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Morphometric Analysis of the Optic Nerve Using MRI in Normal vs. Glaucoma Patients

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ABSTRACT

Background: Glaucoma, a leading cause of irreversible blindness, is characterized by progressive optic nerve damage, primarily affecting retinal ganglion cells and axons.

Objective: To assess and compare MRI-derived optic nerve measurements in POAG patients and healthy controls, and to evaluate the diagnostic accuracy and reliability of these measurements.

Methods: A total of 85 participants (45 POAG patients and 40 healthy controls) were included in this prospective observational study. MRI scans were performed using a 3T MRI scanner with high-resolution T2-weighted fat-suppressed sequences. Optic nerve measurements were taken at three posterior levels (3 mm, 6 mm, and 9 mm).

Results: The POAG group exhibited significantly smaller OND (mean 2.38 ± 0.22 mm) and ON-CSA (mean 4.51 ± 0.81 mm^2) compared to the control group (OND: 2.62 ± 0.24 mm, ON-CSA: 5.39 ± 0.90 mm^2), with p-values < 0.001 for both. The SASW was significantly wider in the POAG group (2.55 ± 0.28 mm) compared to controls (2.27 ± 0.27 mm, p = 0.003). The diagnostic accuracy of OND and ON-CSA was high, with AUC values of 0.83 and 0.81, respectively. The combination of OND and ON-CSA yielded an AUC of 0.88, indicating excellent diagnostic potential. Intra-rater and inter-rater reliability were excellent, with ICC values above 0.90.

Conclusion: MRI-based morphometric analysis reveals significant reductions in optic nerve diameter and cross-sectional area in POAG patients, with a concomitant widening of the subarachnoid space. These findings support the use of MRI-derived metrics, particularly OND and ON-CSA, as reliable biomarkers for detecting glaucoma.

Keywords: *Glaucoma, Optic Nerve, MRI, Optic Nerve Diameter, Optic Nerve Cross-Sectional Area, Primary Open-Angle Glaucoma*

1. INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness worldwide, affecting an estimated 76 million individuals globally and projected to reach over 110 million by 2040 [1]. It is a progressive optic neuropathy characterized by retinal ganglion cell death and axonal degeneration of the optic nerve, ultimately leading to visual field loss [2]. Although elevated intraocular pressure (IOP) remains the most important risk factor, glaucoma is now recognized as a multifactorial disease involving complex vascular, genetic, and biomechanical mechanisms [3]. Early detection of glaucomatous changes is crucial since functional impairment is often preceded by subtle structural alterations within the optic nerve head and retinal nerve fiber layer.

Traditionally, clinical evaluation of glaucoma relies on optic disc examination, visual field testing, and optical coherence tomography (OCT), which provides high-resolution imaging of the peripapillary and macular retinal nerve fiber layer [4]. However, these techniques are limited to the intraocular segment of the optic nerve and cannot directly visualize changes in the retrobulbar portion. This limitation is clinically significant because axonal damage in glaucoma is not confined to the intraocular portion but extends along the length of the optic nerve [5]. Thus, imaging modalities that can capture morphometric changes throughout the entire nerve may provide additional diagnostic and prognostic value.

Magnetic resonance imaging (MRI) offers a unique advantage in this regard, as it allows non-invasive visualization of the optic nerve and surrounding structures, including the optic nerve sheath and perineural subarachnoid space [6]. With the advent of high-resolution, fat-suppressed orbital MRI sequences, it has become possible to obtain reproducible morphometric measurements such as optic nerve diameter (OND), optic nerve sheath diameter (ONSD), and optic nerve cross-sectional area (ON-CSA) at predefined distances posterior to the globe [7]. These parameters can provide objective quantitative markers of axonal integrity, which may help in distinguishing glaucomatous from normal eyes. Several studies have suggested that glaucoma patients exhibit a significant reduction in OND and ON-CSA compared to healthy individuals, reflecting axonal loss and structural remodeling [8]. In contrast, ONSD may remain relatively preserved due to the mechanical stability of the dura-arachnoid complex, resulting in an apparent widening of the perineural subarachnoid space (SASW) in glaucoma [9]. Furthermore, MRI-based morphometric changes have been shown to correlate with both visual field defects and OCT-derived retinal nerve fiber layer thinning, reinforcing their clinical relevance [10].

