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Meningeal Lymphatic System in Neurodegenerative Disorders: A Systematic Review

Komang Trisna Sumadewi
Universitas Warmadewa, Indonesia
Email : trisna.sumadewi@warmadewa.ac.id

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Abstract

The meningeal lymphatic system has emerged as an important component of central nervous system fluid regulation and immune homeostasis, although its causal contribution to neurodegenerative disorders remains uncertain. This systematic review evaluated disease-specific evidence linking meningeal lymphatic function to Alzheimer's disease, Parkinson's disease, and aging-associated neuroimmune alterations. A structured literature search was conducted in PubMed, supplemented by publisher records and backward reference screening, to identify peer-reviewed English-language studies published between January 1, 2015, and October 7, 2026, that investigated meningeal or dural lymphatic structure and function in mammalian models or humans. Primary experimental studies and human imaging investigations were prioritized. Findings were synthesized narratively across three predefined domains because heterogeneity in experimental models, tracer systems, and outcome measures precluded quantitative meta-analysis. Experimental evidence suggested that impaired meningeal lymphatic drainage contributed to increased extracellular tau retention, alterations in selected amyloid-beta (Aβ) pathology measures, exacerbated alpha-synuclein (α-synuclein) pathology, heightened neuroinflammation, accumulation of senescent astrocytes, and oligodendrocyte loss. Human imaging studies also indicated reduced meningeal lymphatic drainage in patients with idiopathic Parkinson's disease. However, sustained meningeal lymphatic atrophy or expansion did not significantly alter overall amyloid plaque burden in two mouse models of Alzheimer's disease, suggesting potential compensatory clearance mechanisms and pathway-dependent effects. Collectively, these findings supported the interpretation that meningeal lymphatic vessels function as a potentially modifiable component of an interconnected cerebral clearance and neuroimmune regulatory network rather than as the sole rate-limiting determinant of pathological protein accumulation. Clinical translation will require standardized human lymphatic imaging protocols, longitudinal validation of disease-relevant biomarkers, and patient stratification according to disease stage to determine when impaired meningeal lymphatic drainage represents a therapeutically relevant limitation.

INTRODUCTION

Neurodegenerative disorders are characterized by progressive neuronal dysfunction and loss, frequently accompanied by abnormal protein accumulation, chronic neuroinflammation, and impaired homeostatic regulation. The traditional understanding of the central nervous

system (CNS) as largely isolated from conventional lymphatic drainage was substantially revised following the identification of functional lymphatic vessels within the dura mater. (Louveau et al., 2015) demonstrated the presence of lymphatic endothelial vessels along the dural venous sinuses that facilitated the transport of fluid and immune cells from the cerebrospinal fluid (CSF) compartment toward the cervical lymph nodes. Similarly, (Aspelund et al., 2015) independently demonstrated that dural lymphatic vessels participated in the drainage of CSF, interstitial fluid-derived solutes, and macromolecules. These discoveries established an anatomical pathway connecting cerebral fluid homeostasis with peripheral immune surveillance and challenged conventional assumptions regarding CNS immune isolation.

The translational significance of the meningeal lymphatic system was further supported by investigations involving humans and nonhuman primates. Absinta et al., (2017) visualized meningeal lymphatic vessels using magnetic resonance imaging (MRI) and confirmed the expression of lymphatic endothelial markers in primate meningeal tissues. Subsequent research identified anatomical connections between intracranial lymphatic drainage pathways and cervical lymph nodes, alongside aging-associated changes in cervical lymph node size and lymphatic channel morphology (Albayram et al., 2022). (Jacob et al., 2022) further characterized a conserved three-dimensional meningeal lymphatic network in mice and humans, including anterior lymphatic structures surrounding the cavernous sinus. Collectively, these findings demonstrated that meningeal lymphatic organization was not restricted to rodent models and provided a foundation for investigating aspects of lymphatic anatomy and drainage in living humans using noninvasive imaging techniques.

The meningeal lymphatic system exhibits considerable anatomical and functional heterogeneity, with distinct vascular regions contributing differently to CSF drainage and macromolecular transport. Ahn et al., (2019) identified basal meningeal lymphatic vessels as major sites of CSF macromolecule uptake and demonstrated aging-associated reductions in lymphatic vessel integrity and drainage capacity. (Yoon et al., 2024) extended these findings by identifying the nasopharyngeal lymphatic plexus as an important drainage pathway connecting cranial fluid outflow to the deep cervical lymph nodes. Their findings also indicated that this plexus underwent age-related regression, whereas downstream cervical collecting lymphatic vessels retained responsiveness to pharmacological modulation. These observations suggested that impaired cerebral fluid clearance during aging might arise from dysfunction at specific anatomical drainage pathways rather than uniform deterioration of the entire lymphatic network. Such regional differences are particularly relevant when interpreting experimental interventions intended to enhance meningeal lymphatic function.

