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Comparison of Macular Choroidal Thickness in Treatment-Naive Normal-Tension Glaucoma and Ocular Hypertension Patients

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ABSTRACT

Introduction: To evaluate foveal, temporal parafoveal, and nasal parafoveal choroidal thicknesses together with retinal nerve fiber layer (RNFL) parameters in treatment-naive patients with normal-tension glaucoma (NTG), and to compare these findings with those of patients with ocular hypertension (OHT).

Methods: This retrospective cross-sectional study included one eye from each of 40 NTG patients and 66 OHT patients. In all participants, quadrant- and clock-hour-based RNFL measurements and foveal, temporal-parafoveal, and nasal-parafoveal choroidal thicknesses were assessed using optical coherence tomography.

Results: No significant differences were observed between the groups regarding age, sex, axial length, or disc area. Mean RNFL thickness and quadrant-based and clock-hour RNFL values were significantly lower in the NTG group than in the OHT group at all locations except the 9 o'clock sector ($p<0.05$). While no significant intergroup differences were detected in foveal or nasal parafoveal choroidal thickness, temporal parafoveal choroidal thickness was greater in the OHT group than in the NTG group ($p=0.047$).

Conclusion: Based on the present results, macular choroidal thickness by itself does not appear to provide sufficient discriminatory value in normal-tension glaucoma. Rather than relying solely on macular choroidal measurements, microvascular changes in the optic nerve head may represent a more relevant contributor to glaucomatous damage. Future investigations integrating functional vascular imaging modalities may clarify the mechanisms underlying the pathophysiology of normal-tension glaucoma.

Keywords: Normal-tension glaucoma, ocular hypertension, choroidal thickness, macular choroidal thickness

Introduction

Glaucoma is characterized by progressive loss of retinal ganglion cells, leading to irreversible visual field (VF) impairment over time (1). Although aging and elevated intraocular pressure (IOP) are considered the principal risk factors for glaucoma development, the presence of progressive optic nerve damage in some patients despite normal IOP levels suggests that pressure-independent mechanisms also contribute to disease pathogenesis (2-4). Among these mechanisms, neurodegenerative processes have been proposed to play a role in normal-tension glaucoma (NTG), whereby mitochondrial dysfunction in retinal ganglion cells, reduced energy metabolism, and increased oxidative stress may increase cellular vulnerability (5).

In patients with NTG, the pathophysiology of retinal ganglion cell loss is frequently associated with impaired microcirculation at the optic nerve head (ONH) and insufficient peripapillary choroidal perfusion (3). While the inner retinal layers are supplied by the retinal vasculature, the metabolic demands of the retinal pigment epithelium and photoreceptor layers are largely met by the choroidal circulation (6,7). Accordingly, choroidal structures are thought to play a role in glaucoma pathogenesis, particularly with respect to vascular mechanisms.

Variability in choroidal thickness has been attributed to multiple ocular and systemic determinants, such as age-related changes and axial length (AL) differences, which complicates its interpretation in glaucomatous eyes (8,9). Previous studies evaluating the relationship between choroidal thickness and glaucomatous damage have reported inconsistent findings. Some studies reported an association between choroidal parameters and glaucomatous injury (10-12). However, others found no significant differences between glaucoma patients and healthy individuals (9,13,14). Furthermore, studies assessing choroidal structures in OHT and glaucoma

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have indicated that choroidal alterations do not occur uniformly across all glaucoma subtypes or anatomical regions (15-17).

In the present study, foveal, temporal parafoveal, and nasal parafoveal choroidal thicknesses, together with quadrant- and clock-hour–based retinal nerve fiber layer (RNFL) parameters, were evaluated in treatment-naive patients with NTG and compared with those of patients with OHT who showed no RNFL damage or VF abnormalities and had a cup-to-disc (C/D) ratio ≤0.3. OHT patients were selected as the control group instead of healthy individuals to permit a more specific assessment of choroidal changes potentially related to glaucomatous damage in eyes with comparable optic disc morphology and without structural glaucomatous injury. The primary aim of this study was to evaluate macular choroidal thickness in treatment-naive NTG patients and to compare these findings with those of OHT patients.

