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The Glymphatic System in Glaucoma and Optic Neuropathy: A Narrative Review of Emerging Neuro-Ophthalmic Evidence

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Abstract **Objectives:** Optic nerve health is essential for proper function of the visual system. However, the pathophysiology of certain neurodegenerative disease processes affecting the optic nerve, such as glaucoma, is not fully understood. Recently, it was hypothesized that a lack of proper clearance of neurotoxins such as amyloid-beta, tau proteins and other metabolic byproducts contributes to neurodegenerative diseases. The ability to clear metabolic waste is essential for tissue homeostasis in mammals, including humans. While the brain lacks the traditional lymphatic drainage system identified in other anatomical regions, there is growing evidence of a Glymphatic system in the central nervous system, which structurally includes the optic nerve. **Aim:** This study performed a narrative review to examine the anatomical and functional relationship between the glymphatic system and the optic nerve, synthesizing evidence from experimental, histopathological and neuroimaging studies. **Methods:** A narrative review methodology was utilized for this study. Relevant literature was identified through structured narrative search of PubMed, Embase, Cochrane Library, Scopus and Google Scholar using keywords such as glymphatic system, optic nerve disorders and neuro-ophthalmology. Eligible studies include randomized controlled trials, observational studies and meta-analyses published within the last five years (2020–2025). Non-English, animal studies were excluded. The search strategy yielded 1 case control study and 2 observational studies met inclusion criteria. **Results:** The pathogenesis of retinal illnesses including glaucoma and age-related macular degeneration is significantly influenced by the presence of a glymphatic-like system in the retina and optic nerve. **Conclusion:** However, only three eligible human studies were identified, representing a major limitation of the current evidence base.

Key Words Glymphatic System, Neuro-Ophthalmology, Narrative Review, Optic Nerve

INTRODUCTION

The optic nerve is a critical structure for optic signal transmission and any damage to the structure and function of the optic nerve can lead to serious loss of vision. Many optic nerve damages are caused by glaucomatous optic neuropathy and glaucoma has become the second cause of irreversible blindness all over the world. Elevated Intraocular Pressure (IOP) is widely recognized as the primary cause of glaucoma. However, in recent years, an increasing number of studies have found that pressure-independent factors may also play an important role in the occurrence and development of glaucoma.

Efficient removal of metabolic byproducts is critical for tissue homeostasis across all organs. While the lymphatic system governs fluid homeostasis, immune surveillance and elimination of waste in the periphery, it remains a mystery what clears waste in the Central Nervous System (CNS) including the brain and spinal cord and the optic nerve. Recent research has uncovered an uncharacterized brain lymphatic conduit termed the glymphatic system. This system acts as a Glial-dependent perivascular sink where CSF and ISF are exchanged, with implications for removal of proteinaceous waste such as amyloid-beta peptides and other deleterious compounds [1,2].

The glymphatic system is a highly coordinated system, in which CSF from the periarterial space enters the brain and diffuses into the ISF within the parenchyma through the Aquaporin-4 (AQP4) water channels located on the astrocytic endfeet, which ultimately drains out through the perivenous space. The glymphatic system has been reported

to be modulated by various physiological parameters including arterial blood pressure, intracranial pressure, sleep-wake cycle and body posture. The integrity of the glymphatic system has been implicated in a number of neurological conditions, including neurodegenerative and cerebrovascular diseases [3,4].

Because of the embryological and anatomical continuity between the brain and eye through the optic nerve and retina, a glymphatic-like system may also be present within ocular tissues. In light of its diencephalic origin, the optic nerve shares common traits with other CNS tissues including: (i) high energy consumption, (ii) restricted extracellular compartment and (iii) lack of traditional lymphatic channels. Efficient fluid regulation and waste removal is thus vital for ensuring optic nerve function [5,6].

It is relatively recent, that neuroimaging studies provided the first evidence that glymphatic pathways are also present in the optic nerve and retina. According to these studies CSF flows in the peri-arterial space towards the eye, while waste products flow in the perivenous space (Figure 1). A defect of glymphatic functions in the eye leads to neurotoxic waste accumulation, oxidative stress and altered axonal transport, that are all shared mechanisms of glaucomatous optic neuropathy [2,7,8].