Research on meningeal lymphatics has progressively expanded from anatomical characterization to investigations of their potential involvement in neurodegenerative disease mechanisms. In experimental models of Alzheimer's disease, impaired meningeal lymphatic drainage has been associated with alterations in amyloid-beta (Aβ) and tau clearance, microglial responses, neurovascular dysfunction, and reduced therapeutic responses to anti-amyloid interventions (Da Mesquita et al., 2018, 2021; Patel et al., 2019). In Parkinson's disease, experimental disruption of brain lymphatic drainage has been linked to increased alpha-

synuclein (α-synuclein) accumulation and exacerbated dopaminergic neurodegeneration, while human imaging investigations have reported reduced meningeal lymphatic drainage in patients with idiopathic Parkinson's disease (Ding et al., 2021; Zou et al., 2019). More recent investigations have broadened the biological relevance of this system by examining its relationships with astrocyte senescence, oligodendrocyte survival, remyelination, and neuroimmune regulation (Das Neves et al., 2024; Li et al., 2022). These findings suggest that meningeal lymphatic dysfunction may influence neurodegenerative processes through interconnected mechanisms involving protein clearance, glial responses, and immune homeostasis.

Despite these advances, important uncertainties remain regarding the causal contribution of meningeal lymphatic dysfunction to neurodegenerative pathology. Experimental findings demonstrating beneficial effects of enhanced lymphatic drainage have sometimes been interpreted as evidence that increasing meningeal lymphatic function consistently reduces pathological protein accumulation. However, this interpretation is not uniformly supported by available evidence. (Antila et al., 2024) demonstrated that sustained meningeal lymphatic atrophy or expansion altered CSF drainage toward cervical lymph nodes in APP/PS1 (APdE9) and 5xFAD mouse models without significantly changing overall cerebral amyloid plaque burden. Their findings further suggested that reduced lymphatic drainage could be partially compensated for by increased CSF transfer into the bloodstream. These observations highlighted the importance of alternative clearance pathways and indicated that changes in meningeal lymphatic drainage do not necessarily translate into corresponding changes in neuropathological outcomes. Consequently, the contribution of meningeal lymphatic dysfunction to neurodegeneration must be interpreted in relation to disease models, anatomical drainage routes, intervention timing, compensatory mechanisms, and the specific pathological or functional outcomes assessed.

A critical gap in the existing literature concerns the limited integration of disease-specific causal evidence with human translational findings and experimental results that challenge the presumed benefits of enhanced lymphatic drainage. Although previous reviews have established the anatomical and physiological importance of meningeal lymphatic vessels, differences in experimental approaches, disease stages, and outcome measurements have complicated the interpretation of their pathological significance. Furthermore, associations between reduced lymphatic drainage and neurodegenerative pathology do not independently establish whether lymphatic dysfunction represents an initiating mechanism, a contributor to disease progression, a compensatory response, or a secondary consequence of established pathology. Addressing these distinctions requires a systematic comparison of studies that directly manipulate meningeal lymphatic function, investigate disease-relevant outcomes, or assess lymphatic drainage in human populations. Such an approach is necessary to distinguish mechanistic evidence from observational associations and to identify the conditions under which meningeal lymphatic dysfunction may be therapeutically relevant.

The present systematic review addressed this gap by critically examining meningeal lymphatic function within an integrated framework of CSF dynamics, vascular clearance, glial activity, and immune surveillance. Rather than conceptualizing the meningeal lymphatic system as an isolated pathway for removing metabolic waste, the review considered its

interactions with complementary clearance mechanisms and neuroimmune processes. Particular emphasis was placed on evidence published since 2015, when the modern characterization of functional dural lymphatic vessels substantially advanced understanding of CNS fluid drainage. The analytical approach prioritized the directness of lymphatic measurements, appropriateness of experimental controls, consistency between pathological and functional outcomes, and relevance to human neurodegenerative conditions. By applying these considerations across different disease contexts, the review sought to clarify the extent to which experimental findings supported causal interpretations and whether these findings could reasonably inform clinical investigations

The principal contribution of this review was its disease-specific synthesis of evidence concerning meningeal lymphatic involvement in neurodegeneration. First, it evaluated the strength and consistency of experimental and translational evidence across Alzheimer's disease, Parkinson's disease, and aging-associated neuroimmune alterations, avoiding the assumption that neurodegenerative disorders share identical lymphatic mechanisms. Second, it examined methodological and biological factors underlying apparently conflicting findings, including alternative CSF clearance pathways, anatomical heterogeneity, disease-stage differences, and variability in outcome measurements. Third, it identified priorities for future investigations, particularly the development of standardized human lymphatic imaging protocols, longitudinal functional biomarkers, and disease-stage-specific approaches to evaluating lymphatic-targeted interventions. These contributions were intended to support a more precise interpretation of meningeal lymphatic dysfunction and its potential therapeutic significance.

