Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Glymphatic System Dysfunction in Thyroid Eye Disease Associated with Disease Activity and Duration

Haiyang Zhang[1,*], Mengda Jiang[2,*], Yuting Liu[1,*], Xin Ning Lee[1], Zilin Fang[1], Jipeng Li[1], Yinwei Li[1], Jing Sun[1], Xiaofeng Tao[2], Xuefei Song[1], Huifang Zhou[1], Xianqun Fan[1]

[1]State Key Laboratory of Eye Health, Department of Ophthalmology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [2]Department of Radiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xianqun Fan; Huifang Zhou, Email fanxq@sjtu.edu.cn; fangzzfang@sjtu.edu.cn

Purpose: To investigate the alterations in the glymphatic system in patients with thyroid eye disease (TED) using diffusion tensor imaging (DTI) analysis along the perivascular space (ALPS) and to explore the correlation between the glymphatic system and clinical features of TED.

Methods: The study included 47 patients with TED, including 20 active TED patients (AP) and 27 inactive TED patients (IP), along with 24 healthy controls (HC). Imaging data including DTI sequence were acquired using a 3.0 Tesla scanner. ALPS values were calculated based on the diffusivity of the bilateral superior corona radiata and superior longitudinal fasciculus. Correlation analysis were thus performed between ALPS values and clinical characteristics.

Results: The DTI-ALPS analysis in the TED patient group collectively showed lower mean and left ALPS values compared to the HC, with statistically significant differences observed (mean ALPS: P=0.0308, left ALPS: P=0.0032). Among the TED subgroups, the IP had significantly lower left ALPS values than HC (P=0.006). Correlation analysis within the IP subgroup indicated that lower ALPS values were significantly associated with longer disease duration (P=0.015) and greater palpebral fissure height (P=0.028).

Conclusions: Glymphatic system dysfunction is evident in TED patients, with its extent influenced by disease activity and duration.

Keywords: thyroid eye disease, glymphatic system, diffusion tensor imaging along the perivascular space, magnetic resonance imaging, disease activity

Introduction

Thyroid eye disease (TED), an autoimmune condition often secondary to Graves' disease, involves inflammation and abnormal proliferation of orbital fibroblasts and adipocytes in the orbit, leading to signs and symptoms such as periorbital edema, lid retraction, proptosis, diplopia, and vision loss due to corneal damage and optic nerve compression.[1–3] The pathogenesis of TED is rooted in the autoimmune response targeting orbital fibroblasts, triggering inflammation and tissue remodeling through cytokine and hyaluronan production.[4] Beyond its ocular effects, TED often manifests with emotional and psychological symptoms including depression, anxiety, memory impairment, and concentration difficulties, possibly stemming from both physical impacts and direct neuroimmune interactions affecting the brain.[5,6]

Recent neuroimaging studies have employed various techniques to investigate the neurobiological changes in TED. Functional magnetic resonance imaging (MRI) has identified abnormalities in local neural activity and functional integration within specific brain regions of TED patients.[7–9] Furthermore, diffusion MRI such as diffusion tensor imaging (DTI) has revealed microstructural alterations in neural pathways associated with vision,[10,11] while metabolic MRI has confirmed abnormal brain metabolism in these individuals.[12] The findings suggest that TED is associated not only with

Received: 4 April 2025
Accepted: 5 July 2025
Published: 4 August 2025

ocular manifestations but also with significant morphological and microstructural changes in the brain, indicating that it may be more of a neuro-related disorder than solely ocular in nature.

Although existing studies have identified abnormalities in brain structure and function in patients with TED, the exact cause of these changes remains unclear. Recent research on certain autoimmune diseases has highlighted that patients exhibit abnormalities in the glymphatic system,[13–15] which are closely associated with changes in brain structure.[16] These findings suggest that glymphatic system abnormalities may underlie the pathophysiologic mechanisms of brain damage in autoimmune patients. The glymphatic system is a recently discovered waste clearance mechanism, which uses perivascular channels formed by astroglia cells to efficiently remove soluble proteins and metabolites from the central nervous system (CNS).[17] This system is closely linked to inflammation and metabolism, with evidence suggesting a cyclic and potentially synergistic relationship between glymphatic function and inflammation.[18] Glymphatic fluid dynamics affect both local and global transportation of signaling molecules and metabolites, which are crucial for maintaining homeostasis and specific behaviors.[19] Importantly, emerging evidence indicates that the glymphatic system also plays a vital role in the orbit and optic nerve, where perivascular fluid dynamics contribute to metabolic waste clearance and tissue homeostasis.[20,21] Disruption of this orbital glymphatic pathway has been implicated in glaucoma[22] and retinal disease,[23] conditions characterized by impaired fluid clearance and astrocytic dysfunction.

In a recent advancement, a non-invasive method based on DTI, known as "Diffusion Tensor Image Analysis aLong the Perivascular Space (DTI-ALPS)", has been used to assess glymphatic clearance function.[24–26] This method measures the directional diffusion of water molecules along the perivascular spaces (PVS), which are pathways that facilitate the exchange of CSF and ISF. The DTI-ALPS index is calculated by comparing the diffusion rates of water molecules along the PVS to those perpendicular to it, providing a quantitative measure of glymphatic function.[27]

Considering that TED is an autoimmune disorder associated with brain alterations, it is plausible to hypothesize that TED patients may experience changes in the glymphatic system. The orbital congestion, inflammation, and elevated pressure seen in TED may similarly impair glymphatic clearance, leading to accumulation of inflammatory cytokines and metabolic byproducts, potentially exacerbating both local tissue damage and neuroinflammatory signaling to the brain. TED is commonly classified into active and inactive phases, a widely accepted approach based on distinct immune responses and pathological features. The active phase is marked by lymphocytic infiltration, edema in the extraocular muscles, and orbital fat expansion, whereas the inactive phase is characterized by fibrosis and fatty degeneration of the extraocular muscles.[28] This study investigated glymphatic system function in TED across different disease activity phases using DTI-ALPS and to explore its correlation with clinical characteristics.