Methods

Study Population

This retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and was approved by the Pamukkale University Ethics Committee (approval number: 60116787-020/956, date: 15.01.2020). Ophthalmological examination findings and OCT data from treatment-naive patients with NTG and OHT who presented to the clinic between March 2017 and January 2020 were reviewed retrospectively. Because of the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Inclusion criteria for the NTG group were defined as a newly established diagnosis of NTG, glaucomatous optic neuropathy characterized by neuroretinal rim thinning, and detectable RNFL defects. In addition, at least three reliable VF tests were required, with a minimum of two fulfilling the Anderson criteria (fixation losses <20% and false-positive/false-negative rates <10%). IOP was required to remain consistently below 21 mmHg, based on measurements obtained on three separate days at different times. Central corneal thickness was required to be within the range of 555–588 µm, and patients with prior glaucoma treatment were excluded.

Eligibility criteria for the OHT group included an IOP greater than 21 mmHg, a C/D ratio ≤0.3 in the absence of glaucomatous optic disc changes, and a central corneal thickness between 555 and 588 µm. Additional requirements were the absence of RNFL defects on OCT, normal findings on standard automated perimetry, and the absence of previous glaucoma treatment.

Only one eye per participant was included in the analysis. When both eyes met the eligibility criteria, the right eye was selected for analysis. Gonioscopy was performed in all cases to confirm an open anterior chamber angle and to exclude additional pathology.

Eyes with best-corrected visual acuity worse than 20/20 or spherical refractive error outside the range of −6.00 to +6.00 diopters were excluded. Other exclusion criteria included a history of ocular surgery or trauma, prior glaucoma treatment, systemic diseases (such as diabetes mellitus, hypertension, and inflammatory vascular disorders), amblyopia, obstructive sleep apnea syndrome, and obesity.

Demographic characteristics (age and sex) and findings from a comprehensive ophthalmologic examination were recorded for all participants. The analysis included VF indices, IOP, AL, and OCT-derived measurements.

Measurements

IOP measurements were obtained by means of Goldmann applanation tonometry, and AL was obtained by A-scan ultrasonography. Mean, quadrant-based, and clock-hour RNFL thicknesses, rim area, disc area, mean and vertical C/D ratios, and cup volume were assessed using the Optic Disc Cube 200 × 200 OCT protocol.

Foveal, temporal parafoveal, and nasal parafoveal choroidal thicknesses were measured using the 5-Line Raster OCT protocol. Foveal choroidal thickness was operationally defined as the vertical distance extending from the posterior margin of the retinal pigment epithelium to the choroid–sclera junction. Parafoveal measurements in the temporal and nasal regions were obtained at points located 500 µm from the foveal center on either side, using the same method. Choroidal thickness measurements were performed manually using the caliper tool provided by the OCT software.

OCT assessments were performed using a Cirrus HD-OCT platform (Carl Zeiss Meditec, Dublin, CA, USA), and images were acquired following standardized scanning procedures. All OCT measurements were performed by a single examiner using the same device and standard scanning procedures. The individual was unaware of the subjects' group assignments. The following parameters were recorded and statistically compared between the NTG and OHT groups: IOP, AL, RNFL thicknesses (mean, quadrant-based, and clock-hour), rim area, disc area, mean and vertical C/D ratios, cup volume, and foveal, temporal parafoveal, and nasal parafoveal choroidal thicknesses.

Statistical Analysis

Statistical analyses were performed using the SPSS software package (version 25.0, SPSS Inc., Chicago, IL, USA). Quantitative variables are reported as mean ± standard deviation together with minimum and maximum values, while categorical data are summarized as frequencies and percentages. The normality of the distribution was evaluated using the Kolmogorov–Smirnov test. For normally distributed parameters, intergroup comparisons were performed using the independent-samples t-test. Statistical significance was defined as a two-sided p value less than 0.05. Correction for multiple testing was not applied. No a priori sample size calculation was performed due to the retrospective design. All eligible patients within the study period were included.