Accordingly, the objective of this systematic review was to synthesize peer-reviewed evidence concerning meningeal lymphatic anatomy, function, and dysfunction in relation to Alzheimer's disease and pathological protein homeostasis, Parkinson's disease and α-synuclein pathology, and aging-associated neuroimmune and myelin-related mechanisms. Relevant studies were identified through structured PubMed searches, verification of publisher records, and backward reference screening. Primary experimental investigations and human imaging studies were prioritized, while existing reviews were consulted to establish the research context and identify unresolved questions. The synthesis aimed to distinguish experimentally supported mechanisms from observational associations, evaluate the consistency of findings across disease models and human populations, and identify methodological limitations affecting their interpretation. The findings may inform experimental research by emphasizing the importance of compensatory clearance pathways and disease-stage considerations, guide clinical investigations through a critical assessment of human imaging evidence, and support therapeutic development by identifying disease contexts and outcome measures most appropriate for evaluating meningeal lymphatic interventions.

METHOD

A structured literature search was conducted to identify relevant studies on meningeal lymphatic anatomy, function, and involvement in neurodegenerative disorders. PubMed served as the primary bibliographic database, supplemented by publisher records and backward

reference screening to verify bibliographic information and identify additional relevant primary studies. The search covered publications from January 1, 2015, through October 7, 2026.

The search strategy combined Boolean operators with terms related to meningeal lymphatic anatomy, cerebral fluid drainage, neurodegenerative disorders, and neuroimmune mechanisms. Keywords included “meningeal lymphatic,” “dural lymphatic,” “meningeal lymphatic vessels,” “cerebrospinal fluid drainage,” “deep cervical lymph nodes,” “neurodegenerative disease,” “Alzheimer's disease,” “Parkinson's disease,” “amyloid-beta,” “tau,” “alpha-synuclein,” “aging,” “neuroinflammation,” “oligodendrocytes,” “myelin,” “remyelination,” “vascular endothelial growth factor C,” and “magnetic resonance imaging.” Search combinations were refined iteratively to identify additional disease-specific studies and relevant lymphatic drainage pathways.

Eligible studies comprised peer-reviewed English-language articles presenting direct evidence of meningeal or dural lymphatic structure or function in mammalian models or humans, with relevance to cerebral clearance, aging, neurodegeneration, neuroimmune regulation, or myelin integrity. Primary experimental investigations and human imaging studies were prioritized for evidence synthesis. Review articles were consulted to establish the research context and identify existing knowledge gaps but were excluded from the primary evidence tables. Studies examining glymphatic transport without a direct meningeal lymphatic component, unrelated peripheral lymphatic disorders, conference abstracts, editorials without original data, and duplicate publications were excluded.

Data were extracted from each included primary study, including study population or animal model, disease characteristics, lymphatic manipulation or imaging techniques, principal pathological and functional outcomes, and methodological limitations. Owing to substantial heterogeneity in experimental models, tracer systems, anatomical drainage pathways, imaging protocols, and outcome measures, quantitative meta-analysis was not performed. Instead, findings were synthesized narratively across three predefined domains: Alzheimer's disease and protein homeostasis, Parkinson's disease and alpha-synuclein pathology, and aging-associated neuroimmune and myelin-related mechanisms.

The strength of evidence was evaluated according to the directness of meningeal lymphatic measurements or experimental manipulations, appropriateness of disease-specific controls, consistency across pathological and functional outcomes, and translational relevance. Findings from human imaging studies were interpreted as associations rather than evidence of causality unless supported by complementary mechanistic investigations. Conflicting results were systematically examined to identify potential differences in disease models, compensatory clearance mechanisms, and experimental conditions that could explain variations in the observed relationships between meningeal lymphatic dysfunction and neurodegenerative pathology.

Table 1. Summary of Relevant Review Studies

Reference	Year	Primary Focus	Coverage of Meningeal Lymphatics	Main Contribution
Rego et al.	2023	Aging and Alzheimer's disease	Extensive	Links meningeal lymphatic aging with immune changes and Alzheimer's related pathology.
Yamada and Iwatsubo	2024	Glymphatic and meningeal clearance in Alzheimer's disease	Extensive	Integrates amyloid beta and tau proteostasis with therapeutic concepts.
Feng et al.	2025	Neurodegenerative disorders	Extensive	Broad review of meningeal lymphatic biology, neuroimmune crosstalk, and therapeutic targeting.
He and Sun	2026	Meningeal lymphatic and peripheral immune axis	Extensive	Frames lymphatic drainage as a mechanistic bridge between proteinopathy, neuroinflammation, and peripheral immunity.