Materials and Methods

Study Participants

Ethical approval for this prospective study was granted by the research ethics committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (approval number: SH9H-2022-T229-2). This study complied with the Declaration of Helsinki guidelines. The diagnosis of TED was made in accordance with the European and Chinese versions of the clinical guidelines.[29,30] Active TED was indicated by a 7-point Clinical Activity Score (CAS) of ≥3 and confirmed by orbital MRI, following clinical guidelines as described in previous study.[7] On MRI, high signal intensity of extraocular muscles on T2-weighted images compared to the ipsilateral temporal muscle or brain white matter suggests active disease. Additionally, enlargement of the lacrimal gland with increased signal intensity also suggests the possibility of active disease.[30] Disease duration was determined from the onset of ocular manifestations. Ultimately, the study enrolled 47 patients with TED, categorized as 20 active TED patients (AP) and 27 inactive TED patients (IP), as well as 24 healthy controls (HC).

According to the Edinburgh Handedness Inventory, all participants were right-handed.[31] The following exclusion criteria were applied to all subjects: (1) signs and prior histories of other ocular pathologies, eg amblyopia, cataracts, and glaucoma; (2) history of eye surgery; (3) history of psychiatric or neurologic illness, eg, depression and bipolar disorder; (4) history of other endocrine diseases despite thyroid disorders; (5) anatomical abnormalities of the brain, eg, tumors,

trauma, and infection; (6) ineligibility for MRI scanning; (7) incomplete MRI data or poor image quality. All study participants provided written informed consent.

Imaging Data Acquisition

MRI examination was done using a 3.0 Tesla scanner (Magnetom Vida, Siemens, Erlangen, Germany) equipped with a 64-channel phased array head coil. Head motion and scanning noise were reduced by using foam padding and earplugs. All subjects were required to close their eyes without falling asleep when undergoing MRI scanning. The MRI protocol included a T1-weighted scan, and DTI scans. The higher resolution sagittal structural T1-weighted scan (3D MPRAGE sequence) with the following parameters: a spatial resolution of 0.8 mm isotropic, matrix: 320 × 320, field of view (FOV): 256 × 256 mm^2, and TR/TE: 2400/2.38 msec. The whole-brain diffusion imaging with echo planar imaging scan with the following parameters: a spatial resolution of 2.0 mm isotropic, matrix: 110 × 110, FOV: 220 × 220 mm^2, TR/TE: 7800/102 msec, b-values including 0 and 1000 sec/mm^2.

DTI Analysis Along the Perivascular Space

The DTI data were processed using FSL (version 6.0.3, FMRIB Software Library; http://www.fmrib.ox.ac.uk/fsl) following the optimized processing pipeline proposed by Maximov et al[32] (Figure 1). The preprocessing steps included Marchenko-Pastur Principal Component (MP-PCA) denoising, Gibbs ringing correction, eddy current and motion-induced distortion corrections, N4 bias field correction. Color-coded fractional anisotropy (FA) maps and diffusivity maps in directions of the x-, y-, and z-axes (Dxx, Dyy, Dzz) were generated. Each subject's FA map was co-registered to the JHU-ICBM-FA template, and the transformation matrix was applied to all the diffusivity maps. The projection and association fibers at the level of the lateral ventricle body were identified as the superior corona radiata (SCR) and the superior longitudinal fasciculus (SLF) based on the JHU-ICBM-DTI-81-white-matter Labeled Atlas.[33] ROIs were automatically defined as spheres with a 5 mm diameter in the bilateral SCR and SLF areas and applied to all subjects' diffusivity maps. The center coordinates of the ROIs were as follows: left SCR (116,110,99), left SLF (128,110,99), right SCR (64,110,99), and right SLF (51,110,99) on the JHU-ICBM-FA template. The diffusivity values of Dxx, Dyy, and Dzz for the bilateral SLF and SCR were automatically extracted for the ALPS calculation.

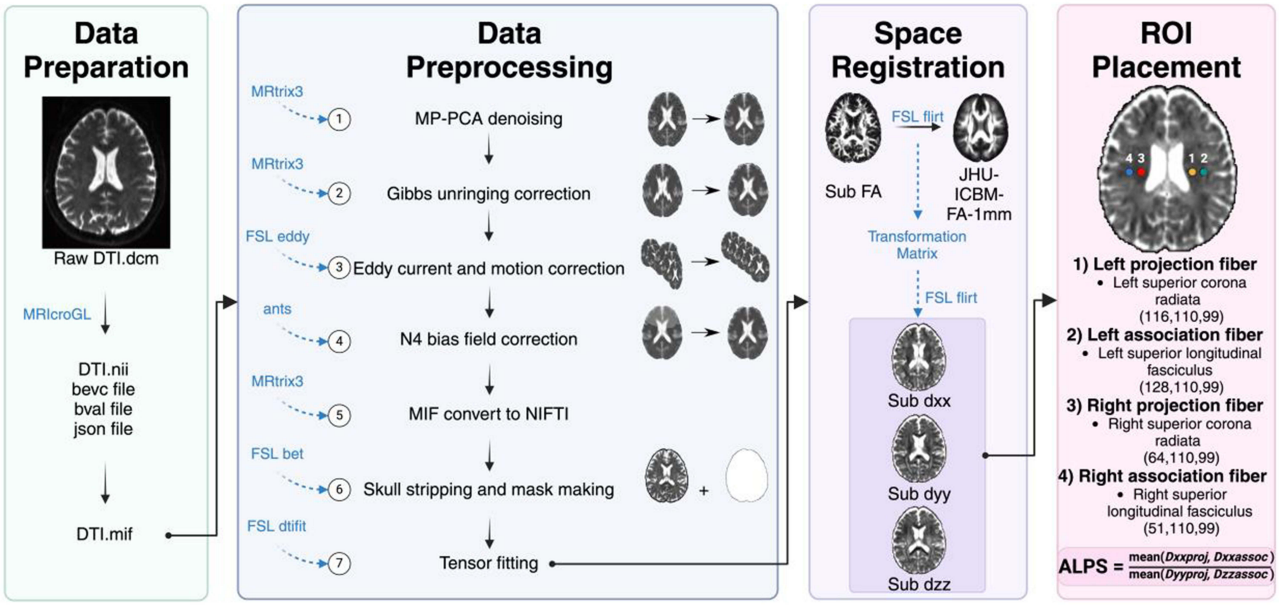

Figure 1 Flowchart of DTI imaging data processing. This flowchart outlines the sequential steps involved in the image data processing workflow. Created in BioRender. Liu, Y. (2025) https://BioRender.com/1z1ptox. The data preprocessing stage incorporates element partly derived from Taoka T, Masutani Y, Kawai H et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-Alps) in Alzheimer's disease cases. *Jpn J Radiol*. 2017;35(4):172–178.[27]

