

CARLA FERNANDA OLIVEIRA GUIMARÃES

**DISFUNÇÃO DO SISTEMA GLINFÁTICO E SUA RELAÇÃO COM DOENÇAS
NEURODEGENERATIVAS: UMA REVISÃO INTEGRATIVA DA LITERATURA**

Ji-Paraná
2026

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Artigo Científico apresentado ao Afya Centro Universitário de Ji-Paraná, como parte dos requisitos para obtenção de nota no Trabalho de Conclusão de Curso no Curso de Medicina, sob orientação do (a) Professor Médico Charles Anthony de Barros e Co-orientação do Professor Jerônimo Vieira Dantas Filho.

**Ji-Paraná
2026**

Dados Internacionais de Catalogação na Publicação - CIP

G963d Guimarães, Carla Fernanda Oliveira.
Disfunção do sistema glinfático e sua relação com doenças neurodegenerativas: uma revisão integrativa da literatura. / Carla Fernanda Oliveira Guimarães; Hilana Cristinna Gomes Nascimento; Renata Angelina Moura Oliveira. – Ji-Paraná, 2026.
19 p.; il.
Artigo Científico (Curso de Medicina) – Afya Centro Universitário de Ji-Paraná, 2026.
Orientador: Prof. Dr. Jerônimo Vieira Dantas Filho.
Co-orientação: Prof. Dr. Charles Anthony de Barros.
Co-orientação: Prof.^a Dra. Natalia Malavasi Vallejo.
1. Envelhecimento. 2. Fisiologia do Sono. 3. Homeostase Cerebral. 4. Linfáticos Meníngeos. I. Nascimento, Hilana Cristinna Gomes. II. Oliveira, Renata Angelina Moura. III. Dantas Filho, Jerônimo Vieira. IV. Barros, Charles Anthony de. V. Vallejo, Natalia Malavasi. VI. Título.
CDU 616.894

Ficha Catalográfica Elaborada pelo Bibliotecário Giordani Nunes da Silva CRB 11/1125



**GLYMPHATIC SYSTEM DYSFUNCTION AND ITS RELATIONSHIP
WITH NEURODEGENERATIVE DISEASES: NA INTEGRATIVE
LITERATURE REVIEW**

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DE LA LITERATURA**

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DOI: 10.54890/dcs.v23i88.4820

Recibido: 03/03/2026 | Aceptado: 05/03/2026 | Publicación en línea: 13/03/2026.

ABSTRACT

This integrative review aimed to synthesize scientific evidence on the relationship between glymphatic system dysfunction and neurodegenerative diseases, contributing theoretical support for advances in prevention, early diagnosis, and clinical management. The study followed Whittlemore and Knaff's methodology and adopted the PICO strategy to guide selection of articles addressing glymphatic alterations and their association with disorders such as Alzheimer's and Parkinson's disease. Searches conducted in PubMed, Scopus, Web of Science, Scielo, and LILACS (2015–2025) identified peer-reviewed studies across experimental, clinical, observational, and review designs. The findings consistently demonstrate that impaired glymphatic clearance—driven by AQP4 depolarization, vascular stiffness, sleep disruption, and aging—promotes the accumulation of neurotoxic proteins including β -amyloid, tau, and α -synuclein. Evidence also highlights the role of meningeal lymphatic drainage, hydrodynamic forces, and sleep physiology in maintaining clearance efficiency. Emerging imaging biomarkers such as DTI-ALPS provide promising avenues for early detection of glymphatic impairment, while therapeutic perspectives include improving slow-wave sleep, optimizing cardiovascular function, and modulating AQP4 organization. Overall, the review indicates that glymphatic

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Curso: medicina
Título do trabalho: Disfunção do sistema glinfático e sua relação com doenças neurodegenerativas: uma revisão integrativa da literatura
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SUMÁRIO

	PÁGINA DE TÍTULOS DO ARTIGO.....	05
	ABSTRACT.....	06
	RESUMO.....	07
1	INTRODUÇÃO.....	08
2	METODOLOGIA.....	09
3	RESULTADOS.....	11
4	CONCLUSÃO.....	18
5	REFERÊNCIAS BIBLIOGRÁFICAS.....	20

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dysfunction is a potentially early and modifiable mechanism underlying neurodegeneration, reinforcing its relevance as a target for preventive strategies and disease-modifying interventions.