The recent literature review confirms that meningeal lymphatics are now considered relevant to both protein clearance and immune regulation. Rego et al. (2023) concentrated on aging and Alzheimer's disease, while Yamada and Iwatsubo (2024) placed meningeal lymphatic drainage within the wider framework of brain proteostasis. Feng et al. (2025) broadened the field to neurodegenerative disorders and therapeutic targeting, and He and Sun (2026) emphasized the meningeal lymphatic and peripheral immune axis. These reviews provide strong conceptual coverage but also illustrate why disease specific evidence grading is needed: mechanistic confidence is not equal across Alzheimer's disease, Parkinson disease, demyelinating disease, and less studied neurodegenerative conditions.

Accordingly, the present synthesis gives greatest weight to direct manipulations of meningeal lymphatic function, disease specific human imaging, and convergent outcomes across independent laboratories. Associations based only on anatomical proximity or on glymphatic dysfunction are treated as supportive rather than definitive evidence of meningeal lymphatic causality.

RESULTS AND DISCUSSIONS

Alzheimer Disease, Amyloid Beta, and Tau Proteostasis

The strongest preclinical evidence for a role of meningeal lymphatics in Alzheimer's related pathology comes from studies that directly impair or augment drainage. (Da Mesquita et al., 2018) showed that meningeal lymphatic dysfunction in mice reduced cerebrospinal fluid influx and interstitial solute efflux, impaired cognitive performance, and worsened amyloid related pathology in transgenic Alzheimer's models. In aged mice, vascular endothelial growth

factor C treatment improved meningeal lymphatic drainage, brain perfusion, and performance on learning and memory tasks. These findings established a plausible age linked mechanism in which deterioration of lymphatic outflow reduces the efficiency of a broader clearance network.

Evidence for tau clearance is mechanistically distinct from amyloid plaque deposition. Patel et al., (2019) used mice with impaired dural lymphatic development and showed greater retention of extracellular tau after intracerebral administration, particularly at 48 and 72 hours. Because extracellular tau is relevant to transneuronal propagation of tauopathy, delayed clearance provides a credible route by which impaired lymphatic function could influence disease spread even when total parenchymal plaque burden is unchanged. The study supports a substrate specific view of lymphatic function rather than a generalized claim that all pathogenic proteins are cleared through identical pathways.

Deep cervical lymph node ligation provides complementary evidence because it disrupts downstream lymphatic drainage. Wang et al., (2019) studied APP/PS1 and wild type mice, with 16 animals per experimental group, and found that cervical drainage obstruction aggravated amyloid beta accumulation, neuroinflammation, synaptic protein loss, aquaporin 4 depolarization, and cognitive and exploratory deficits in the Alzheimer's model. The experiment is important because it connects meningeal outflow failure with both parenchymal pathology and glymphatic organization. However, cervical ligation is not anatomically selective for a single meningeal vessel segment, so downstream lymphatic obstruction may affect several fluid and immune routes simultaneously.

Meningeal lymphatics also appear to influence the response to disease modifying therapy. Da Mesquita et al., (2021) reported that ablation of meningeal lymphatics in 5xFAD mice worsened the response to anti amyloid beta immunotherapy, with greater amyloid accumulation, microgliosis, neurovascular dysfunction, and behavioral impairment. Enhancement of lymphatic function with vascular endothelial growth factor C improved antibody mediated amyloid clearance. These results suggest that therapeutic antibodies may depend partly on intact clearance and immune interfaces after binding their targets, which is clinically relevant because anti amyloid therapies are administered to older individuals whose lymphatic function may already be reduced.

Physical modulation of lymphatic endothelial function has also produced positive results. Wang et al., (2024) used near infrared light to enhance meningeal lymphatic drainage in aged mice and in 5xFAD and APP/PS1 models. Treatment improved drainage and cognitive performance and reduced amyloid burden, neuroinflammation, and neuronal injury. Mechanistic experiments implicated improved mitochondrial metabolism and endothelial junctional integrity in meningeal lymphatic endothelial cells. Across experiments, reported group sizes varied by outcome, including approximately 15 to 16 animals for 5xFAD behavioral analyses and 8 to 10 for APP/PS1 behavioral analyses, with smaller groups for histological endpoints. This illustrates both the breadth of the observed effect and the need for replication in larger, independently powered studies.

The most important counterpoint comes from Antila et al., (2024). In APdE9 and 5xFAD mice, sustained manipulation of the vascular endothelial growth factor C pathway produced marked meningeal lymphatic atrophy or expansion and changed tracer drainage to cervical lymph nodes, yet neither manipulation significantly altered the overall cerebral amyloid plaque

load. Lymphatic atrophy also did not produce clear behavioral worsening, and reduced cervical drainage was accompanied by increased cerebrospinal fluid transfer to blood. These findings do not invalidate earlier studies. Instead, they show that brain clearance is redundant and route dependent. Amyloid outcome may be shaped by the duration and anatomical site of lymphatic manipulation, disease stage, transgenic model, plaque kinetics, compensatory venous clearance, and whether the endpoint is soluble amyloid, deposited plaque, treatment associated removal, or cognition.