The integration of MRI into glaucoma research is also motivated by its potential to explore pathophysiological mechanisms beyond IOP. Alterations in the optic nerve sheath and CSF dynamics, for example, have been proposed as contributing factors to glaucomatous damage through disturbed translaminar pressure gradients [11]. Hence, MRI-based morphometry may not only serve as a diagnostic biomarker but also provide insights into disease mechanisms. Given these considerations, the present study aims to compare optic nerve morphometrics between glaucoma patients and healthy controls using MRI. By focusing on quantitative measurements of OND, ONSD, SASW, and ON-CSA at standardized retrobulbar levels, this work seeks to establish the diagnostic value and reliability of MRI-derived metrics in differentiating glaucomatous from normal optic nerves.

Objective:

To assess and compare MRI-derived optic nerve measurements in POAG patients and healthy controls, and to evaluate the diagnostic accuracy and reliability of these measurements.

2. METHODOLOGY

This was a prospective observational study designed to evaluate optic nerve morphometry using high-resolution MRI in patients with primary open-angle glaucoma (POAG) compared to healthy controls. The study was conducted at Mardan Medical Complex, Mardan from June 2023 to June 2024. A total of 85 participants were included, recruited through non-probability consecutive sampling.

Inclusion Criteria

- Adults aged 18 years and above.
- Patients diagnosed with primary open-angle glaucoma (POAG) in at least one eye, confirmed by ophthalmologic evaluation, including visual field testing, and optical coherence tomography (OCT).
- Healthy control subjects without a history of ocular diseases, glaucoma, or systemic conditions affecting the optic nerve.
- Written informed consent obtained from participants or their legal guardians.

Exclusion Criteria

- Secondary glaucoma (e.g., angle-closure glaucoma, congenital glaucoma, or steroid-induced glaucoma).
- History of optic neuritis, optic neuropathies, or retinal diseases (e.g., diabetic retinopathy).
- Major neurological or systemic disorders affecting the optic nerve (e.g., multiple sclerosis).
- Severe media opacity that would prevent clear MRI imaging.
- Any condition that contraindicates MRI (e.g., metal implants, claustrophobia).

Data Collection:

After obtaining written informed consent from all participants, detailed demographic and clinical data were collected. This included age, gender, systemic health status, type of glaucoma (if applicable), disease stage, and best-corrected visual acuity. Intraocular pressure (IOP) measurements and axial length of the eye were also recorded for each participant. The MRI

imaging was performed using a 3T MRI scanner, with high-resolution T2-weighted fat-suppressed sequences to capture detailed images of the optic nerve. Measurements of optic nerve diameter (OND), optic nerve sheath diameter (ONSD), optic nerve cross-sectional area (ON-CSA), and subarachnoid space width (SASW) were obtained at three standard levels: 3 mm, 6 mm, and 9 mm posterior to the globe. These measurements were taken by two trained and blinded neuroradiologists using specialized post-processing software to ensure accuracy and minimize bias. The MRI images were analyzed to assess differences in these optic nerve metrics between the POAG group and healthy controls.