Statistical Analysis

The demographic and clinical data were analyzed using GraphPad Prism 9 (GraphPad, CA, USA). Normality was assessed using the Kolmogorov–Smirnov test. To ascertain differences in the ALPS values between patients with TED and HC, independent two-sample t-tests were conducted for Gaussian distribution variables and Mann–Whitney *U*-tests were conducted for non-Gaussian distributed continuous variables. For the purpose of discerning group-wise disparities among the AP, IP, and HC groups, continuous variables with a Gaussian distribution were compared using one-way ANOVA for three-group comparisons and non-Gaussian distributed continuous variables were compared using Kruskal–Wallis tests. Categorical variables were assessed using chi-square tests. Statistical significance was defined as $P < 0.05$. Subsequently, ALPS values with significant differences and clinical characteristics, including disease duration, CAS, palpebral fissure height, and exophthalmos, were included in Spearman correlation analysis to explore their relationships. Post hoc power analyses were conducted using G*Power 3.1.[34]

Result

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of all participants. There are no significant differences among the three groups regarding sex (P = 0.978), age (P = 0.761), or years of education (P = 0.060). Additionally, there were no significant differences between the AP and IP groups in terms of palpebral fissure height (P = 0.323) and exophthalmos (P = 0.075). However, the AP group exhibited a significantly higher CAS compared to the IP group (P < 0.0001). Additionally, the IP group exhibited a significantly longer disease duration compared to the AP group (P = 0.037). There were no significant differences between the AP and IP groups in treatment history or thyroid status.

Differences in DTI-ALPS Among Different Groups

In the comparative analysis between TED patients and HC, significant differences were observed in the mean ALPS values (P = 0.031) and left ALPS values (P = 0.003), indicating that the TED group exhibited lower ALPS values compared to the HC group. Subsequent analysis of TED subgroups revealed that the left ALPS values were significantly reduced in IP group compared to HC (P = 0.006), whereas the right ALPS values did not differ significantly from those

Table 1 Demographic and Clinical Characteristics of TED Patients and Healthy Controls

	TED (N = 47)	AP (N = 20)	IP (N = 27)	HC (N = 24)	p-Value		
					AP vs IP	AP vs IP vs HC	TED vs HC
Sex (male/female)	25/22	11/9	14/13	13/11	>0.999	0.978	>0.999
Age (year)	48.7 ± 11.7	50.2 ± 10.9	47.7 ± 12.2	48.4 ± 11.9	0.747	0.761	0.9
Education (year)	12.0 (9.00, 16.0)	10.5 (9.00, 15.0)	15.0 (9.00, 16.0)	15.0 (12.0, 16.00)	0.293	0.06	0.09
Handness (R/L)	47/0	20/0	27/0	24/0	/	/	/
Clinical characteristics							
Disease duration (month)	13.0 (7.00, 28.0)	10.5 (5.75, 16.0)	18.0 (7.00, 45.0)	/	0.037	/	/
CAS	1.00 (0.50, 3.00)	3.00 (2.00, 4.00)	1.00 (0.00, 1.00)	/	<0.0001	/	/
Palpebral fissure height (mm)	10.0 (8.25, 11.0)	9.00 (6.50, 11.5)	10.0 (9.00, 11.0)	/	0.323	/	/
Exophthalmos (mm)	20.0 (17.5, 21.5)	21.0 (18.0, 21.5)	19.5 (16.3, 20.8)	/	0.075	/	/
Treatment history							
Intravenous steroids (n/N)	16/47	10/20	6/27	/	0.065	/	/
Oral steroids (n/N)	6/47	4/20	2/27	/	0.379	/	/
Local therapy (n/N)	9/47	4/20	5/27	/	0.723	/	/
Radiotherapy (n/N)	3/47	0/20	3/27	/	0.251	/	/
Thyroid status (euthyroid/thyroid dysfunction)	21/26	7/13	14/13	/	0.392	/	/

Notes: Continuous variables are presented as the mean (± standard deviation) or as the median (interquartile range). Categorical variables are presented as counts.

Abbreviations: TED, thyroid eye disease; AP, active patients; IP, inactive patients; HC, healthy controls; CAS, clinical activity score; BCVA, best-corrected visual acuity.

Table 2 Comparison of ALPS Parameters of TED Patients and Healthy Controls

Characteristics	TED (n=47)	AP (n = 20)	IP (n = 27)	HC (n = 24)	p-Value				
					AP vs IP	AP vs HC	IP vs HC	AP vs IP vs HC	TED vs HC
Left ALPS	1.35 ± 0.120	1.37 ± 0.124	1.33 ± 0.117	1.44 ± 0.121	0.565	0.131	0.006	0.008	0.003
Right ALPS	1.37 ± 0.148	1.37 ± 0.134	1.37 ± 0.160	1.41 ± 0.133	>0.999	0.646	0.605	0.564	0.283
Mean ALPS	1.36 ± 0.119	1.37 ± 0.118	1.35 ± 0.122	1.43 ± 0.117	0.866	0.283	0.080	0.087	0.031

Notes: Continuous variables are presented as the mean (± standard deviation) or as the median (interquartile range). Categorical variables are presented as the number (%) and counts.
Abbreviation: ALPS analysis along the perivascular space.

of HC. The mean ALPS values between the AP and IP groups were not significantly different, yet there was a noticeable trend towards lower values in both AP and IP groups when compared with HC. The variations in DTI-ALPS among the three groups are detailed in Table 2 and Figure 2.