Results

A total of 66 eyes from 66 patients with OHT and 40 eyes from 40 patients with NTG were included in the study. Demographic characteristics and baseline ocular parameters were comparable between groups, and no significant differences were observed in age, AL, or disc area (Table 1).

Choroidal thickness measurements are presented in Table 2. Temporal parafoveal choroidal thickness was significantly greater in the OHT group compared with the NTG group, whereas no significant intergroup

differences were observed in foveal or nasal parafoveal choroidal thickness.

In contrast, several ONH and RNFL parameters differed significantly between the groups. The NTG group demonstrated significantly lower mean RNFL thickness, as well as reduced RNFL thicknesses in the superior, temporal, inferior, and nasal sectors compared with the OHT group. In addition, rim area was significantly smaller in the NTG group, whereas mean and vertical C/D ratios and cup volume were significantly greater (Table 3, Figure 1).

Clock-hour analysis revealed significantly lower RNFL thickness in most sectors in the NTG group compared with the OHT group. The only sector without a significant intergroup difference was the 9 o'clock position (Table 3).

Table 1. Demographic and baseline ocular characteristics of the ocular hypertension and normal-tension glaucoma groups

Parameter	Ocular hypertension (group 1) n=66	Normotensive glaucoma (group 2) n=40	p value
Age (years)	51–69 (59.5±4.4)	51–69 (60.2±5.1)	0.480
Sex (M/F)	20/46 (30.3/69.7)	18/22 (45.0/55.0)	0.187
Axial length (mm)	21.86–25.32 (23.24±0.67)	22.05–25.35 (23.28±0.68)	0.763
Disc area (mm²)	1.32–3.19 (1.99±0.30)	1.06–2.89 (1.98±0.42)	0.904

*Data are presented as minimum–maximum (mean ± standard deviation). Between-group comparisons were performed using the independent samples t-test. A p value <0.05 was considered statistically significant. M/F: Male/female

Table 2. Comparison of macular choroidal thickness parameters between the ocular hypertension and normal-tension glaucoma groups

Parameter	Ocular hypertension (group 1) n=66	Normotensive glaucoma (group 2) n=40	p value
Temporal parafoveal choroidal thickness (µm)	150–296 (213.09±31.7)	131–278 (199.6±36.3)	0.047
Foveal choroidal thickness (µm)	175–316 (243.76±31)	168–304 (236.6±34.1)	0.270
Nasal parafoveal choroidal thickness (µm)	160–298 (222.89±33)	146–280 (216.9±35.9)	0.389

Table 3. Comparison of intraocular pressure, optic nerve head, and RNFL parameters between ocular hypertension and normal-tension glaucoma groups