Statistical Analysis:

All collected data were entered into a database and analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL). Continuous variables, including age and the MRI-derived measurements (OND, ONSD, ON-CSA, SASW), were presented as means ± standard deviation and were compared between the POAG and control groups using independent t-tests. For categorical variables such as gender and glaucoma diagnosis, frequencies and percentages were calculated, and group comparisons were performed using chi-square tests. In order to control for potential confounders, such as age and axial length, analysis of covariance (ANCOVA) was utilized to adjust the optic nerve measurements for these variables. Diagnostic performance of the MRI-derived metrics was assessed by constructing receiver operating characteristic (ROC) curves, which were used to determine the area under the curve (AUC) for each optic nerve measurement. The optimal cut-off values for distinguishing POAG from healthy controls were determined by the Youden index. To assess the reliability of the MRI measurements, both inter-rater and intra-rater reliability were calculated using intraclass correlation coefficients (ICCs). A p-value of ≤ 0.05 was considered statistically significant for all analyses.

3. RESULTS

In this study, 85 participants were included, with 45 having primary open-angle glaucoma (POAG) and 40 healthy controls. The average age of participants in both groups was similar, around 58 years for POAG and 57 years for controls, with no significant age difference ($p = 0.72$). The gender distribution was also comparable, with slightly more males in both groups. The POAG group had a significantly higher intraocular pressure (IOP) of 22.1 ± 3.5 mmHg compared to the controls' 15.3 ± 2.4 mmHg ($p < 0.001$). The visual acuity was notably worse in the POAG group (mean 0.48 ± 0.30) compared to the healthy controls (mean 0.99 ± 0.05), highlighting the expected functional impairment in glaucoma patients. The axial length was also similar between groups (POAG: 23.5 ± 0.9 mm, Control: 23.6 ± 0.8 mm), reinforcing that the two groups were comparable in terms of eye size.

Table 1. Demographics and Baseline Characteristics of Participants (n = 85)

Variable	POAG Group (n = 45)	Control Group (n = 40)	p-value
Age (years), mean ± SD	58.3 ± 10.1	57.2 ± 9.8	0.72
Male, n (%)	24 (53.3%)	22 (55%)	0.84
Female, n (%)	21 (46.7%)	18 (45%)	0.84
Axial Length (mm), mean ± SD	23.5 ± 0.9	23.6 ± 0.8	0.62
IOP (mmHg), mean ± SD	22.1 ± 3.5	15.3 ± 2.4	<0.001
Glaucoma Stage, n (%)			
Mild	12 (26.7%)	—	—
Moderate	15 (33.3%)	—	—
Severe	18 (40%)	—	—
Visual Acuity, mean ± SD	0.48 ± 0.30	0.99 ± 0.05	<0.001

The measurements of the optic nerve diameter (OND) revealed significant differences between the POAG group and controls. At the 3 mm posterior level, the POAG group had an average OND of 2.40 ± 0.23 mm, significantly smaller than the control group's 2.62 ± 0.24 mm ($p < 0.001$). Similarly, at the 6 mm and 9 mm levels, the POAG group had smaller OND values (2.36 ± 0.22 mm and 2.38 ± 0.21 mm) compared to the controls (2.60 ± 0.25 mm and 2.61 ± 0.24 mm), with all differences being statistically significant. The optic nerve sheath diameter (ONSD) did not show significant differences between the two groups (POAG: 4.85 ± 0.35 mm, Controls: 4.86 ± 0.32 mm), suggesting that the structural changes in glaucoma primarily affect the nerve itself rather than the surrounding sheath. Additionally, the cross-sectional area of the optic nerve (ON-CSA) was significantly smaller in the POAG group at all levels (e.g., 4.56 ± 0.79 mm^2 at 3 mm) compared to the controls (5.39 ± 0.90 mm^2). Lastly, the subarachnoid space width (SASW) was wider in the POAG group (2.55 ± 0.28 mm) than in controls (2.27

± 0.27 mm), with a significant difference at the 6 mm and 9 mm levels (p = 0.04).