Correlation Analysis

Correlation analysis within the TED group was conducted to explore the relationship between distinct ALPS values and clinical characteristics (disease duration, palpebral fissure height, CAS, and exophthalmos). The results demonstrated a significant correlation between lower ALPS values and greater palpebral fissure height, with the left ALPS values

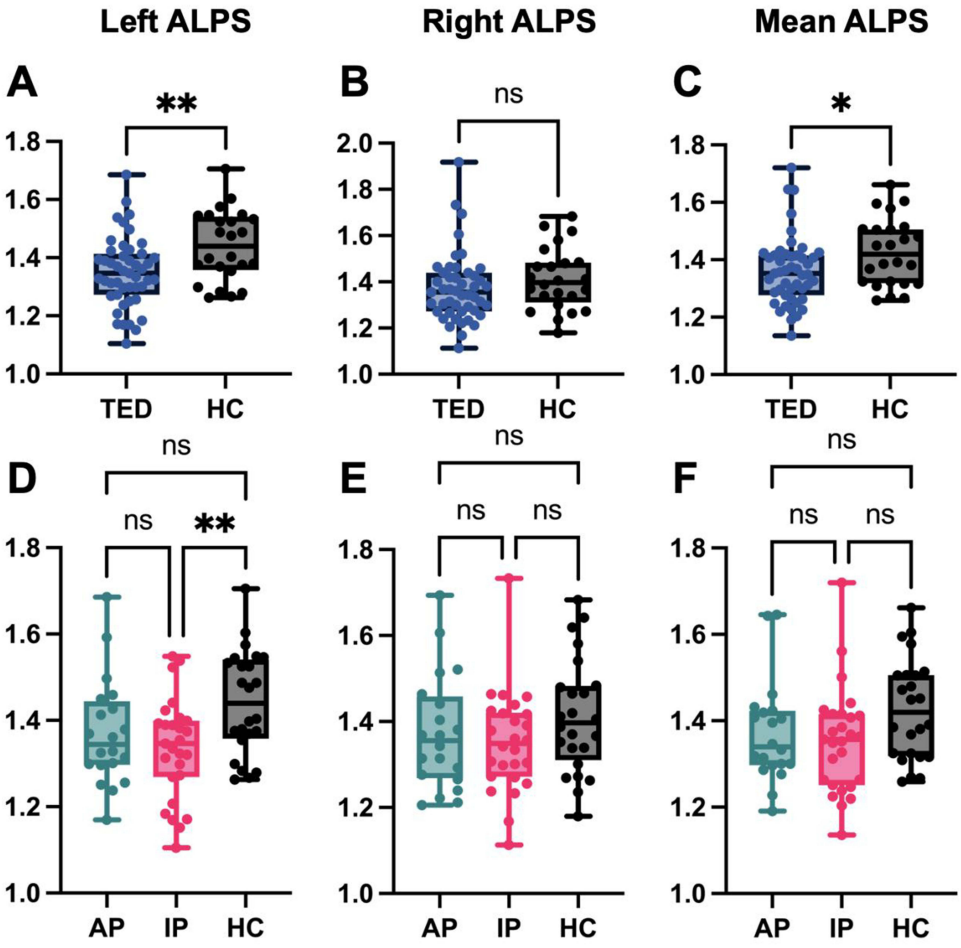

Figure 2 Box-and-whisker plots showing the Alps values. (**A**) Left ALPS between TED and HC (**B**) Right ALPS between TED and HC (**C**) Mean ALPS between TED and HC (**D**) Left ALPS among the three subgroups (**E**) Right ALPS among the three subgroups (**F**) Mean ALPS among the three subgroups. The median is represented by the middle line within each box, and the second and third quartiles are represented by the lower and upper segments of the box, respectively. *p < 0.05; **p < 0.01.
Abbreviations: ALPS, analysis along the perivascular space; AP, active TED patients; IP, inactive TED patients; HC, healthy controls; ns, non significant.