Taken together, the Alzheimer's literature supports a role for meningeal lymphatics in proteostatic and immune homeostasis but does not establish lymphatic flow as the single rate limiting determinant of amyloid plaque burden. Evidence is stronger for effects on fluid exchange, extracellular tau clearance, inflammatory state, and the efficacy of selected amyloid interventions. The clinically meaningful question is therefore not whether lymphatics matter, but when impaired lymphatic function becomes sufficiently limiting that restoring it changes disease trajectory.

Table 2. Performance Summary of Meningeal Lymphatic Studies in Alzheimer's Related Models

Reference	Model or Method	Dataset or Application	Main Result	Drawbacks
Da Mesquita et al., 2018	Aging and transgenic Alzheimer's mouse models; lymphatic impairment or VEGF C enhancement	Aging, cognition, amyloid pathology	Impaired drainage reduced fluid exchange and cognition; VEGF C improved drainage and cognitive measures in aged mice.	Predominantly preclinical; intervention effects depend on model and disease stage.
Patel et al., 2019	Mice with deficient dural lymphatic function	Extracellular tau clearance	Greater tau retention at 48 and 72 hours when lymphatic function was impaired.	Injected extracellular tau does not reproduce the full natural history of human tauopathy.
Wang et al., 2019	Deep cervical lymph node ligation in APP/PS1 mice	Amyloids, inflammation, synapses, cognition	Ligation worsened amyloid accumulation, inflammation, synaptic loss, aquaporin 4 polarization, and behavior.	Cervical ligation affects downstream drainage broadly and is not specific to one meningeal vessel segment.
Da Mesquita et al., 2021	5xFAD mice with meningeal lymphatic ablation or VEGF C modulation	Anti amyloid beta immunotherapy	Lymphatic ablation worsened treatment outcome; VEGF C improved antibody mediated amyloid clearance.	Transgenic model and experimental antibody context limit direct clinical extrapolation.

Reference	Model or Method	Dataset or Application	Main Result	Drawbacks
Wang et al., 2024	Near infrared modulation in aged, 5xFAD, and APP/PS1 mice	Drainage, amyloid, cognition	Improved drainage and cognition with reductions in amyloid, neuroinflammation, and neuronal injury.	Multiple experimental endpoints used different group sizes; human efficacy is unknown.
Antila et al., 2024	Sustained VEGF C pathway manipulation in APdE9 and 5xFAD mice	Cervical drainage, amyloid plaque burden, behavior	Changed lymphatic drainage without significant change in overall amyloid plaque burden; atrophy increased cerebrospinal fluid to blood clearance.	Demonstrates compensatory clearance and challenges a simple linear lymphatic amyloid model.

Parkinson Disease and Alpha Synuclein Pathology

Parkinson's disease provides a second disease context in which the meningeal lymphatic hypothesis is supported by both causal animal experiments and human imaging. Zou et al., (2019) blocked deep cervical lymphatic drainage in 18 week old A53T alpha synuclein transgenic mice and examined pathology six weeks later. Drainage obstruction worsened glymphatic dysfunction, alpha synuclein accumulation, glial activation, inflammatory signaling, dopaminergic neuronal loss, and motor impairment. Several quantitative analyses were based on three to four mice per group, and the reported genotype and ligation effects on alpha synuclein, glial markers, and inflammatory proteins were statistically strong. The study therefore demonstrates biological plausibility but also illustrates the small sample sizes typical of mechanistic animal work.

The critical translational advance came from Ding et al., (2021), who used dynamic contrast enhanced magnetic resonance imaging in people with idiopathic Parkinson's disease, atypical parkinsonian disorders, and cognitively normal controls. Patients with idiopathic Parkinson's disease showed significantly reduced meningeal lymphatic flow along the superior sagittal and sigmoid sinuses and delayed perfusion of deep cervical lymph nodes. Importantly, vessel cross sectional area did not differ significantly among diagnostic groups, indicating that functional impairment may be detectable even without gross anatomical loss. In a complementary alpha synuclein preformed fibril mouse model, pathology preceded delayed lymphatic drainage, disruption of lymphatic endothelial tight junctions, and meningeal inflammation. Experimental blockade of lymphatic flow then amplified alpha synuclein pathology and worsened motor and memory deficits. This sequence supports a bidirectional model in which proteinopathy can damage drainage and impaired drainage can subsequently accelerate pathology.

The meningeal lymphatic route is also being explored as a therapeutic access pathway. Liu et al., (2023) delivered a natural killer cell membrane biomimetic liposomal curcumin formulation through the meningeal lymphatic route in Parkinson mouse models. Brain delivery of curcumin was approximately 20 fold higher than conventional intravenous administration, accompanied by lower reactive oxygen species, reduced alpha synuclein aggregation and

spread, improved movement, and reduced neuronal loss. This result demonstrates the potential of the route for targeted delivery, but it should not be interpreted as evidence that the same administration strategy is ready for human use because route accessibility, dosing, safety, and reproducibility remain unresolved.