Keywords: Aging. Brain Homeostasis. Meningeal Lymphatics. Sleep Physiology.

RESUMO

Esta revisão integrativa teve como objetivo sintetizar as evidências científicas que relacionam a disfunção do sistema glinfático ao desenvolvimento e à progressão de doenças neurodegenerativas, oferecendo suporte teórico para avanços em prevenção, diagnóstico precoce e manejo clínico. O estudo seguiu a metodologia de Whittemore e Knafl e utilizou a estratégia PICO para selecionar estudos que abordassem alterações glinfáticas associadas a doenças como Alzheimer e Parkinson. As buscas realizadas nas bases PubMed, Scopus, Web of Science, SciELO e LILACS (2015–2025) incluíram estudos experimentais, clínicos, observacionais e revisões. Os achados demonstram de forma consistente que a redução da clearance glinfática, influenciada pela despolarização de AQP4, rigidez vascular, distúrbios do sono e envelhecimento, favorece o acúmulo de proteínas neurotóxicas, como β -amiloide, tau e α -sinucleína. Evidências adicionais destacam o papel dos linfáticos meníngeos, das forças hidrodinâmicas e da fisiologia do sono na manutenção da eficiência de depuração. Biomarcadores emergentes, como o DTI-ALPS, mostram potencial para detecção precoce, enquanto perspectivas terapêuticas incluem otimização do sono de ondas lentas, controle cardiovascular e modulação da AQP4. Conclui-se que a disfunção glinfática é mecanismo precoce e modificável da neurodegeneração, configurando alvo promissor para estratégias preventivas e intervenções modificadoras da doença.

Palavras-chave: Envelhecimento. Fisiologia do Sono. Homeostase Cerebral. Linfáticos Meníngeos.

RESUMEN

Esta revisión integradora tuvo como propósito sintetizar la evidencia científica que relaciona la disfunción del sistema glinfático con el desarrollo y la progresión de enfermedades neurodegenerativas, proporcionando una base teórica para avanzar en estrategias de prevención, diagnóstico temprano y manejo clínico. El estudio siguió la metodología de Whittemore y Knafl y utilizó la estrategia PICO para seleccionar investigaciones que abordaran alteraciones glinfáticas asociadas a enfermedades como Alzheimer y Parkinson. Las búsquedas realizadas en PubMed, Scopus, Web of Science, SciELO y LILACS (2015–2025) incluyeron estudios experimentales, clínicos, observacionales y revisiones. Los hallazgos muestran consistentemente que la reducción de la depuración glinfática, influenciada por la despolarización de AQP4, la rigidez vascular, las alteraciones del sueño y el envejecimiento, favorece la acumulación de proteínas neurotóxicas como β -amiloide, tau y α -sinucleína. Además, la literatura destaca la importancia del drenaje linfático meníngeo, las fuerzas hidrodinámicas y la fisiología del sueño en la eficiencia de limpieza cerebral. Biomarcadores emergentes como DTI-ALPS ofrecen potencial para la detección precoz, mientras que enfoques terapéuticos incluyen la optimización del sueño profundo, el control cardiovascular y la modulación de AQP4. En conjunto, la disfunción glinfática surge como un mecanismo temprano y modificable de la neurodegeneración.

Palabras clave: Envejecimiento. Fisiología del Sueño. Homeostasis Cerebral. Linfáticos Meníngeos.



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INTRODUCTION

Neurodegenerative diseases represent one of the greatest challenges to global public health and contemporary science. Marked by a slow, progressive, and irreversible process of neuronal degeneration, these pathologies directly affect cognitive, motor, and behavioral functions, culminating in the loss of patients' autonomy and functional independence. It is estimated that, by 2050, the number of people diagnosed with Alzheimer's disease and other forms of dementia may triple worldwide, impacting not only healthcare systems but also families and society (Tourinho *et al.*, 2023). This exponential growth is closely related to population aging, a phenomenon that reinforces the urgency of understanding the underlying mechanisms of these diseases.