Parameter	Ocular hypertension (Group 1) n=66	Normal-tension glaucoma (Group 2) n=40	p value
Intraocular pressure (mmHg)	24–28 (24.5±1.3)	13–20 (15.75±1.7)	<0.001
Average RNFL thickness (µm)	78–110 (94.47±6.8)	55–96 (74.3±9)	<0.001
Rim area (mm²)	0.92–1.97 (1.35±0.2)	0.37–1.6 (0.89±0.22)	<0.001
Average C/D ratio	0.3–0.77 (0.53±0.11)	0.28–0.84 (0.71±0.1)	<0.001
Vertical C/D ratio	0.15–0.73 (0.49±0.11)	0.47–0.86 (0.7±0.09)	<0.001
Cup volume (mm³)	0.004–0.771 (0.198±0.166)	0.003–0.812 (0.421±0.227)	<0.001
Superior RNFL thickness (µm)	93–150 (118.7±11)	64–130 (86.6±17.2)	<0.001
Temporal RNFL thickness (µm)	52–98 (68.6±10.6)	42–83 (55.9±10.5)	<0.001
Inferior RNFL thickness (µm)	55–144 (119.5±15.6)	50–132 (89.8±19.4)	<0.001
Nasal RNFL thickness (µm)	23–113 (69.98±10.5)	34–93 (62.6±12.6)	0.002
RNFL thickness clock hour 1 (µm)	44–173 (106.1±23.4)	44–150 (79.6±24.7)	<0.001
RNFL thickness clock hour 2 (µm)	59–127 (81.5±15.3)	37–99 (66.5±14.2)	<0.001
RNFL thickness clock hour 3 (µm)	39–84 (56.4±12.3)	31–72 (51.3±10.2)	0.033
RNFL thickness clock hour 4 (µm)	48–98 (67.8±12.5)	32–76 (57.1±10.1)	<0.001
RNFL thickness clock hour 5 (µm)	68–188 (116.7±27.4)	39–162 (86.2±24.6)	<0.001
RNFL thickness clock hour 6 (µm)	79–171 (128.9±23)	58–147 (100.6±24.9)	<0.001
RNFL thickness clock hour 7 (µm)	55–177 (117.8±30.9)	41–142 (90.2±23.0)	<0.001
RNFL thickness clock hour 8 (µm)	45–107 (69.8±12.9)	36–89 (57.6±12.5)	<0.001
RNFL thickness clock hour 9 (µm)	32–84 (55±9.4)	34–86 (54.7±12.3)	0.855
RNFL thickness clock hour 10 (µm)	56–146 (82±16.3)	46–103 (72.7±17.5)	0.007
RNFL thickness clock hour 11 (µm)	85–173 (123.3±21.1)	43–149 (90±28.2)	<0.001
RNFL thickness clock hour 12 (µm)	80–168 (125.3±22.2)	59–162 (91.6±26.8)	<0.001