A different strategy attempts to repair damaged lymphatic vessels themselves. Han et al. (2025) reported that ultrasmall copper selenide nanoparticles promoted structural and functional recovery of damaged meningeal lymphatic vessels through activation of vascular endothelial growth factor C and its receptor VEGFR3. In a preformed fibril Parkinson model, treatment enhanced lymphatic drainage, reduced alpha synuclein in brain and cerebrospinal fluid, and improved motor coordination and memory. The concept is innovative because it treats lymphatic dysfunction as a therapeutic target rather than just a biomarker, yet nanoparticle biodistribution, long term toxicity, and the consequences of sustained lymphangiogenic signaling require rigorous evaluation before translation.

The Parkinson literature is therefore more coherent than the Alzheimer amyloid literature in one respect: experimental obstruction, human functional imaging, and restorative interventions all converge on an association between impaired drainage and alpha synuclein pathology. Nevertheless, causality in patients remains unproven. Cross sectional imaging cannot determine whether lymphatic dysfunction initiates Parkinson disease or develops as a consequence of ongoing alpha synuclein related inflammation. Longitudinal imaging beginning in prodromal or genetically at risk populations would be particularly informative.

Table 3. Performance Summary of Meningeal Lymphatic Studies in Parkinson's Disease

Reference	Method	Population or Model	Results	Drawbacks
Zou et al., 2019	Deep cervical lymph node ligation	A53T alpha synuclein transgenic mice	Drainage blockade increased alpha synuclein accumulation, glial activation, inflammation, dopaminergic loss, and motor deficits.	Mechanistic groups were small and cervical ligation affects multiple downstream drainage routes.
Ding et al., 2021	Dynamic contrast enhanced MRI plus fibril mouse experiments	Idiopathic Parkinson's disease, atypical parkinsonism, controls, and alpha synuclein fibril mice	Idiopathic Parkinson's disease showed reduced meningeal lymphatic flow and delayed cervical node perfusion; blockade worsened mouse pathology.	Human component is observational and contrast based imaging lacks universally standardized quantification.
Liu et al., 2023	Biomimetic liposome delivery through meningeal lymphatic route	Parkinson mouse models	Approximately 20 fold greater brain curcumin delivery than intravenous administration with improved pathological and behavioral outcomes.	Experimental delivery strategy has uncertain feasibility and safety in humans.
Han et al., 2025	Copper selenide nanoparticle mediated lymphatic repair	Alpha synuclein fibril Parkinson mouse model	Enhanced lymphatic drainage, reduced brain and cerebrospinal fluid alpha synuclein, and improved motor and memory outcomes.	Nanoparticle safety, persistence, and long term lymphatic effects require further study.

Aging, Human Drainage Anatomy, Neuroimmune Regulation, And Myelin Homeostasis

Aging is a central modifier of meningeal lymphatic biology and may explain why drainage related vulnerability becomes particularly relevant to late life neurodegeneration. Ahn et al. (2019) identified basal meningeal lymphatic vessels as specialized cerebrospinal fluid clearance sites with valves and anatomical proximity to the subarachnoid space. Both structural integrity and cerebrospinal fluid drainage declined with age. The finding is mechanistically consistent with the age associated rise in Alzheimer's and Parkinson's disease risk, but it also cautions against treating dorsal meningeal vessels as representative of the entire system.

Human imaging supports anatomical conservation while revealing additional complexity. Absinta et al. (2017) demonstrated meningeal lymphatic vessels alongside dural venous sinuses in humans and nonhuman primates using high resolution clinical magnetic resonance imaging. Albayram et al. (2022) used a noncontrast three dimensional T2 FLAIR approach to visualize dural lymphatic structures and connections to cervical lymph nodes and reported age related cervical lymph node atrophy with thicker lymphatic channels in older participants. Jacob et al. (2022) combined whole head light sheet imaging in mice with human vessel wall magnetic resonance imaging and identified a conserved meningeal network, including anterior pathways surrounding the cavernous sinus with exit routes through foramina associated with emissary veins. Together, these studies provide a structural basis for translational imaging, although differences in sequence design, contrast use, and what signal is interpreted as lymphatic fluid or vessel wall remain important methodological issues.

Recent anatomical work also shifts attention beyond classical dorsal and basal dural vessels. Yoon et al. (2024) identified the nasopharyngeal lymphatic plexus as a major cerebrospinal fluid outflow hub connected to deep cervical collecting lymphatics. Aging produced regression of the nasopharyngeal plexus, whereas downstream deep cervical lymphatics were relatively preserved and remained responsive to alpha adrenergic and nitric oxide signaling. This suggests that age related drainage failure can be anatomically selective and potentially modifiable downstream, a concept that may explain why some interventions improve tracer clearance despite persistent upstream pathology.