Among the main conditions are Alzheimer's disease, responsible for 60% to 70% of dementia cases, Parkinson's disease, and Amyotrophic Lateral Sclerosis (ALS), all characterized by neurodegenerative changes that compromise essential brain circuits (WHO, 2021). Despite advances in recent decades, available treatments remain limited, acting predominantly on symptomatic relief and lacking proven efficacy in halting or reversing the progression of neuronal degeneration (Garcia *et al.*, 2023). This highlights the need for new perspectives that broaden the understanding of the pathophysiology of these diseases and open space for innovative therapeutic approaches.

In this context, the glymphatic system emerges as a promising hypothesis. Initially described by Iliff *et al.* (2012), this mechanism plays an essential role in maintaining brain homeostasis by promoting the clearance of metabolic waste accumulated in the parenchyma, especially during deep sleep. Through cerebrospinal fluid (CSF), which circulates driven by the action of glial cells, the glymphatic system facilitates the removal of neurotoxic metabolites, such as beta-amyloid and tau proteins, whose deposition is strongly associated with the pathogenesis of Alzheimer's disease and other neurodegenerative conditions (Rasmussen *et al.*, 2018; Nedergaard; Goldman, 2020; Hablitz; Nedergaard, 2020).

Recent studies suggest that dysfunction in this system may reduce the brain's clearance capacity, contributing to the accumulation of abnormal proteins and, consequently, to the progression

of neurodegenerative diseases (Ding *et al.*, 2022; Paganelli *et al.*, 2022). In addition, factors such as aging, sleep disorders, chronic inflammation, and traumatic brain injuries have been identified as potential negative modulators of glymphatic efficiency. Nevertheless, despite growing scientific evidence regarding its relevance, important gaps remain concerning the functioning of the glymphatic system at different stages of life and its direct relationship with the pathophysiological processes of neurodegeneration.

Considering this context, the following question emerges: could impairment of the glymphatic system be directly related to the pathogenesis of neurodegenerative diseases, contributing to the accumulation of neurotoxic proteins and, consequently, to the progression of neurodegeneration? Addressing this question is of utmost importance, as it may provide a solid foundation for the development of new therapeutic and preventive strategies aimed at improving glymphatic function, paving the way for interventions that may help delay or even prevent the progression of these diseases, which represent one of the greatest challenges in modern medicine.

The present study aims to describe and analyze, through an integrative literature review, the scientific evidence linking glymphatic system function to the development and progression of neurodegenerative diseases. It seeks to contribute to a deeper discussion on the topic by providing theoretical support that may assist future research focused on prevention, early diagnosis, and clinical management of these conditions, which remain among the greatest challenges of contemporary medicine.

METHODOLOGY

This study was designed as an integrative literature review aimed at gathering, analyzing, and synthesizing scientific evidence regarding glymphatic system dysfunction and its relationship with neurodegenerative diseases. The integrative review method was chosen because it allows the inclusion of experimental, observational, and review studies, providing a comprehensive and critical understanding of the available literature. The methodological framework followed the six stages proposed by Whittemore and Knafl, ensuring rigor and systematic organization throughout the research process.

The research question was structured according to the PICO strategy (Population, Intervention/Exposure, Comparison, Outcome), which guided the search, selection, and analysis of the studies. The components were defined as follows: P (Population): studies involving human subjects or

experimental models addressing the glymphatic system; I (Intervention/Exposure): assessment of alterations, dysfunctions, or modulators of the glymphatic system; C (Comparison): individuals or models without glymphatic dysfunction or presenting normal functional parameters; and O (Outcome): association with the development, progression, prevention, or pathophysiological mechanisms of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and related disorders.

The study was conducted remotely through systematic searches in recognized scientific databases: PubMed, Scopus, Web of Science, SciELO, and LILACS. Controlled descriptors were identified using the DeCS (Health Sciences Descriptors) and MeSH terms, ensuring terminological standardization. The main descriptors included: "glymphatic system," "glymphatic dysfunction," "brain clearance," "metabolite clearance," "neurodegenerative diseases," "Alzheimer disease," and "Parkinson disease." These terms were combined using Boolean operators AND and OR to refine the search strategy. A representative search string applied in the databases was: ("glymphatic system" OR "glymphatic dysfunction" OR "brain clearance") AND ("neurodegenerative diseases" OR "Alzheimer disease" OR "Parkinson disease") AND ("pathophysiology" OR "disease progression").