RNFL: Retinal nerve fiber layer, C/D: Cup-to-disc

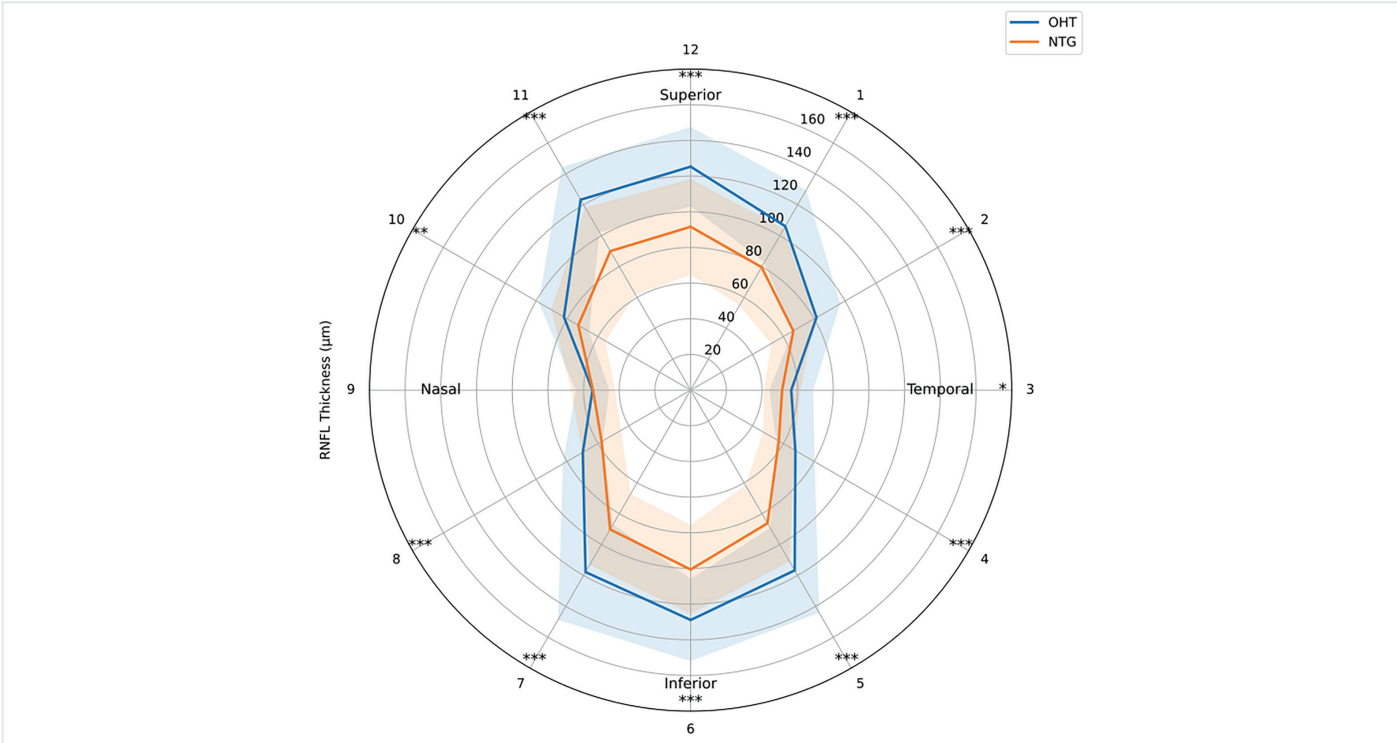

Figure 1. Clock-hour distribution of peripapillary retinal nerve fiber layer (RNFL) thickness in the ocular hypertension and normal-tension glaucoma (NTG) groups. RNFL thickness was generally lower in the NTG group across most sectors, with no significant difference in the 9 o'clock sector. Values are presented as mean ± SD. Statistical significance is indicated as *p<0.05, **p<0.01, ***p<0.001
SD: Standard deviation, OHT: Ocular hypertension

Discussion

Although VF loss detected by perimetry remains central to the diagnosis and monitoring of glaucoma, it should be interpreted in conjunction with RNFL loss and structural alterations of the ONH. OCT derived RNFL and ONH parameters provide a quantitative and objective assessment of the structural components of glaucomatous damage (18). Nevertheless, pressure-independent vascular factors have also been reported to contribute to disease pathogenesis, particularly in NTG (3). Given their roles in retinal metabolism and peripapillary circulation, choroidal structures have been considered potential contributors to glaucomatous damage (12,19,20). Accordingly, in the present study, foveal, temporal parafoveal, and nasal parafoveal choroidal thicknesses were evaluated, together with quadrant- and clock-hour–based RNFL parameters, in treatment-naive NTG patients and compared with those in individuals with OHT.

Reduced RNFL thickness is closely associated with glaucoma, and mean, quadrant-based, and clock-hour RNFL measurements, together with rim area and vertical C/D ratio, are regarded as key structural indicators of glaucomatous damage (21-25). RNFL thinning particularly in the 6th, 7th, and 8th clock-hour sectors has been reported to be strongly associated with glaucomatous injury (26). Previous studies in NTG have demonstrated significant reductions in RNFL thickness in the mean, superior, and inferior quadrants (27). Most published studies have compared patients with glaucoma to healthy controls. In contrast, the present study compared NTG patients with OHT patients without structural or functional glaucomatous damage. Significant thinning was observed in the NTG group, not only in mean RNFL thickness but also in all four quadrants (superior, temporal, inferior, and nasal). Clock-hour analysis further demonstrated a reduction in RNFL thickness in all sectors except at the 9 o'clock position compared with the OHT group, indicating the coexistence of diffuse and regional nerve fiber loss in NTG.

Choroidal thickness is influenced by multiple factors, including age, AL, other ocular biometric parameters, and systemic conditions (12,13). In the present study, choroidal thickness was evaluated in treatment-naive patients diagnosed with NTG and OHT. Demographic characteristics such as age, sex, and AL were comparable between the two groups. To minimize the potential impact of glaucoma medications on choroidal measurements, only untreated individuals were included.