Table 2. MRI Optic Nerve Measurements at 3 mm, 6 mm, and 9 mm Posterior to the Globe

Measurement	3 mm Level (mm)	6 mm Level (mm)	9 mm Level (mm)	p-value
Optic Nerve Diameter (OND), mean ± SD	2.40 ± 0.23	2.36 ± 0.22	2.38 ± 0.21	<0.001
Optic Nerve Sheath Diameter (ONSD), mean ± SD	4.85 ± 0.35	4.90 ± 0.34	4.92 ± 0.33	0.10
Optic Nerve Cross-Sectional Area (ON-CSA, mm²), mean ± SD	4.56 ± 0.79	4.49 ± 0.83	4.51 ± 0.80	<0.001
Subarachnoid Space Width (SASW, mm), mean ± SD	2.55 ± 0.28	2.59 ± 0.29	2.62 ± 0.27	0.04

The results confirm that the POAG group exhibited significantly smaller optic nerve diameters compared to controls. The mean OND for POAG was 2.38 ± 0.22 mm, which was 0.24 mm smaller than the control group's 2.62 ± 0.24 mm (p < 0.001). Optic nerve cross-sectional area (ON-CSA) was also reduced in POAG, with a mean of 4.51 ± 0.81 mm² compared to 5.39 ± 0.90 mm² in controls (p < 0.001). However, the optic nerve sheath diameter (ONSD) showed no significant difference between groups (p = 0.52), indicating that while the optic nerve itself was affected, the surrounding sheath remained relatively intact in both groups. The subarachnoid space width (SASW) was significantly wider in the POAG group (2.55 ± 0.28 mm) compared to the controls (2.27 ± 0.27 mm), further supporting the idea of altered CSF dynamics in glaucoma patients (p = 0.003).

Table 3. Group Comparison of Optic Nerve Measurements Between POAG and Control Groups

Measurement	POAG Group (mean ± SD)	Control Group (mean ± SD)	Mean Difference (95% CI)	p-value
Optic Nerve Diameter (OND, mm)	2.38 ± 0.22	2.62 ± 0.24	−0.24 (−0.32, −0.16)	<0.001
Optic Nerve Sheath Diameter (ONSD, mm)	4.91 ± 0.34	4.86 ± 0.32	+0.05 (−0.07, +0.18)	0.52
Optic Nerve Cross-Sectional Area (ON-CSA, mm²)	4.51 ± 0.81	5.39 ± 0.90	−0.88 (−1.22, −0.54)	<0.001
Subarachnoid Space Width (SASW, mm)	2.55 ± 0.28	2.27 ± 0.27	+0.27 (+0.10, +0.44)	0.003

The diagnostic accuracy of optic nerve measurements was assessed using receiver operating characteristic (ROC) analysis. The optic nerve diameter (OND) performed well, with an AUC of 0.83 (95% CI 0.74–0.90), indicating good diagnostic power for distinguishing POAG from controls. An optimal cut-off of ≤2.50 mm for OND provided 78% sensitivity and 78% specificity. The ON-CSA also showed good diagnostic performance (AUC = 0.81), with a cut-off of ≤4.90 mm² offering 73% sensitivity and 80% specificity. However, the subarachnoid space width (SASW) had a lower diagnostic performance (AUC = 0.64) and was less useful in differentiating between the groups. The combined use of OND and ON-CSA in a logistic regression model improved diagnostic performance, reaching an AUC of 0.88, with 82% sensitivity and 83% specificity.

Table 4. ROC Analysis for Diagnostic Accuracy of MRI-Derived Measurements

Measurement	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)
Optic Nerve Diameter (OND, mm)	0.83 (0.74–0.90)	≤2.50	78	78
Optic Nerve Cross-Sectional Area (ON-CSA, mm²)	0.81 (0.72–0.89)	≤4.90	73	80
Subarachnoid Space Width (SASW, mm)	0.64 (0.53–0.75)	≥2.40	58	68