Meningeal lymphatics also regulate cellular and immune homeostasis. Li et al. (2022) showed that deep cervical lymph node ligation impaired clearance of senescent astrocytes from the aging mouse brain and increased neuroinflammation. Increasing meningeal lymphatic vessel diameter with adeno associated viral vascular endothelial growth factor C improved senescent astrocyte clearance and reduced inflammatory changes, while interference with CCL21 signaling worsened short memory deficits. These observations expand the clearance concept from soluble proteins to dysfunctional cells and implicate chemokine guided trafficking as a mechanism.

The relationship between aging and vascular endothelial growth factor C may be nonlinear. Liu et al. (2024) compared young, middle aged, and aged mice and found that middle aged animals had expanded meningeal lymphatic vessels, enhanced drainage function, and better Y maze performance relative to both young and aged groups. These changes were closely associated with cortical vascular endothelial growth factor C expression. The result implies that

lymphatic aging may involve an intermediate compensatory phase before later decline rather than a monotonic loss beginning in early adulthood.

The functional scope extends to oligodendrocytes and myelin. Das Neves et al. (2024) showed that meningeal lymphatic vessel ablation in adult mice altered glial gene expression, reduced mature oligodendrocytes and selected lipid species, changed meningeal adaptive immunity, activated brain myeloid cells, delayed remyelination, and increased axonal loss. The effects depended on an intact immune system, supporting a neuroimmune mechanism rather than simple fluid stagnation. Patients with multiple sclerosis also showed lower cerebrospinal fluid vascular endothelial growth factor C, particularly soon after clinical relapses. Multiple sclerosis is not a prototypical primary neurodegenerative proteinopathy, but this human observation provides important evidence that lymphatic signaling is relevant to disorders in which inflammation, demyelination, and neurodegeneration interact.

Overall, this third evidence domain supports a broader model of meningeal lymphatic function. The system influences not only bulk clearance but also where antigens, immune cells, chemokines, senescent cells, and potentially therapeutic agents move. This helps explain why altering meningeal lymphatics can affect cognition or pathology even when a single aggregate endpoint, such as total amyloid plaque burden, remains unchanged.

Table 4. Performance Summary of Aging, Human Imaging, and Neuroimmune Studies

Reference	Method	Main Finding	Limitations
Ahn et al., 2019	Anatomical and tracer studies in mice	Basal meningeal lymphatics are major cerebrospinal fluid clearance sites; integrity and drainage decline with aging.	Rodent anatomy does not fully establish human functional contribution.
Albayram et al., 2022	Noncontrast three dimensional T2 FLAIR human MRI	Visualized brain lymphatic networks connected to cervical nodes; older participants showed cervical node atrophy and thicker channels.	Imaging signal interpretation and clinical thresholds require external standardization.
Jacob et al., 2022	Mouse light sheet imaging and human vessel wall MRI	Demonstrated conserved three dimensional lymphatic anatomy including anterior cavernous sinus pathways.	Primarily anatomical; disease specific functional consequences were not directly tested.
Li et al., 2022	Cervical ligation and VEGF C modulation in aged mice	Lymphatic routes cleared senescent astrocytes; blockade increased inflammation, whereas enhancement improved clearance.	Cell migration mechanisms and relevance to human neurodegeneration remain incompletely defined.
Liu et al., 2024	Age comparison in mice	Middle aged mice had greater lymphatic expansion and function than young or aged mice, associated with cortical VEGF C.	Cross sectional age groups cannot fully define individual longitudinal trajectories.
Yoon et al., 2024	Tracer mapping and physiological modulation in mice	Nasopharyngeal lymphatic plexus is an outflow hub that regresses with aging; downstream cervical transport remains modifiable.	Human equivalence of the physiological control mechanisms requires direct testing.

Reference	Method	Main Finding	Limitations
Das Neves et al., 2024	Lymphatic ablation, remyelination models, and human cerebrospinal fluid	Dysfunction reduced mature oligodendrocytes, delayed remyelination, increased axonal loss; multiple sclerosis patients had lower cerebrospinal fluid VEGF C.	Multiple sclerosis findings extend mechanism beyond classic neurodegenerative proteinopathies and are not direct proof of treatment efficacy.

Challenges And Future Directions

Despite rapid progress, the field faces several conceptual and translational challenges. First, meningeal lymphatic function cannot be isolated from the glymphatic system, vascular pulsatility, arachnoid and venous routes, cranial nerve associated outflow, and cervical collecting lymphatics. Many experimental manipulations change more than one compartment. Future studies should therefore quantify multiple outflow routes in the same animal or participant and distinguish vessel anatomy from net solute clearance.

Second, disease stage is likely to determine whether lymphatic modulation is beneficial. Enhancing drainage before substantial protein deposition may have different effects from intervention after plaques, tangles, or alpha synuclein inclusions are established. The divergent Alzheimer's findings of Da Mesquita et al. (2018, 2021), Wang et al. (2024), and Antila et al. (2024) strongly support this point. Experiments should be prospectively stratified by age, pathological stage, and soluble versus deposited protein endpoints.