Glymphatic dysfunction may be a contributing factor to optic nerve damage in eyes where there is no evidence of high IOP, such as in normal-tension glaucoma. Proposed contributing factors include changes in cerebrospinal fluid (CSF) hydrodynamics, abnormal function of the AQP4 channels and altered pressure gradients across the lamina cribrosa. As with vascular and mechanical damage to the optic nerve, clearance-related damage may be a multi-factorial phenomenon [2,5].

There is an increasing interest in the glymphatic system and despite this, little is known about its involvement in optic nerve disease, especially in humans. Current data is heavily based on experimental models and little information is available on human studies except for imaging findings. It is essential to conduct a review of human data in order to determine the significance of glymphatic involvement in neuro-ophthalmic diseases.

The purpose of the present review is to clarify the relationship between the glymphatic system and the optic nerve from an anatomical, physiological perspective in relation to glaucoma and optic neuropathies and to provide an insight into glymphatic contribution based on current neuroimaging and clinical studies and therefore to guide future investigations. This review focuses specifically on glymphatic involvement in glaucoma and optic neuropathies, rather than all optic nerve disorders broadly.

METHODS

A narrative review methodology was utilized for this study. Relevant literature was identified through systematic searches of PubMed, Embase, the Cochrane Library, Scopus and Google Scholar, focusing on publications from the last five years (2020–2025). The search strategy incorporated controlled vocabulary, such as Medical Subject Headings (MeSH) terms-including "Glymphatic System" and "Optic Nerve Disorders" as well as relevant keywords and variations of root terms like "Glaucoma and "Neuro-Ophthalmology".

Search queries were constructed by combining terms related to studies describing the condition of interest (Glymphatic system, optic nerve disorders, as well as relevant keywords and variations of root terms like glaucoma and neuro-ophthalmology). Additionally, the reference lists of articles selected for final analysis, along with pertinent review papers, were examined to identify further relevant publications.

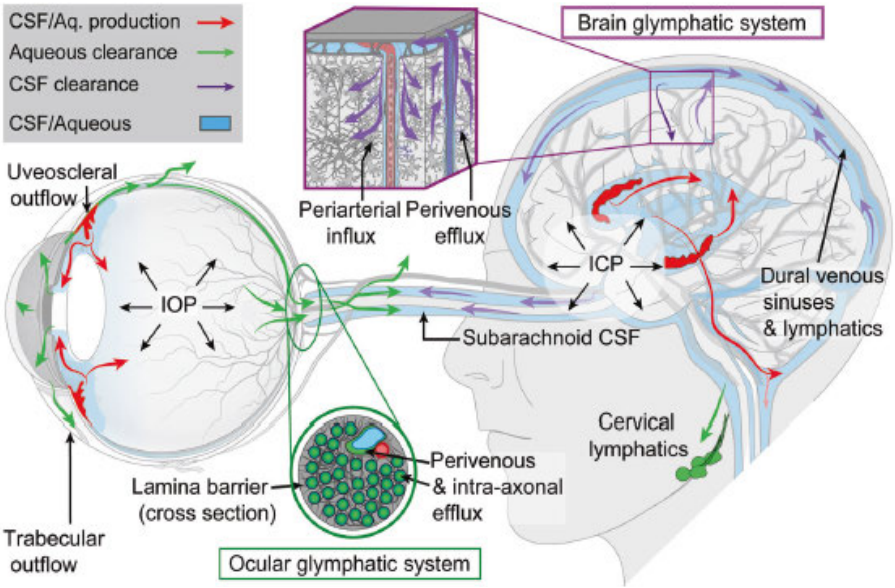

Figure 1: Macroscopic Overview of the Brain and Ocular Glymphatic Systems, Emphasizing the Role Played by Pressure Gradients, Hydrostatic Barriers and Lymphatic Drainage, Shown in the Context of known Pathways for Aqueous Humour and Cerebrospinal Fluid (CSF) Efflux

Data Extraction and Risk of Bias Assessment

All randomized controlled trials, meta-analyses and observational studies of glymphatic system and optic nerve disorders as well as relevant keywords and written in English at the last five years (2020-2025) were included in the review. Exclusion criteria included studies published science more than five years and animal studies. Animal studies were excluded to focus on clinically relevant human evidence; however, this may have limited mechanistic depth, as glymphatic physiology is largely derived from experimental models. Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were not followed when conducting the review. Accordingly, no meta-analysis was performed and no formal risk-of-bias or methodological quality assessment of the included studies was undertaken. No formal risk-of-bias assessment or evidence grading was performed, which limits the ability to compare study quality and strength of evidence.

