueous humor may indicate astrocyte activation and ongoing neuroinflammatory processes. This might reflect a heightened inflammatory environment that contributes to RGC degeneration. Both MBP and S100B can influence the release of pro-inflammatory cytokines. Dysregulation of these biomarkers may lead to increased RGC apoptosis via inflammatory signaling pathways. For instance, S100B can stimulate TNF-α and other cytokine release from glial cells, promoting a neuroinflammatory environment that exacerbates RGC damage [12].

In glaucomatous canine eyes, abnormal MBP and S100B levels suggest ongoing neuroinflammation and nerve injury. The simultaneous increases in these biomarkers correlate with the progression of the disease, reinforcing their roles as potential indicators of severity [27]. Abnormal MBP and S100B expression may reflect demyelination and a reactive state in glial cells. This reactivity can lead to the loss of normal glial functions, worsening outcomes for RGCs. Elevated S100B levels, in particular, indicate not just inflammation but also stress on astrocytes as they attempt to respond to the neuronal injury, showcasing the dual role of these cells as both protectors and contributors to pathology [8].

- Neuroinflammatory

Neuroinflammation plays a significant role in the development and progression of canine glaucoma, serving as an important inflammatory biomarker. Key proteins, such as glial fibrillary acidic protein (GFAP) and ionised calcium-binding adaptor molecule 1 (IBA1), indicate neuroinflammatory activity in glaucomatous eyes. Their expression reflects the activation of glial cells, which are critical to neuronal health and viability. In response to elevated IOP and oxidative stress, astrocytes and microglia become activated, as evidenced by GFAP upregulation, primarily expressed in astrocytes. GFAP is a reliable biomarker for astrocyte activation, indicating a neuroinflammatory response [16]. Similarly, IBA1 is a marker of microglial activation, crucial for assessing morphological changes in microglia during neuroinflammatory processes [25]. The elevation of neuroinflammatory biomarkers, such as GFAP and IBA1, alongside increased oxidative stress, indicates a decline in RGC health. Studies have shown that as neuroinflammation progresses, GSH levels in RGCs and surrounding glial cells decrease. This decline compromises RGC viability and contributes to the neurodegenerative processes characteristic of glaucoma [13]. Abnormal upregulation of GFAP indicates reactive astrogliosis, a process in which astrocytes proliferate and become hypertrophic in response to injury, releasing inflammatory mediators that can harm surrounding neurons. This offers insight into the severity of the neuroinflammatory response in glaucomatous eyes. Enhanced expression of IBA1 in microglia signifies an active immune response, suggesting that neuroinflammation may play a role in the ongoing degeneration of RGCs [19]. This exacerbates the cycle of inflammation and RGC death, leading to significant visual impairment over time.

3. Conclusions

Canine glaucoma is characterized by elevated IOP that can lead to irreversible optic nerve damage and vision loss. Clinical markers are critical in diagnosing glaucoma and monitoring disease progression. Inflammatory markers demonstrate a strong association with RGC death and disease severity. Oxidative stress markers reflect cellular damage and contribute to RGC apoptosis, shedding light on the oxidative pathways involved in glaucoma pathogenesis. Genetic biomarkers provide essential information regarding hereditary predispositions to canine glaucoma. The combination of these factors underscores the complexity of canine glaucoma, wherein clinical markers, inflammatory processes, oxidative stress, and genetic predispositions collectively inform the understanding and diagnosis of this debilitating condition. These biomarkers not only aid in the early detection and monitoring of glaucoma but also offer opportunities to develop targeted therapies to mitigate the disease's progression in canines.

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