https://doi.org/10.2147/JIR.S532401

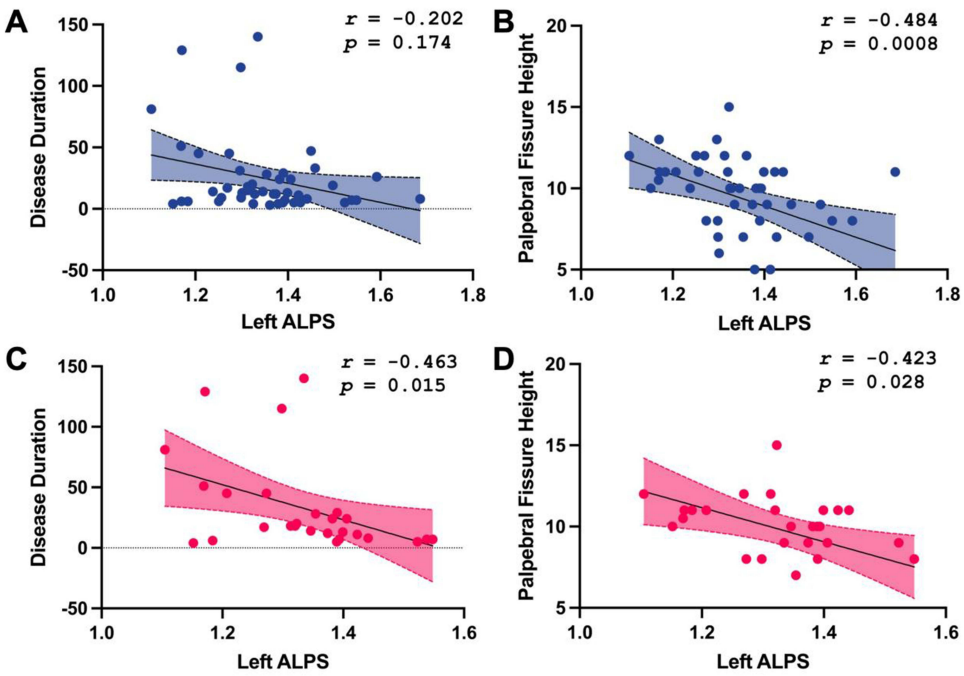

Figure 3 Correlation analysis between ALPS values and clinical features in the patients. (**A**) Left ALPS values in TED patients were not significantly correlated with disease duration. (**B**) Left ALPS values in TED patients were negatively correlated with palpebral fissure height. (**C**) Left ALPS values in inactive TED patients were negatively correlated with disease duration. (**D**) Left ALPS values in inactive TED patients were negatively correlated with palpebral fissure height. Dark lines depict linear regression with a 95% confidence interval (shadow in blue and red).
Abbreviations: ALPS, analysis along the perivascular space.

showing a strong association (P = 0.0008) in TED group. In the IP group, a significant correlation was observed between lower ALPS values and longer disease duration (P = 0.015), as well as greater palpebral fissure height (P = 0.028). The correlation analysis results are graphically represented in Figure 3. No other significant correlations were identified.

For the significant correlations observed in TED (ρ = −0.484, N = 47), and in the inactive TED subgroup (ρ = −0.463 and –0.423, N = 27), the estimated statistical powers were 0.94, 0.71, and 0.61, respectively (two-tailed, α = 0.05). These results indicate that while the overall sample size was adequate to detect strong correlations, the subgroup analyses were moderately powered and warrant validation in larger cohorts.

Discussion

In this study, we utilized a non-invasive imaging method, namely DTI-ALPS, to analyze the glymphatic activity in both active and inactive TED patients as well as in healthy controls. Our findings revealed that both the overall TED group and the subgroup with inactive TED exhibited significantly lower left ALPS values compared to healthy controls, suggesting glymphatic function dysfunction. Additionally, we observed a negative correlation between the ALPS values and both disease duration and palpebral fissure height, indicating that disease activity and duration are associated with glymphatic system dysfunction.

This is the first attempt to investigate glymphatic dysfunction in TED patients. Our study found that in both the overall TED group and the subgroup with inactive TED, there were abnormal left DTI-ALPS values, suggesting that glymphatic activity in inactive TED may be impaired. These observations suggest a potential disruption in glymphatic activity specifically within the left hemisphere of individuals with TED. The lateralization observed in our findings could be attributed to the initiation of glymphatic impairments in the left hemisphere among right-handed individuals. Notably, this phenomenon of lateralized glymphatic impairment has also been observed in research on other diseases.[35–37] Scholars have suggested that it is plausible to assume that the denser fiber bundles in the left hemisphere evolved to reduce the likelihood of losing perpendicularity between the fiber axis and the surrounding space of the vessels in right-handed subjects.[37]

TED is an orbital disease characterized by inflammatory cytokines that attack orbital tissues, leading to edema and fibrosis of the extraocular muscles.[38,39] The natural progression of TED is characterized by distinct phases: an initial active phase dominated by inflammatory changes, a subsequent brief static phase, and ultimately, the inactive phase.[40] Patients in the inactive phase of TED are generally observed to have a more prolonged disease duration. The extended exposure to inflammatory processes in these patients may culminate in a cumulative effect, leading to more extensive tissue damage and functional impairment. This prolonged inflammatory condition is likely to be the culprit for the marked reduction in ALPS values observed in patients with inactive TED rather than active TED. This chronic state may gradually undermine the glymphatic system's functionality, hindering its capacity to clear waste and maintain homeostasis. Our correlation analysis, which demonstrate a negative correlation between the ALPS values and disease duration, substantiates the inference that longer disease duration is associated with diminished glymphatic function. Notably, a greater palpebral fissure height, which is indicative of more severe disease, may also contribute to a more severe glymphatic system dysfunction. Therefore, disease duration of TED and severity of ocular manifestations as reflected by palpebral fissure height could be critical factors in the dysfunction of the glymphatic system.

The glymphatic system, a structure akin to the lymphatic system, plays a critical role in the brain and eye, facilitating the clearance of metabolic waste and maintaining tissue homeostasis.[20] Recent studies have significantly highlighted the critical role of the ocular glymphatic system in maintaining the health of the optic nerve and in responding to diseases, particularly in the clearance of metabolic waste and the maintenance of ocular fluid homeostasis. In glaucoma mouse models and patients, research has indicated that increased intraocular pressure may lead to increased resistance to CSF flow in the eye, thereby affecting the function of the glymphatic system.[41] Furthermore, elevated intraocular pressure has been associated with a decrease in the expression of aquaporin-4 (AQP4) water channel proteins in the retina, while an increase in expression at the optic nerve head, which may promote the activation of astrocytes and the upregulation of water channels, considered a marker of axonal injury in glaucoma.[42,43] Additional research through animal models has found that after optic nerve injury, the expression levels of AQP4 are significantly downregulated, which may be related to the dysfunction of the glymphatic system.[44] Patients with TED typically present with high intraocular pressure and optic nerve damage, suggesting that this may be one of the reasons for the altered function of the brain's glymphatic system in TED patients. Given that TED is an autoimmune inflammatory disease, the observed dysfunction in the glymphatic system may be attributed to the elevated levels of inflammatory cytokines, such as IL-6, which has been shown to be increased in TED patients.[45] Current evidence supports the notion that these cytokines can either directly infiltrate the CNS or cause leakage of the blood-brain barrier.[46–49] This infiltration or leakage leads to an increase in the concentration of pro-inflammatory cytokines within the brain.[50] Once in the CNS, these cytokines induce reactive morphological changes in glial cells, including astrocytes and microglia.[51] These changes contribute to a decrease in the exchange of CSF and ISF, impairing the glymphatic flow and leading to a decrease in the system's ability to clear metabolic waste from the brain.[52,53] The resulting accumulation of waste and cytokines within the CNS is hypothesized to further exacerbate inflammation, thereby creating a vicious cycle that suppresses glymphatic flow and culminates in glymphatic system dysfunction.[54,55] This proposed mechanism could explain the observed impairments in glymphatic activity in TED patients, particularly in those inactive patients with longer disease duration, where the cumulative effects of chronic inflammation are likely to have a more pronounced impact on the glymphatic system. However, the current evidence is still not sufficient enough to establish a direct causal relationship, and there may be additional, as-yet-unexplored mechanisms influencing the glymphatic system's functionality.