Third, human measurement remains insufficiently standardized. Magnetic resonance approaches vary in contrast agent, pulse sequence, acquisition timing, anatomical region, and signal quantification. A clinically useful biomarker will require reproducible normative ranges, test and retest reliability, multicenter harmonization, and validation against independent indicators of cervical drainage or cerebrospinal fluid turnover. Parkinson disease currently has the strongest disease specific human functional evidence, but even there longitudinal validation is needed.

Fourth, vascular endothelial growth factor C is biologically powerful but not necessarily a universally safe therapeutic switch. Chronic lymphangiogenic stimulation could alter immune cell trafficking, antigen presentation, meningeal inflammation, or fluid balance. Intervention studies should assess immune phenotype, vascular permeability, intracranial fluid dynamics, and off target lymphangiogenesis in addition to cognitive or protein outcomes.

Fifth, therapeutic delivery through meningeal lymphatic routes and nanoparticle based vessel repair are promising but remain early stage. The approximately 20 fold increase in brain curcumin delivery reported by Liu et al. (2023) and the lymphatic repair observed with copper selenide nanoparticles by Han et al. (2025) are notable proof of concept findings, yet clinical translation will require detailed pharmacokinetics, biodistribution, long term toxicology, and scalable administration methods.

Sixth, the disease spectrum is uneven. Alzheimer's disease and Parkinson's disease dominate direct mechanistic work, whereas evidence for amyotrophic lateral sclerosis, Huntington's disease, frontotemporal degeneration, and other proteinopathies is comparatively sparse. Future reviews and experiments should resist extrapolating Alzheimer or Parkinson mechanisms to disorders that have not been directly tested.

Finally, causal direction must be established in humans. The most plausible model is a feedback loop in which aging or proteinopathy damages lymphatic endothelial function, impaired drainage promotes retention of inflammatory mediators or pathological proteins, and the resulting inflammation further disrupts the drainage network. Longitudinal studies in prodromal populations, combined with fluid biomarkers and quantitative lymphatic imaging, are needed to test this sequence.

CONCLUSION

Evidence accumulated since 2015 has established meningeal lymphatic vessels as important components of central nervous system (CNS) fluid regulation and immune homeostasis. Experimental studies have demonstrated that impaired meningeal lymphatic drainage can exacerbate extracellular tau accumulation, alter selected amyloid-beta (Aβ) pathology measures, aggravate alpha-synuclein (α-synuclein) pathology, increase neuroinflammation, promote the accumulation of senescent astrocytes, contribute to oligodendrocyte loss, and impair behavioral outcomes in specific experimental models. Human imaging studies have confirmed the presence of anatomically conserved meningeal lymphatic networks and provided evidence of reduced lymphatic drainage in patients with idiopathic Parkinson's disease. Nevertheless, the available findings do not support the assumption that enhanced meningeal lymphatic drainage consistently reduces pathological protein accumulation across neurodegenerative conditions. Evidence published in 2024 demonstrated that sustained meningeal lymphatic atrophy or expansion altered cerebrospinal fluid drainage without significantly affecting overall cerebral amyloid plaque burden in two mouse models of Alzheimer's disease, highlighting the potential roles of compensatory clearance pathways, anatomical heterogeneity, disease stage, and outcome selection. Collectively, these findings suggest that meningeal lymphatic vessels function as potentially modifiable components of an interconnected cerebral clearance and neuroimmune regulatory network rather than as independent determinants of neurodegenerative pathology. Their therapeutic relevance will depend on identifying patients with measurable lymphatic dysfunction, determining disease stages at which impaired drainage contributes meaningfully to pathological progression, and establishing whether targeted interventions improve clinically relevant outcomes without compromising immune surveillance or fluid homeostasis. Future investigations should therefore prioritize standardized human lymphatic imaging protocols, longitudinal validation of functional biomarkers, and rigorously controlled translational studies to clarify the safety, efficacy, and disease-specific applicability of meningeal lymphatic-targeted therapies.

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CONFLICT OF INTEREST

The author states that there are no conflicts of interest, whether personal, commercial, or financial, that can affect the implementation and results of this study.

AUTHOR CONTRIBUTION

Komang Trisna Sumadewi, Dewa Ayu Agung Alit Suka Astini, Luh Gde Evayanti, Ida Ayu Laxmi Ananda Dewi Manuaba, Ni Made Gita Kusuma Dewi contributed to research

design, data collection and processing, system development, result analysis, and article manuscript preparation.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

In the process of compiling this article, the author uses generative artificial intelligence (AI) as a tool in language refinement, writing structure, and grammar improvement. The use of AI is carried out on a limited basis and remains under the supervision of the author. All data, analysis, interpretation, and scientific substance in this article have been checked and verified by the author. The author is solely responsible for the accuracy, authenticity, and final content of the manuscript.

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