While some studies have reported that glaucoma therapy may be associated with increased choroidal thickness (14), others have found no significant difference between glaucomatous eyes and healthy controls in this regard (22,28). Similarly, a study investigating unilateral glaucoma reported no meaningful interocular difference in choroidal thickness (29). Taken together, these findings suggest that choroidal structural changes are not uniform across all types of glaucoma and may vary depending on the anatomical region examined. In line with these observations, the present study did not demonstrate a significant difference in foveal and nasal-parafoveal choroidal thicknesses between NTG and OHT patients, although a regional difference was observed in the temporal parafoveal area.

Contradictory findings regarding choroidal thickness in patients with OHT and NTG have been reported in the literature. In OHT, elevated

IOP may lead to choroidal thinning through mechanical compression. In contrast, in NTG, vascular dysfunction and microcirculatory disturbances may affect choroidal structure despite normal IOP levels. The coexistence of these mechanisms may partly account for the difficulty in identifying clear differences in choroidal thickness between the two groups.

Previous studies in OHT patients have suggested an association between choroidal thinning and impaired ocular hemodynamics. Bayraktar et al. (20) reported that reduced choroidal thickness may be related to increased vascular resistance and decreased ocular blood flow parameters. Similarly, Yilmaz et al. (30) demonstrated reduced macular choroidal thickness, particularly in the temporal region, compared with healthy controls. These differences may be related to variations in patient characteristics, disease severity, or measurement methods.

Choroidal thickness is a structural parameter and does not directly reflect choroidal perfusion. In the present study, temporal parafoveal choroidal thickness was higher in the OHT group than in the NTG group ($p=0.047$). However, this finding should be interpreted with caution because it was limited to a single macular region, was of borderline statistical significance, and was not accompanied by consistent differences in the foveal or nasal parafoveal areas. This isolated result may reflect regional variability, measurement-related factors associated with manual caliper assessment, or limited sample size, rather than a stable disease-specific pattern. In addition, discrepancies with previous studies may be related to differences in treatment status, patient characteristics, anatomical regions analyzed, and measurement methodology. Taken together, these findings further support the view that macular choroidal thickness alone has limited discriminatory value in differentiating NTG from OHT.

Importantly, the absence of a significant difference in choroidal thickness should not be interpreted as evidence against a role for choroidal circulation in glaucomatous damage. Microvascular alterations at the level of the ONH may not be adequately reflected by macular choroidal thickness measurements. Therefore, functional vascular assessments may provide more meaningful insights than structural measurements in understanding the pathophysiology of NTG, highlighting the need for further studies supported by advanced vascular imaging techniques.

Study Limitations

This study has several limitations. The retrospective design does not allow for causal inferences. Interobserver and intraobserver reproducibility were not formally assessed. In addition, the relatively small sample size may have reduced the sensitivity of some analyses.

Finally, peripapillary choroidal thickness was not evaluated. Given the potential role of the ONH microenvironment in glaucomatous damage, this aspect may not have been fully addressed in the present study.

Conclusion

In this study, foveal and nasal parafoveal choroidal thicknesses were comparable between patients with NTG and OHT, whereas only a marginal difference was observed in the temporal parafoveal region. Given the number of regional comparisons performed, this finding should be interpreted with caution. Overall, the results indicate that macular choroidal thickness alone may not be sufficient to distinguish normal-tension glaucoma from ocular hypertension. It is possible that microvascular changes at the level of the ONH play a more relevant role in disease mechanisms than macular choroidal structure alone. Further studies incorporating functional vascular imaging techniques may provide a more comprehensive understanding of the underlying pathophysiology of NTG.

Ethics

Ethics Committee Approval: This retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and was approved by the Pamukkale University Ethics Committee (approval number: 60116787-020/956, date: 15.01.2020).

Informed Consent: Because of the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.S.A.; Concept - M.S.A.; Design - F.Ç., S.Z., M.S.A.; Data Collection or Processing - M.S.A.; Analysis or Interpretation - F.Ç., S.Z.; Literature Search - F.Ç., S.Z.; Writing - M.S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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