Combined OND + ON-CSA (logistic regression)	0.88 (0.80–0.93)	—	82	83

The intra-rater and inter-rater reliability of the MRI measurements were excellent, indicating that the measurements were consistently reproducible. For optic nerve diameter (OND), the intra-rater ICC was 0.95 (95% CI 0.92–0.97), and the inter-rater ICC was 0.93 (95% CI 0.89–0.96), suggesting strong agreement between measurements taken by the same rater and different raters. For optic nerve sheath diameter (ONSD), the intra-rater ICC was 0.94 (95% CI 0.90–0.96), and the inter-rater ICC was 0.92 (95% CI 0.88–0.95). The optic nerve cross-sectional area (ON-CSA) also demonstrated excellent reliability, with an intra-rater ICC of 0.96 (95% CI 0.94–0.98) and an inter-rater ICC of 0.94 (95% CI 0.91–0.97). The subarachnoid space width (SASW) had slightly lower ICC values (intra-rater: 0.93, inter-rater: 0.91), but still demonstrated good reliability for clinical use.

Table 5. Intra-rater and Inter-rater Reliability of MRI Measurements (ICC Values)

Measurement	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)
Optic Nerve Diameter (OND, mm)	0.95 (0.92–0.97)	0.93 (0.89–0.96)
Optic Nerve Sheath Diameter (ONSD, mm)	0.94 (0.90–0.96)	0.92 (0.88–0.95)
Optic Nerve Cross-Sectional Area (ON-CSA, mm²)	0.96 (0.94–0.98)	0.94 (0.91–0.97)
Subarachnoid Space Width (SASW, mm)	0.93 (0.89–0.96)	0.91 (0.87–0.94)

Logistic regression analysis revealed that both optic nerve diameter (OND) and optic nerve cross-sectional area (ON-CSA) were significant independent predictors of glaucoma status. For each 0.1 mm decrease in mean OND, the odds of having glaucoma increased by 1.48 times (95% CI 1.22–1.82, $p < 0.001$). Similarly, each 0.5 mm² reduction in ON-CSA was associated with a 1.37 times higher likelihood of having glaucoma (95% CI 1.12–1.69, $p = 0.002$). Age and axial length were not significant predictors in the multivariable model, with p-values of 0.22 and 0.55, respectively, indicating that these factors did not have a significant impact on the likelihood of having glaucoma when controlling for optic nerve measurements.

Table 6. Logistic Regression for Predictors of Glaucoma Status

Predictor	Adjusted OR (95% CI)	p-value
Mean OND (per 0.1 mm decrease)	1.48 (1.22–1.82)	<0.001
Mean ON-CSA (per 0.5 mm² decrease)	1.37 (1.12–1.69)	0.002
Age (per 5 years increase)	1.09 (0.95–1.26)	0.22
Axial Length (per 0.5 mm increase)	1.07 (0.86–1.34)	0.55

4. DISCUSSION

The results of this study provide valuable insights into the morphometric changes of the optic nerve in patients with primary open-angle glaucoma (POAG) compared to healthy controls. Our findings highlight significant structural differences in the optic nerve between the two groups, with smaller optic nerve diameters (OND) and cross-sectional areas (ON-CSA) in POAG patients, as well as wider subarachnoid space widths (SASW). These results are consistent with previous research that has demonstrated a reduction in optic nerve dimensions in glaucomatous eyes, likely reflecting the loss of retinal ganglion cells and axonal thinning as part of the disease process [12]. The most striking finding in this study was the significant reduction in optic nerve diameter (OND) at all three measured levels in the POAG group compared to controls. The POAG group exhibited a mean OND of 2.38 mm at the 3 mm level, 2.36 mm at the 6 mm level, and 2.38 mm at the 9 mm level, all significantly smaller than the control group's OND, which was 2.62 mm, 2.60 mm, and 2.61 mm, respectively. This reduction in OND is consistent with previous research, which has reported a similar thinning of the optic nerve in glaucomatous eyes. The thinning is likely attributable to the degeneration of retinal ganglion cells and axonal loss, which are hallmark features of glaucoma [13]. This structural change is thought to precede functional impairment, which is typically detected later through visual field testing. In addition to OND, the optic nerve cross-sectional area (ON-CSA) was also significantly smaller in the POAG group, with a mean value of 4.51 mm², compared to the controls, who had a mean ON-CSA of 5.39 mm². This reduction in ON-CSA in POAG patients aligns with findings from previous research, which suggests that glaucomatous damage leads to a reduction in the total axonal content of the optic nerve [14]. The loss of axons results in a smaller nerve cross-sectional area, making ON-CSA a reliable marker of glaucomatous damage. Moreover, the substantial reduction in ON-CSA observed here supports the utility of MRI as a non-invasive tool for assessing structural changes in the optic nerve,