The temporal filter included studies published within the last ten years (2015–2025), ensuring that the review reflects the most current scientific evidence on the topic. Articles published in English, Portuguese, and Spanish were considered eligible, broadening the scope of analysis and increasing the diversity of scientific contributions. Only peer-reviewed articles published in indexed scientific journals were included to ensure methodological quality and reliability.

Inclusion criteria comprised experimental studies (including laboratory and preclinical research), clinical trials, observational studies (cross-sectional, cohort, and case-control), systematic reviews, and meta-analyses addressing the relationship between glymphatic system function or dysfunction and neurodegenerative diseases. Exclusion criteria included conference abstracts, editorials, letters to the editor, undergraduate theses, dissertations, duplicated articles, and studies not available in full text. Articles that did not directly address the proposed PICO components were also excluded after screening.

The selection process followed a structured sequence. Initially, all identified records were exported to a reference management system, and duplicates were removed. Subsequently, titles and abstracts were screened according to the predefined eligibility criteria. Studies considered potentially relevant were submitted to full-text reading for final eligibility assessment. The selection process was conducted systematically to minimize bias and ensure transparency.

Data extraction was performed using a standardized form developed by the authors, including the following variables: author(s), year of publication, country of origin, study design, sample characteristics, evaluation methods of the glymphatic system, main outcomes related to neurodegenerative diseases, and reported limitations. The extracted data were organized into thematic categories to facilitate comparison and synthesis of findings.

The methodological quality of the included studies was critically appraised according to their design, considering aspects such as sample size, control of confounding variables, reproducibility of methods, and clarity of reported outcomes. This critical evaluation contributed to a more robust interpretation of the evidence and to the identification of potential methodological limitations within the literature.

Data analysis was conducted qualitatively through content analysis. A narrative synthesis was developed to identify convergences, divergences, and emerging patterns among the studies. The findings were organized into thematic axes, such as glymphatic dysfunction mechanisms, accumulation of neurotoxic proteins (e.g., beta-amyloid and alpha-synuclein), imaging evidence of glymphatic impairment, and potential therapeutic or preventive implications.

As this study is based exclusively on previously published secondary data and does not involve direct experimentation with human or animal subjects, ethical committee approval was not required. Nevertheless, all ethical principles of scientific research were respected, including accurate citation of sources and maintenance of academic integrity.

Through this rigorous methodological approach, the integrative review aims to provide a comprehensive and updated synthesis of the scientific evidence linking glymphatic system dysfunction to neurodegenerative diseases, offering theoretical support for future research focused on prevention, early diagnosis, and clinical management strategies.

RESULTS

Table 1 summarizes the principal studies included in this integrative review on the glymphatic system. It presents three columns: article title, citation (author/year), and main findings. The selected studies encompass foundational experimental research, narrative and systematic reviews, imaging investigations, and translational analyses. Collectively, they describe the anatomical basis of the glymphatic pathway, including perivascular spaces and aquaporin-4 polarization, as well as its physiological drivers such as sleep and arterial pulsatility. The table also highlights evidence linking

glymphatic dysfunction to aging, neurodegenerative diseases, cardiovascular risk factors, and neuroinflammation, while outlining emerging diagnostic imaging techniques and therapeutic perspectives.

Table 1

Summary of Articles Included in the Integrative Review on the Glymphatic System.