The possibility that glymphatic system dysfunction in TED is associated with microglial dysregulation is tentatively suggested by recent neuroimaging studies.[10,11] These studies have reported alterations in brain neuroimaging that align with the pathophysiological shifts characterized by heightened microglial activation. Specifically, an increase in activated microglia has been observed to suppress neuronal activity and is negatively correlated with fractional anisotropy.[56,57] This evidence might offer some initial support to the hypothesis that the brain alterations in TED are associated with the activation of glial cells, which impacts the glymphatic system and leads to the accumulation of toxic molecules in the brain. This accumulation may result in structural and functional alterations in the brains of TED patients, contributing to the emotional and psychological symptoms.

Our study using DTI-ALPS revealed significant glymphatic dysfunction in TED patients, particularly in the left hemisphere and those with longer disease duration. These findings suggest that impaired glymphatic clearance may contribute to the buildup of metabolic waste and inflammatory cytokines, exacerbating both orbital and CNS involvement in TED. Clinically, this supports early and sustained intervention to limit chronic inflammation and preserve glymphatic function. Incorporating DTI-ALPS into routine assessment could improve disease monitoring and enable more personalized treatment by identifying patients at risk of neurological complications.

Moreover, both therapeutic interventions and thyroid hormone fluctuations may impact glymphatic function. Commonly used treatments, including corticosteroids, immunomodulators, and biologics, may indirectly support glymphatic flow by modulating astrocyte activity and blood-brain barrier integrity, which are known to be disrupted by pro-inflammatory cytokines.[58,59] Similarly, variations in thyroid hormone levels can influence immunity system[60] and metabolic processes,[61] potentially affecting glymphatic dynamics in TED. Further research is needed to clarify these mechanisms and determine whether targeting glymphatic function can improve ocular and neurocognitive outcomes.

Our study on the glymphatic system in TED patients using DTI-ALPS has several limitations. The cross-sectional nature of the study, coupled with its constrained sample size, warrants careful interpretation of the findings, as further validation in larger, more diverse populations is needed. Future studies should consider longitudinal designs to monitor changes in the ALPS values over time. While DTI-ALPS has offered valuable insights, the exclusive use of this single modality may not fully capture the complexity of the glymphatic system. Integrating additional analysis methods, such as quantifying PVS volume, could enhance the credibility and depth of our findings. Moreover, the application of multimodal MRI techniques has the potential to clarify the complex interplay between glymphatic function and the structural and functional brain alterations in TED. Furthermore, the conduct of future animal studies for pathological validation is essential to establish the mechanisms connecting TED with glymphatic dysfunction, thereby offering a more profound biological insight.

Conclusion

In conclusion, our study utilized DTI-ALPS to investigate glymphatic system dysfunction in TED. We discovered that TED patients, particularly those who were inactive, exhibited a significant reduction in the left ALPS values which were negatively associated with disease duration, indicating that glymphatic system dysfunction demonstrating an association with disease activity and duration. Our findings suggest that abnormalities in the glymphatic system might play an important role in the pathophysiology of brain alterations in TED. This study underscores the value of further research into the glymphatic system in TED. Further studies are essential to validate these preliminary findings, elucidate the underlying pathophysiological mechanisms, and determine the clinical relevance of the observed glymphatic system alterations in TED.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (82388101, 82271122, 82201235), the Science and Technology Commission of Shanghai (20DZ2270800), the Shanghai Key Clinical Specialty, Shanghai Eye Disease Research Center (2022ZZ01003), the Biobank Project of Shanghai Ninth People's Hospital (YBKB202211), the Research Center for Eye Disease and Visual Rehabilitation, and the Key Project of Yuanshen Rehabilitation Institute, Shanghai Jiao Tong University School of Medicine (yskf1-24-0926-2; yskf2-24-0926-2).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a consensus statement by the American Thyroid Association and the European Thyroid Association. *Thyroid*. 2022;32(12):1439–1470. doi:10.1089/thy.2022.0251
2. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of graves' disease and ophthalmopathy. *Endocrine Reviews*. 2003;24(6):802–835. doi:10.1210/er.2002-0020
3. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362(8):726–738. doi:10.1056/NEJMra0905750

4. Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: implications for immunotherapy. *Curr Opin Ophthalmol*. 2011;22(5):385–390. doi:10.1097/ICU.0b013e3283499446
5. Estcourt S, Quinn AG, Vaidya B. Quality of life in thyroid eye disease: impact of quality of care. *Eur J Endocrinol*. 2011;164(5):649–655. doi:10.1530/EJE-11-0055
6. Sharma A, Stan MN, Rootman DB. Measuring Health-Related Quality of Life in Thyroid Eye Disease. *J Clin Endocrinol Metab*. 2022;107 (Suppl_1):S27–S35. doi:10.1210/clinem/dgac230
7. Zhang H, Liu Y, Xia D, et al. The insular cortex is not insular in thyroid eye disease: neuroimaging revelations of central-peripheral system interaction. *J Neuroinflammation*. 2024;21(1):51. doi:10.1186/s12974-024-03044-4
8. Zhang H, Liu Y, Jiang M, et al. Immune-related visual dysfunction in thyroid eye disease: a combined orbital and brain neuroimaging study. *Eur Radiol*. 2024;34(7):4516–4526. doi:10.1007/s00330-023-10309-8
9. Jiang WH, Liu J, Zhou J, et al. Altered dynamic brain activity and functional connectivity in thyroid-associated ophthalmopathy. *Hum Brain Mapp*. 2023;44(16):5346–5356. doi:10.1002/hbm.26437IF
10. Wu Q, Hu H, Chen W, et al. Morphological and microstructural brain changes in thyroid-associated ophthalmopathy: a combined voxel-based morphometry and diffusion tensor imaging study. *J Endocrinol Invest*. 2020;43(11):1591–1598. doi:10.1007/s40618-020-01242-4
11. Li R, Li J, Wang Z. Thyroid-associated ophthalmopathy: Using diffusion tensor imaging to evaluate visual pathway microstructural changes. *Front Neurol*. 2022;13:1025666. doi:10.3389/fneur.2022.1025666
12. Luo L, Zhang L, Huang H, et al. 3.0 T multi-parametric MRI reveals metabolic and microstructural abnormalities in the posterior visual pathways in patients with thyroid eye disease. *Front Neurosci*. 2024;17:1306364. doi:10.3389/fnins.2023.1306364
13. Margoni M, Pagani E, Meani A, et al. Cognitive Impairment Is Related to Glymphatic System Dysfunction in Pediatric Multiple Sclerosis. *Ann Neurol*. 2024;95(6):1080–1092. doi:10.1002/ana.26911
14. Kim M, Hwang I, Park JH, et al. Comparative analysis of glymphatic system alterations in multiple sclerosis and neuromyelitis optica spectrum disorder using MRI indices from diffusion tensor imaging. *Hum Brain Mapp*. 2024;45(5):e26680. doi:10.1002/hbm.26680
15. Mo J, Han K, Deng K, et al. Glymphatic abnormality in systemic lupus erythematosus detected by diffusion tensor image analysis along the perivascular space. *Rheumatology*. 2024. doi:10.1093/rheumatology/keae251
16. Carotenuto A, Cacciaguerra L, Pagani E, Preziosa P, Filippi M, Rocca MA. Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. *Brain*. 2022;145(8):2785–2795. doi:10.1093/brain/awab454
17. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochem Res*. 2015;40(12):2583–2599. doi:10.1007/s11064-015-1581-6
18. Cai Y, Zhang Y, Leng S, et al. The relationship between inflammation, impaired glymphatic system, and neurodegenerative disorders: A vicious cycle. *Neurobiol Dis*. 2024;192:106426. doi:10.1016/j.nbd.2024.106426
19. Hablitz LM, Nedergaard M. The glymphatic system: a novel component of fundamental neurobiology. *J Neurosci*. 2021;41(37):7698–7711. doi:10.1523/JNEUROSCI.0619-21.2021
20. Naganawa S, Taoka T, Ito R, Kawamura M. The glymphatic system in humans: investigations with magnetic resonance imaging. *Invest Radiol*. 2024;59(1):1–12. doi:10.1097/RLI.0000000000000969
21. Mathieu E, Gupta N, Ahari A, Zhou X, Hanna J, Yücel YH. Evidence for cerebrospinal fluid entry into the optic nerve via a glymphatic pathway. *Invest Ophthalmol Vis Sci*. 2017;58(11):4784–4791. doi:10.1167/iovs.17-22290
22. Wostyn P, De Groot V, Van Dam D, Audenaert K, Killer HE, De Deyn PP. The glymphatic hypothesis of glaucoma: a unifying concept incorporating vascular, biomechanical, and biochemical aspects of the disease. *Biomed Res Int*. 2017;2017:5123148. doi:10.1155/2017/5123148
23. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface. *Prog Retin Eye Res*. 2018;63:20–68. doi:10.1016/j.preteyeres.2017.10.006
24. Liu S, Sun X, Ren Q, et al. Glymphatic dysfunction in patients with early-stage amyotrophic lateral sclerosis. *Brain*. 2024;147(1):100–108. doi:10.1093/brain/awad274
25. Siow TY, Toh CH, Hsu JL, et al. Association of sleep, neuropsychological performance, and gray matter volume with glymphatic function in community-dwelling older adults. *Neurology*. 2022;98(8):e829–e838. doi:10.1212/WNL.0000000000013215
26. Huang SY, Zhang YR, Guo Y, et al. Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. *Alzheimers Dement*. 2024;20(5):3251–3269. doi:10.1002/alz.13789
27. Taoka T, Masutani Y, Kawai H, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol*. 2017;35(4):172–178. doi:10.1007/s11604-017-0617-z
28. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of graves' orbitopathy. *Front Endocrinol*. 2020;11:615993.
29. Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves'orbitopathy. *Eur J Endocrinol*. 2021;185(4):G43–G67. doi:10.1530/EJE-21-0479
30. Oculoplastic and Orbital Disease Group of Chinese Ophthalmological Society of Chinese Medical Association. Thyroid Group of Chinese Society of Endocrinology of Chinese Medical Association. *Zhonghua Yan Ke Za Zhi*. 2022;58(9):646–668. doi:10.3760/cma.j.cn112142-20220421-00201
31. Espírito-Santo H, Pires CF, Garcia IQ, Daniel F, Silva AG, Fazio RL. Preliminary validation of the Portuguese Edinburgh Handedness Inventory in an adult sample. *Appl Neuropsychol Adult*. 2017;24(3):275–287. doi:10.1080/23279095.2017.1290636
32. Maximov II, Alnaes D, Westlye LT. Towards an optimised processing pipeline for diffusion magnetic resonance imaging data: Effects of artefact corrections on diffusion metrics and their age associations in UK Biobank. *Hum Brain Mapp*. 2019;40(14):4146–4162. doi:10.1002/hbm.24691
33. Liu X, Barisano G, Shao X, et al. Cross-vendor test-retest validation of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating glymphatic system function. *Aging Dis*. 2023. doi:10.14336/AD.2023.0321-2
34. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149–1160. doi:10.3758/BRM.41.4.1149
35. Pang H, Wang J, Yu Z, et al. Glymphatic function from diffusion-tensor MRI to predict conversion from mild cognitive impairment to dementia in Parkinson's disease. *J Neurol*. 2024;271(8):5598–5609. doi:10.1007/s00415-024-12525-8
36. Sacchi L, D'Agata F, Campisi C, et al. A "glympse" into neurodegeneration: diffusion MRI and cerebrospinal fluid aquaporin-4 for the assessment of glymphatic system in Alzheimer's disease and other dementias. *Hum Brain Mapp*. 2024;45(12):e26805. doi:10.1002/hbm.26805