potentially complementing other clinical tests like OCT.

Interestingly, the subarachnoid space width (SASW) was significantly wider in the POAG group (2.55 mm) compared to controls (2.27 mm). This widening of the subarachnoid space has been attributed to alterations in the pressure dynamics within the optic nerve, particularly changes in the translaminar pressure gradient that may occur in glaucoma. The increased SASW could reflect an adaptive or compensatory response to the axonal loss and subsequent changes in the nerve's structural integrity. Similar findings have been observed in previous research, which also reported a widening of the subarachnoid space in glaucoma patients, potentially reflecting increased perineural cerebrospinal fluid (CSF) dynamics due to axonal thinning [15]. While SASW is less studied than OND and ON-CSA, it may offer additional insights into the pathophysiology of glaucoma. Contrary to expectations, the optic nerve sheath diameter (ONSD) did not show significant differences between the POAG and control groups. The ONSD remained similar in both groups (POAG: 4.91 mm, Control: 4.86 mm), suggesting that while the optic nerve itself undergoes significant structural changes, the surrounding nerve sheath remains relatively preserved. This finding is in line with previous research, which has shown that the optic nerve sheath may not be as affected by glaucomatous damage as the nerve itself [16]. The preservation of ONSD in the context of glaucomatous optic neuropathy suggests that changes in the nerve structure are more localized to the nerve fibers rather than the surrounding sheath, which may be more resistant to the disease. The ROC analysis revealed that OND and ON-CSA were both excellent diagnostic markers for distinguishing POAG from healthy controls. The AUC for OND was 0.83, and for ON-CSA, it was 0.81, indicating good diagnostic accuracy. This aligns with previous research, which found that MRI-based morphometry, especially OND and ON-CSA, can serve as reliable biomarkers for detecting glaucomatous changes in the optic nerve. The combined use of OND and ON-CSA improved the diagnostic performance, with an AUC of 0.88, further supporting the idea that combining multiple MRI metrics enhances diagnostic accuracy [17]. The lower diagnostic performance of SASW (AUC = 0.64) suggests that while SASW may provide supplementary information, it is not as robust as OND and ON-CSA in distinguishing glaucoma from healthy eyes. For each 0.1 mm decrease in OND, the odds of having glaucoma increased by 1.48 times, and for each 0.5 mm^2 decrease in ON-CSA, the odds of glaucoma increased by 1.37 times. This supports the notion that smaller optic nerve diameters and cross-sectional areas are strong indicators of glaucomatous damage, as has been found in previous research. Interestingly, age and axial length did not significantly contribute to predicting glaucoma status in this model, suggesting that the primary structural changes in glaucoma are more closely linked to optic nerve degeneration rather than demographic or ocular parameters.

5. CONCLUSION

It is concluded that MRI-based morphometric analysis of the optic nerve, particularly OND and ON-CSA, provides valuable insights into glaucomatous changes. The significant reduction in OND and ON-CSA in POAG patients, coupled with the widening of SASW, supports the role of MRI in detecting structural alterations in glaucoma. These findings are consistent with previous research and highlight the potential of MRI as a non-invasive, reliable biomarker for glaucoma assessment. The diagnostic accuracy of OND and ON-CSA further suggests that these measurements could be useful in both clinical practice and research settings to complement traditional diagnostic methods such as IOP measurement and visual field testing.

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