Article Title	Citation (Author/Year)	Main Results
A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β	Iliff <i>et al.</i> , 2012	First formal description of the glymphatic system as a glia-dependent paravascular clearance pathway. Demonstrated CSF influx through periarterial spaces, exchange with interstitial fluid, and β -amyloid clearance.
Sleep Drives Metabolite Clearance from the Adult Brain	Xie <i>et al.</i> , 2013	Showed glymphatic activity increases during NREM sleep with ~60% expansion of interstitial space, enhancing metabolic waste clearance.
The Glymphatic System and Waste Clearance with Brain Aging: A Review	Nedergaard, 2015	Identified aging-related AQP4 depolarization as a key factor in reduced clearance efficiency and increased neurodegenerative risk.
The Glymphatic Pathway in Neurological Disorders	Rasmussen; Nedergaard; Iliff, 2018	Highlighted glymphatic dysfunction as an upstream mechanism in neurodegenerative diseases and discussed imaging advances.
Aquaporin-4 in Brain Health and Disease	Papadopoulos; Verkhratsky, 2013	Identified AQP4 polarization in astrocytic endfeet as critical for glymphatic efficiency.
Impairment of Paravascular Clearance Pathways in the Aging Brain	Kress <i>et al.</i> , 2014	Demonstrated aging reduces glymphatic clearance due to AQP4 depolarization, contributing to β -amyloid accumulation.
The Meningeal Lymphatic System: A New Player in CNS Immunity	Louveau <i>et al.</i> , 2015	Demonstrated anatomical continuity between CNS and cervical lymph nodes, integrating meningeal lymphatics with glymphatic drainage.
The Glymphatic System: A Novel Component of Fundamental Neurobiology	Hablit; Nedergaard, 2020	Described arterial pulsatility, respiration, vasomotion, and osmotic gradients as drivers of glymphatic flow.
Glymphatic Dysfunction in Alzheimer's Disease	Aguzzi; Liu, 2022	Strengthened recognition of glymphatic failure as a contributor to protein aggregation and therapeutic target.
Emerging Concepts in Glymphatic Imaging and Therapy	Harrison; Kaye; Nedergaard, 2023	Highlighted advanced MRI techniques (e.g., DTI-ALPS) and proposed glymphatic modulation as preventive strategy.
α -Synuclein Clearance and	Ding <i>et al.</i> , 2022	Demonstrated impaired

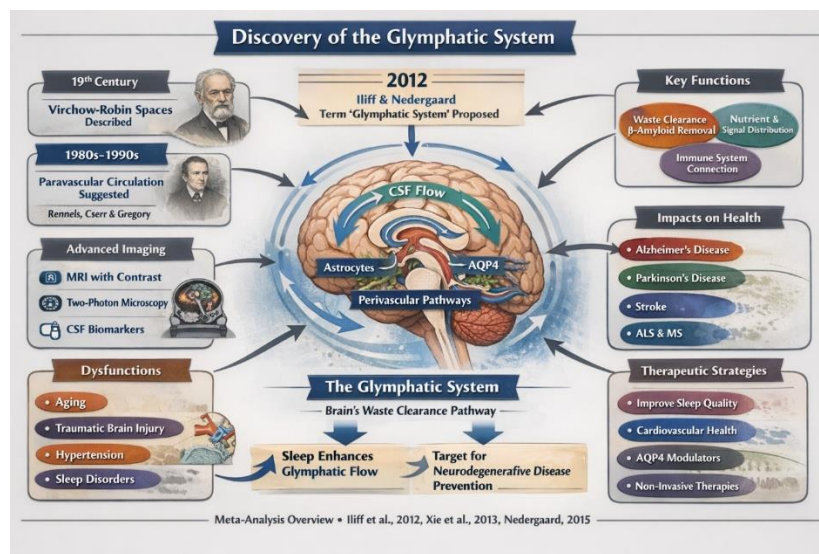
Glymphatic Function in Parkinson's Disease		glymphatic clearance of α -synuclein and suggested AQP4 modulation as therapy.
Glymphatic Alterations in Parkinson's Disease	Benfredj <i>et al.</i> , 2022	Identified reduced glymphatic efficiency associated with Lewy body formation and dopaminergic neuronal loss.
Imaging Biomarkers of Glymphatic Dysfunction in Parkinson's Disease	Zhang <i>et al.</i> , 2023	Reported DTI-ALPS alterations as potential early biomarkers of glymphatic impairment.
Glymphatic Impairment in Neuroinflammatory Disorders	Paganelli <i>et al.</i> , 2022	Demonstrated disruption of AQP4 organization in inflammatory conditions such as multiple sclerosis.
Cardiovascular Risk Factors and Glymphatic Flow	Jin <i>et al.</i> , 2016	Identified hypertension and reduced arterial pulsatility as contributors to impaired perivascular clearance.
Arterial Stiffness and Brain Clearance Mechanisms	Plá <i>et al.</i> , 2021	Showed vascular stiffness reduces glymphatic transport efficiency.
Hypertension-Induced Glymphatic Dysfunction	Wang <i>et al.</i> , 2022	Demonstrated chronic hypertension compromises perivascular dynamics and metabolic waste removal.
Glymphatic Flow and Cerebrovascular Injury	Silva <i>et al.</i> , 2023	Associated chronic sleep deprivation and vascular impairment with increased protein accumulation and neurodegenerative risk.