RESULTS

Table 1 summary of included studies evaluating glymphatic system dysfunction in optic nerve disorders. The table presents study design, population characteristics, imaging methods and key findings of the three eligible human studies included in this narrative review. Glymphatic function was primarily assessed using advanced neuroimaging techniques, including Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) and functional Magnetic Resonance Imaging (fMRI) with Blood Oxygen Level-Dependent–Cerebrospinal Fluid (BOLD-CSF) coupling. The findings consistently demonstrate associations between impaired glymphatic activity and optic nerve pathology, particularly in Thyroid Eye Disease (TED), Normal-Tension Glaucoma (NTG) and Primary Open-Angle Glaucoma (POAG). However, interpretation of these findings should be made cautiously due to the limited number of studies and observational nature of the evidence.

Overall, all three studies demonstrated impaired glymphatic function associated with optic nerve pathology, particularly glaucoma. However, findings remain limited due to small sample sizes and observational designs.

DISCUSSION

This review comments on the potential impact of the glymphatic system on the pathology of the optic nerve in the context of glaucoma. The glymphatic system is responsible for the CSF/ISF interchange which allows the wash out of neurotoxic waste products from the brain. It is primarily dependent on Aquaporin-4 (AQP4) water channel containing astrocytes whose end-feet reside on the blood vessels surrounding the brain; facilitating the CSF/ISF flux along perivascular spaces [2,6,9].

Damage to this clearnace system leads to the accumulation of neurotoxic compounds, oxidative and inflammatory mediators, that are detrimental to retinal ganglion cells. Dysfunction in the optic nerve can disrupt axonal transport leading to increased neurodegeneration. In light of recent research linking glymphatic function to the pathophysiology of neurodegenerative disease, it is plausible that similar effects can also occur in the visual pathway [4,2].

Although the current human evidence base is restricted, a number of potentially valuable insights can be gleaned from the available literature. The three studies included in this review demonstrated altered glymphatic-related imaging markers in various optic nerve injuries. For example, diffusion tensor imaging along the perivascular space (DTI-ALPS) has shown reduced glymphatic activity in patients with normal-tension glaucoma and there has been a correlation between glymphatic dysfunction and cortical activity as well as visual field loss [5].

Functional MRI studies assessing BOLD-CSF coupling found correlations between glymphatic function and retinal nerve fiber layer damage as well as between IOP and primary open-angle glaucoma [8]. These recent studies have also shown that the extent of glymphatic dysfunction varies with disease activity and severity in patients with Thyroid Eye Disease (TED) suggesting an evolving inflammatory process and potential involvement of the ocular glymphatic system [10].

Table 1: Summary of Study Design, Population, Methods and Key Findings on Glymphatic Dysfunction in Optic Nerve Disorders

Study	Design	Population	Methods	Main Findings
Zhang *et al.* [10]	Case-Control using Diffusion Tensor Imaging (DTI) analysis	47 patients with TED, including 20 active TED Patients (AP) and 27 inactive TED Patients (IP), along with 24 Healthy Controls (HC)		Patients with TED have lymphatic system impairment, to varying degrees depending on the course and severity of the illness.
Li *et al.* [5]	Observational study	Normal-tension glaucoma patients Vs controls (37 NTG Vs 37 NC)	DTI-ALPS & resting-state fMRI	Significantly reduced ALPS index in NTG; associated with cortical ALFF and visual field deficits
Sheng *et al.* [8]	Observational study	Primary Open-Angle Glaucoma (POAG) Vs controls	Functional MRI + BOLD-CSF coupling, CP volume metrics	Negative correlations of glymphatic functional indicators with the thickness of the Retinal Nerve Fibre Layer (RNFL) (r from -0.427 to -0.351, p from 0.033 to 0.045) were observed and positive correlations between BOLD-CSF of the posterior region and intraocular pressure were found (r = 0.375, p = 0.033).