37. Wu L, Zhang Z, Liang X, et al. Glymphatic system dysfunction in recovered patients with mild COVID-19: A DTI-ALPS study. *iScience*. 2023;27(1):108647. doi:10.1016/j.isci.2023.108647
38. Smith TJ, Hegedüs L, Douglas RS. Role of insulin-like growth factor-1 (IGF-1) pathway in the pathogenesis of Graves' orbitopathy. *Best Pract Res Clin Endocrinol Metab*. 2012;26:291–302.
39. Zhou M, Lin B, Wu P, et al. SOX9 induces orbital fibroblast activation in thyroid eye disease Via MAPK/ERK1/2 Pathway. *Invest Ophthalmol Vis Sci*. 2024;65(2):25. doi:10.1167/iovs.65.2.25
40. Rundle FF. Management of exophthalmos and related ocular changes in Graves'disease. *Metabolism*. 1957;6(1):36–48.
41. Mathieu E, Gupta N, Paczka-Giorgi LA, et al. Reduced cerebrospinal fluid inflow to the optic nerve in glaucoma. *Invest Ophthalmol Vis Sci*. 2018;59(15):5876–5884. doi:10.1167/iovs.18-24521
42. Dibas A, Yang MH, He S, Bobich J, Yorio T. Changes in ocular aquaporin-4 (AQP4) expression following retinal injury. *Mol Vis*. 2008;14:1770–1783.
43. Tehrani S, Johnson EC, Cepurna WO, Morrison JC. Astrocyte processes label for filamentous actin and reorient early within the optic nerve head in a rat glaucoma model. *Invest Ophthalmol Vis Sci*. 2014;55(10):6945–6952. doi:10.1167/iovs.14-14969
44. Suzuki H, Oku H, Horie T, et al. Changes in expression of aquaporin-4 and aquaporin-9 in optic nerve after crushing in rats. *PLoS One*. 2014;9(12):e114694. doi:10.1371/journal.pone.0114694
45. Leszczynska A, Molins B, Fernández E, Adán A, Ortiz-Perez S. Cytokine production in thyroid eye disease: in vitro effects of dexamethasone and IL-6 blockade with tocilizumab. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(10):2307–2314. doi:10.1007/s00417-019-04419-7
46. Banks WA. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. *Curr Pharm Des*. 2005;11(8):973–984. doi:10.2174/1381612053381684
47. Engelhardt B, Carare RO, Bechmann I, Flügel A, Laman JD. Weller RO vascular, glial, and lymphatic immune gateways of the central nervous system. *Acta Neuropathol*. 2016;132:317–338. doi:10.1007/s00401-016-1606-5
48. Banks WA, Kastin AJ, Gutierrez EG. Penetration of interleukin-6 across the murine blood-brain barrier. *Neurosci Lett*. 1994;179:53–56. doi:10.1016/0304-3940(94)90933-4
49. Huang X, Hussain B, Chang J. Peripheral inflammation and blood–brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*. 2021;27:36–47. doi:10.1111/cns.13569
50. Craig CF, Filippone RT, Stavely R, Bornstein JC, Apostolopoulos V, Nurgali K. Neuroinflammation as an etiological trigger for depression comorbid with inflammatory bowel disease. *J Neuroinflammation*. 2022;19:4. doi:10.1186/s12974-021-02354-1
51. Di Benedetto S, Müller L, Wenger E, Düzel S, Pawelec G. Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. *Neurosci Biobehav Rev*. 2017;75:114–128. doi:10.1016/j.neubiorev.2017
52. Iliff JJ, Chen MJ, Plog BA, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci*. 2014;34:16180–16193. doi:10.1523/JNEUROSCI.3020-14.2014
53. Kress BT, Iliff JJ, Xia M, et al. Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol*. 2014;76:845–861. doi:10.1002/ana.24271
54. Sun Y, Koyama Y, Shimada S. Inflammation from peripheral organs to the brain: how does systemic inflammation cause neuroinflammation? *Front Aging Neurosci*. 2022;14:903455. doi:10.3389/fnagi.2022.903455
55. Mogensen FL, Delle C, Nedergaard M. The glymphatic system (en)during inflammation. *Int J Mol Sci*. 2021;22(14):7491. doi:10.3390/ijms22147491
56. Badimon A, Strasburger HJ, Ayata P, et al. Negative feedback control of neuronal activity by microglia. *Nature*. 2020;586(7829):417–423. doi:10.1038/s41586-020-2777-8
57. Preziosa P, Kiljan S, Steenwijk MD, et al. Axonal degeneration as substrate of fractional anisotropy abnormalities in multiple sclerosis cortex. *Brain*. 2019;142(7):1921–1937. doi:10.1093/brain/awz143
58. Kim ME, Lee JS. Mechanisms and emerging regulators of neuroinflammation: exploring new therapeutic strategies for neurological disorders. *Curr Issues Mol Biol*. 2024;47(1):8. doi:10.3390/cimb47010008
59. Li J, Chen L, Liu S, et al. Hydrocortisone mitigates alzheimer's-related cognitive decline through modulating oxidative stress and neuroinflammation. *Cells*. 2023;12(19):2348. doi:10.3390/cells12192348
60. Wenzek C, Boelen A, Westendorf AM, Engel DR, Moeller LC, Führer D. The interplay of thyroid hormones and the immune system - where we stand and why we need to know about it. *Eur J Endocrinol*. 2022;186(5):R65–R77. doi:10.1530/EJE-21-1171
61. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev*. 2014;94:355–382.