Source: Authors archives.

The integrative literature review demonstrates that the glymphatic system has emerged as a central physiological mechanism linking cerebral homeostasis to the development and progression of neurodegenerative diseases. The evidence analyzed consistently indicates that impaired glymphatic clearance is associated with the accumulation of neurotoxic proteins, sleep disturbances, vascular dysfunction, and age-related neurodegeneration. Collectively, the selected studies support the hypothesis that glymphatic dysfunction may represent an early and potentially modifiable event in the pathophysiological cascade of several neurological disorders (Figure 1).

Figure 1

Glymphatic System: An Integrative Review of Brain Clearance, Physiology, and Neurodegeneration.



Source: Authors archives. Title: Illustration created from the information collected and produced by Copilot.

The historical and conceptual consolidation of the glymphatic system reflects a progressive scientific evolution. Early anatomical observations by Rudolf Virchow describing perivascular spaces laid the foundation for understanding fluid exchange pathways in the brain. However, it was only in 2012 that Iliff *et al.* (2012) formally described the glymphatic system as a glia-dependent perivascular clearance network responsible for cerebrospinal fluid (CSF) circulation and metabolic waste removal. This discovery represented a paradigm shift in neuroscience. Subsequent investigations reinforced and expanded this framework. Xie *et al.* (2013) demonstrated that glymphatic activity increases significantly during slow-wave (NREM) sleep, establishing a direct physiological link between sleep and metabolic detoxification. Later comprehensive reviews (Nedergaard, 2015; Rasmussen; Nedergaard; Iliff, 2018) consolidated the concept, identifying glymphatic dysfunction as a potential upstream factor in neurodegenerative processes. More recent contributions (Aguzzi; Liu, 2022; Harisson; Kaye; Nedergaard, 2023) further strengthen the recognition of the glymphatic system as a promising diagnostic and therapeutic target.

From an anatomical and physiological perspective, the literature consistently identifies perivascular (Virchow–Robin) spaces, astrocytic end feet enriched with aquaporin-4 (AQP4) channels, and cerebrospinal fluid circulation integrated with meningeal lymphatic drainage as the core structural components of the glymphatic system. Iliff *et al.* (2012) and Nedergaard (2015) describe the glymphatic pathway as a convective mechanism in which CSF enters periarterial spaces, exchanges with interstitial fluid (ISF), and exits through perivenous routes toward meningeal

lymphatic vessels. Louveau *et al.* (2015) demonstrated anatomical continuity between the central nervous system and cervical lymph nodes, challenging the traditional concept of the brain as entirely immune-privileged. The polarization of AQP4 channels on astrocytic endfeet is identified as a decisive factor for glymphatic efficiency (Papadopoulos; Verkhratsky, 2013; Rasmussen; Nedergaard; Iliff, 2018). Aging, inflammation, and trauma disrupt this polarization and significantly reduce clearance capacity (Kress *et al.*, 2014; Zhao *et al.*, 2022). Physiologically, glymphatic flow is driven by arterial pulsatility, respiratory dynamics, vasomotion, and osmotic gradients (Hablitz; Nedergaard, 2020), supporting its classification as an active convective transport system rather than a passive diffusion process.

The functional roles of the glymphatic system extend beyond metabolic clearance. The reviewed evidence demonstrates that the system operates along three primary axes: metabolic waste removal, nutrient and signaling molecule distribution, and immune communication. Iliff *et al.* (2012) and Xie *et al.* (2013) provide experimental evidence that β -amyloid and tau proteins are cleared via glymphatic pathways. In models lacking functional AQP4, clearance efficiency is drastically reduced, accelerating pathological accumulation (Kress *et al.*, 2014). In addition to detoxification, glymphatic circulation contributes to the distribution of glucose, amino acids, lipids, and neuromodulators throughout the brain (Nedergaard, 2015; Guyton; Hall, 2017), reinforcing its broader role in maintaining metabolic and synaptic homeostasis. Sleep emerges as a central regulator of this process. Xie *et al.* (2013) demonstrated approximately 60% expansion of interstitial space during NREM sleep, markedly enhancing glymphatic flow. Chronic sleep deprivation compromises this mechanism and is associated with increased protein accumulation and heightened neurodegenerative risk (Hablitz; Nedergaard, 2020; Silva *et al.*, 2023).