Abbreviations: CSF, Cerebrospinal Fluid; DTI-ALPS, Diffusion Tensor Imaging Along the Perivascular Space; fMRI, functional Magnetic Resonance imaging; BOLD-CSF, Blood Oxygen Level-Dependent–Cerebrospinal Fluid Coupling; TED, Thyroid Eye Disease; NTG, Normal-Tension Glaucoma; POAG, Primary Open-Angle Glaucoma; RNFL, Retinal Nerve Fiber Layer

Interestingly enough, the authors are unable to find any serious issues with their conclusion given the existing body of research that is limited by small sample size, cross-sectional design and by relying on imaging biomarkers that only observe the glymphatic system indirectly. Most concerning is that that none of the papers in the field have yet to include a longitudinal or intervention study to confirm that impaired glymphatic flow actually impacts any aspect of disease pathology.

A particularly relevant consequence of the impaired glymphatic function is that it may explain the occurrence of optic nerve damage which cannot be attributed to the known Intraocular Pressure (IOP) effects. Hence, normal-tension glaucoma is a clinical condition characterized by progressive optic nerve degeneration in eyes with intraocular pressure within the statistically normal range. The studies included in this review strongly suggest that decreased CSF dynamics and altered translaminar pressure gradients may lead to decreased glymphatic clearance. These changes in CSF and glymphatic function may thus be involved in the pathogenesis of normal-tension glaucoma [2,5].

Additional risk factors that may contribute to the pathogenesis of OND include modulators of glymphatic function, such as sleep, blood flow and intracranial pressure. For example, impaired sleep leads to reduced glymphatic clearance function and thus may lead to the accumulation of toxins within the CSF. Thus, an increased number of physiological factors may contribute to the pathogenesis of neuro-ophthalmic disease than is currently recognized.

However, the clinical implications of aqueous humour drainage through the scleral spur remain purely theoretical. To date, there is no evidence that suggests its alteration would necessitate clinical intervention in routine ophthalmic practice, at least until the similarly theoretical evidence for the glymphatic system is borne out in humans.

Very limited human studies have been performed. Only 3 studies met the inclusion criteria for this review. A substantial body of theoretical and experimental work has advanced the knowledge of glymphatic physiology, yet very little of this has been translated to the human or at least has not reached publications in the major journals. In fact, the anatomy and physiology of the human optic nerve may be somewhat different from that found in rodents and other commonly used animals [11].

Moreover, the lack of standardisation in imaging techniques and methodological variability in studies hampers direct comparison of findings. There is also no formal risk-of-bias assessment available.

One more significant gap is related to the disease-specific studies in the glymphatic field. Although glaucoma has been investigated a bit more, other optic neuropathies are studied far less. The temporal relationship between the onset of glymphatic dysfunction and disease progression also remains poorly understood.

We think that future studies should endeavour to recruit larger cohorts of human participants in prospective and longitudinal studies. Further research may also involve the use of high-resolution MRI as well as other multimodal imaging techniques in order to further elucidate glymphatic function in vivo and that the imaging and outcome measures be uniformly standardized.

Other potential avenues of research include incorporating the results of animal studies into clinical trials, as there is currently a significant gap in knowledge of disease mechanisms that would be filled by such work. Another possibility is investigating modifiable risk factors such as sleep, vascular function and intracranial pressure. In all of these cases, learning more about traumatic brain injury could potentially open doors to earlier intervention and the prevention of long-term complications of the condition.

Glymphatic dysfunction is emerging as a developing concept in neuro-ophthalmology. The authors reviewed the existing literature on glymphatic dysfunction in relation to optic nerve disease, including glaucoma. The evidence to date suggests that glymphatic dysfunction is associated with optic nerve disease, but there is not yet enough information to determine whether it is a cause or consequence of the disease. At this time, glymphatic dysfunction is more of a working hypothesis for understanding optic nerve disease, rather than a proven pathophysiology.

Limitations

A key limitation of this narrative review is the much of mechanistic understanding of the ocular glymphatic system including its flow dynamics, regulation and role in disease is derived from animal models, particularly rodents. Direct translation of these findings to human optic nerve physiology involves significant uncertainty due to anatomical, physiological and scale-related differences between species. Additionally, Human studies in this area remain limited in number and are largely observational, often relying on imaging techniques like high-resolution MRI.

CONCLUSION

Emerging research indicates that the glymphatic system plays a potentially significant role in maintaining optic nerve health and may contribute to its pathology. A growing body researches suggest that impaired glymphatic clearance could heighten optic nerve vulnerability through several interconnected mechanisms: the buildup of metabolic waste products, disruption of normal fluid dynamics and the amplification of neuroinflammatory responses.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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