A strong association between glymphatic dysfunction and neurodegenerative diseases is consistently reported across the analyzed studies. In Alzheimer's disease, impaired clearance of β -amyloid and tau proteins is directly linked to glymphatic failure (Iliff *et al.*, 2012; Xie *et al.*, 2013). Age-related AQP4 depolarization appears as a potential early event preceding clinical cognitive decline (Kress *et al.*, 2014; Nedergaard, 2015). In Parkinson's disease, inefficient removal of α -synuclein contributes to Lewy body formation and dopaminergic neuronal loss (Ding *et al.*, 2022; Benfredj *et al.*, 2022; Zhang *et al.*, 2023). Inflammatory conditions such as Multiple sclerosis demonstrate disruption of AQP4 organization secondary to chronic inflammation (Paganelli *et al.*, 2022), while preliminary findings suggest possible involvement in Amyotrophic lateral sclerosis (Rasmussen; Nedergaard; Iliff, 2018). Cerebrovascular events, including Stroke, impair the

hydrodynamic forces necessary for glymphatic circulation, contributing to long-term cognitive deficits (Hablitz; Nedergaard, 2020). Furthermore, hypertension and arterial stiffness reduce perivascular pulsatility, compromising clearance efficiency and establishing a mechanistic link between cardiovascular disease and neurodegeneration (Jin *et al.*, 2016; Plá *et al.*, 2021; Wang *et al.*, 2022).

Advances in diagnostic imaging and biomarker research have provided indirect and direct methods to assess glymphatic function. Contrast-enhanced magnetic resonance imaging allows visualization of paravascular flow in humans (Rasmussen; Nedergaard; Iliff, 2018), while two-photon microscopy enables real-time observation in animal models (Iliff *et al.*, 2012). Biomarkers in CSF and plasma, including β -amyloid, tau, and α -synuclein, serve as indirect indicators of impaired clearance (Ding *et al.*, 2022). Positron emission tomography (PET) imaging quantifies protein deposition and complements structural imaging findings. Additionally, the evaluation of meningeal lymphatic drainage has expanded understanding of the interface between immune surveillance and glymphatic activity (Louveau *et al.*, 2015). Emerging MRI techniques such as DTI-ALPS have been proposed as potential early biomarkers for glymphatic dysfunction, particularly in Alzheimer's and Parkinson's disease.

Therapeutically, the literature suggests that enhancing glymphatic function may represent a paradigm shift from symptomatic management to preventive intervention. Strategies aimed at optimizing slow-wave sleep (Xie *et al.*, 2013), controlling cardiovascular risk factors (Hablitz; Nedergaard, 2020), and pharmacologically modulating AQP4 expression or polarization (Ding *et al.*, 2022) are highlighted as promising approaches. Non-invasive neuromodulation and respiratory-based interventions have also shown experimental potential in improving glymphatic flow (Paganelli *et al.*, 2022). The concept of a "flow therapy" model emerges from this body of evidence, proposing enhancement of cerebral drainage before irreversible protein aggregation occurs.

In summary, the integrative review confirms that glymphatic dysfunction represents a converging pathophysiological mechanism linking aging, sleep disturbance, vascular impairment, inflammation, and neurodegeneration. The evidence supports the interpretation that impaired metabolic clearance may precede and accelerate neuronal damage. The interrelationship among slow-wave sleep, AQP4 polarization, arterial pulsatility, and protein clearance establishes a multidimensional framework integrating neurology, cardiovascular medicine, and sleep science. Thus, the glymphatic system should be regarded as a central determinant of long-term neurological

health, with significant implications for early diagnosis, prevention strategies, and the development of disease-modifying interventions for neurodegenerative disorders.

DISCUSSION

The findings of this integrative review consolidate the glymphatic system as a central mechanism linking cerebral homeostasis to the development and progression of neurodegenerative diseases. Across the analyzed literature, impaired glymphatic clearance consistently emerges as a potential upstream event in the pathological cascade, particularly in conditions characterized by toxic protein accumulation. Rather than being a secondary consequence of neuronal degeneration, glymphatic dysfunction appears to precede and possibly accelerate pathological processes, reinforcing its relevance as an early and modifiable risk factor (Benveniste *et al.*, 2019).

The historical evolution of this concept reflects a major paradigm shift in neuroscience. The formal characterization of the glymphatic system as a glia-dependent perivascular clearance pathway redefined the understanding of cerebrospinal fluid (CSF) dynamics and metabolic waste removal in the brain. Experimental evidence demonstrated that CSF enters periarterial spaces, exchanges with interstitial fluid, and exits along perivenous pathways, ultimately draining into meningeal lymphatic vessels. This convective mechanism, dependent on aquaporin-4 (AQP4) polarization in astrocytic endfeet, challenges the traditional view of the brain as a structure relying primarily on passive diffusion (Iliff *et al.*, 2012; Louveau *et al.*, 2015).

A strong point of convergence among the reviewed studies is the structural and functional importance of AQP4 channels. Aging, inflammation, and trauma disrupt AQP4 polarization, reducing clearance efficiency and facilitating protein accumulation (Kress *et al.*, 2014). This mechanism is particularly relevant in Alzheimer's disease, in which impaired removal of β -amyloid and tau proteins is closely associated with glymphatic failure. Reviews published in Elsevier journals emphasize that age-related decline in glymphatic function may represent an early contributor to amyloid deposition, linking vascular alterations and metabolic clearance deficits to cognitive decline (Benveniste *et al.*, 2019; Rasmussen *et al.*, 2018).

Sleep physiology constitutes another robust axis of convergence. Experimental studies demonstrated that slow-wave (NREM) sleep significantly enhances glymphatic activity by expanding interstitial space and facilitating convective flow. Conversely, chronic sleep deprivation impairs clearance capacity and increases β -amyloid accumulation, strengthening the mechanistic link between

sleep disturbances and neurodegeneration (Hablitz & Nedergaard, 2020). These findings integrate sleep medicine with neurodegenerative research and suggest that behavioral factors may influence long-term neurological outcomes through modulation of glymphatic dynamics.

In Parkinson's disease, the literature similarly identifies inefficient α -synuclein clearance as a relevant factor in Lewy body formation and dopaminergic neuronal loss. Although the molecular substrates differ from Alzheimer's pathology, both conditions share a common clearance deficit model, reinforcing glymphatic dysfunction as a convergent pathogenic pathway (Ding *et al.*, 2022). Moreover, cerebrovascular conditions such as hypertension and arterial stiffness reduce arterial pulsatility—one of the primary driving forces of glymphatic flow, thereby establishing a mechanistic bridge between cardiovascular disease and neurodegeneration (Plá *et al.*, 2021).

Despite these convergences, divergences persist. Much of the mechanistic evidence originates from rodent models using two-photon microscopy, raising questions regarding direct translation to humans. While advanced imaging techniques such as diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) and contrast-enhanced MRI provide indirect measures of glymphatic function, standardization remains limited. Additionally, debate continues regarding the relative contribution of bulk flow versus diffusion processes, indicating that aspects of glymphatic physiology are still evolving conceptually (Hablitz & Nedergaard, 2020).

Therapeutically, the literature suggests a paradigm transition from symptomatic treatment to modulation of clearance dynamics. Strategies targeting sleep optimization, cardiovascular risk control, and pharmacological modulation of AQP4 expression have been proposed as potential disease-modifying approaches. This emerging “flow-based” model highlights the possibility of intervening before irreversible protein aggregation and neuronal loss occur (Benveniste *et al.*, 2019).

In summary, the evidence supports glymphatic dysfunction as a unifying mechanism connecting aging, sleep disturbance, vascular impairment, and neurodegeneration. By synthesizing current findings, this review contributes to the literature by reinforcing the conceptual integration of metabolic clearance within neurodegenerative pathophysiology and by identifying promising avenues for early diagnosis and preventive intervention.

CONCLUSION

In conclusion, this integrative review demonstrates that the glymphatic system plays a central role in maintaining cerebral homeostasis and represents a critical link between sleep physiology,

vascular dynamics, aging, and neurodegeneration. The analyzed evidence consistently supports the association between impaired glymphatic clearance and the accumulation of neurotoxic proteins in disorders such as Alzheimer's disease and Parkinson's disease. Glymphatic dysfunction emerges as a potentially early and modifiable event, reinforcing its relevance as a promising target for preventive strategies, early diagnostic biomarkers, and the development of disease-modifying therapeutic interventions in contemporary neurology.

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