Research Article / Araştırma Makalesi

Effects of Anxiety Disorder on Choroidal Vascularity Index and Central Macular Thickness: A Comprehensive Retrospective Analysis

Anksiyete Bozukluğu Hastalarında Santral Makula Kalınlığı ve Koroidal Vaskülarite İndeksinin Spektral-Domain Optik Koherens Tomografi ile Değerlendirilmesi

İbrahim Edhem YILMAZ [1], Mustafa BERHUNİ [1], Gizem GÜRBOSTAN SOYSAL [2], Nesime Setge TISKAOĞLU [3], Ali Hakim REYHAN [4], Nükhet YIĞITBAŞI GÖREN [2]

[1]Gaziantep Islam, Science and Technology University, School of Medicine, Department of Ophthalmology, Gaziantep, TÜRKİYE
[2] Gaziantep City Hospital, Department of Ophthalmology, Gaziantep, TÜRKİYE
[3]Manisa City Hospital, Department of Ophthalmology, Manisa, TÜRKİYE
[4]Harran University, School of Medicine, Department of Ophthalmology, Şanlıurfa, TÜRKİYE

Abstract

Materials and Methods: This retrospective comparative study analyzed 85 participants (38 generalized anxiety disorder patients, 47 age- and sex-matched healthy controls). Comprehensive ophthalmic examinations and macular SD-OCT imaging with enhanced depth imaging (EDI) were performed. CMT was measured automatically, while CVI was calculated using standardized ImageJ binarization protocols. Statistical analyses included independent t-tests, sensitivity analyses, effect size calculations, and correlation assessments (α = 0.05).
Results: Groups demonstrated comparable demographics (age p=0.492; sex p=0.659; IOP p=0.472). No significant differences emerged in CMT (249.4±20.5 µm vs. 246.0±32.5 µm; p=0.582; Cohen's d=0.12) or CVI (70.3±3.3% vs. 70.5±3.6%; p=0.787; d=-0.06). Sensitivity analyses (medication-free subgroup, non-smokers) and anxiety severity correlations yielded consistent null findings.
Conclusions: This robust analysis found no evidence of structural posterior segment alterations in generalized anxiety disorder, challenging prevailing psychophysiological models. Findings highlight the choroid's resilience to chronic stress and underscore the need for multimodal biomarker approaches in psychophysiological ophthalmology research.

Keywords: Generalized anxiety disorder, Choroidal vascularity index, Central macular thickness, Optical coherence tomography, Psychophysiology, Biomarkers

Öz

Amaç: Yaygın anksiyete bozukluğu hastalarında spektral-domain optik koherens tomografi (SD-OKT) kullanarak santral makula kalınlığı (SMK) ve koroidal vaskülarite indeksinde (KVİ) potansiyel değişikliklerin araştırılması.
Materyal ve Metod: Bu retrospektif karşılaştırmalı çalışmada yaşa göre eşleştirilmiş 85 katılımcı (38 yaygın anksiyete bozukluğu hastası, 47 sağlıklı kontrol) analiz edildi. Kapsamlı oftalmolojik muayeneler ve geliştirilmiş derinlik görüntüleme (EDI) ile makular SD-OKT görüntülemesi yapıldı. SMK otomatik olarak ölçüldü, KVİ ise standart ImageJ binarizasyon protokolleri kullanılarak hesaplandı. İstatistiksel analizler bağımsız t-testleri, duyarlılık analizleri, etki büyüklüğü hesaplamaları ve korelasyon değerlendirmelerini içerdi (α = 0.05).
Bulgular: Gruplar benzer demografik özellikler gösterdi (yaş p=0.492; cinsiyet p=0.659; göz içi basıncı p=0.472). SMK (249.4±20.5 µm karşı 246.0±32.5 µm; p=0.582; d=0.12) veya KVİ (70.3±3.3% karşı 70.5±3.6%; p=0.787; d=-0.06) açısından anlamlı fark bulunmadı. Duyarlılık analizleri (ilaçsız alt grup, sigara içmeyenler) ve anksiyete şiddeti korelasyonları tutarlı anlamlı olmayan sonuçlar verdi.
Sonuç: Bu analiz yaygın anksiyete bozukluğunda posterior segment değişikliklerinin bulunmadığına dair kanıt sağladı ve mevcut psikofizyolojik modelleri sorguladı. Bulgular koroidin kronik strese karşı direncini vurgulamakta ve psikofizyolojik oftalmoloji araştırmalarında multimodal biomarker yaklaşımlarının gerekliliğini göstermektedir.

Anahtar Kelimeler: Yaygın anksiyete bozukluğu, Koroidal vaskülarite indeksi, Santral makula kalınlığı, Optik koherens tomografi, Psikofizyoloji, Biomarkerlar

Corresponding Author / Sorumlu Yazar

Dr. Ali Hakim REYHAN
Harran University, School of Medicine, Department of Ophthalmology, Şanlıurfa, TÜRKİYE

E-mail: alihakimreyhan@gmail.com

Received / Geliş tarihi: 16.06.2025

Accepted / Kabul tarihi: 10.07.2025

DOI: 10.35440/hutfd.1720809

Introduction

Anxiety disorders constitute a substantial global health burden, affecting approximately 284 million individuals worldwide and representing the most prevalent class of mental health conditions (1). These conditions extend beyond psychological manifestations, characterized by pathological activation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system dysregulation. This neuroendocrine dysfunction triggers systemic cascades impacting cardiovascular, immune, and endocrine function (2), with emerging evidence suggesting potential ocular manifestations through the theoretical "brain-eye axis" (3).

The choroid, a highly vascularized tissue layer supplying the outer retinal segments, exhibits distinctive physiological properties that render it susceptible to stress-mediated modulation. With the highest blood flow per unit tissue in the human body (1,500–2,000 ml/min/100g) (4), dense autonomic innervation (5), and glucocorticoid receptor expression (6), it represents a prime candidate for investigating anxiety-related alterations. Advances in spectral-domain optical coherence tomography (SD-OCT) with enhanced depth imaging (EDI) have enabled precise quantification of the choroidal vascularity index (CVI), a biomarker demonstrating superior stability to choroidal thickness measurements due to minimal diurnal variation (<5%) and axial length independence (7). Concurrently, central macular thickness (CMT) serves as a sensitive indicator of retinal integrity, with documented alterations in neuroinflammatory conditions (8).

Existing literature reveals paradoxical inconsistencies regarding posterior segment changes in anxiety disorders. While Ayyildiz et al.(9) reported increased choroidal thickness in pediatric anxiety, Acan et al.(10) documented reduced CVI in generalized anxiety disorder, and Ozisik et al.(11) observed macular thinning. These discrepancies may reflect methodological heterogeneity in OCT acquisition protocols, phenotypic diversity across anxiety disorder subtypes, and inadequate control of confounding variables including psychotropic medication effects (12). This study addresses these gaps through a rigorously controlled investigation comparing CMT and CVI in anxiety patients against matched controls using standardized automated protocols, while examining anxiety severity correlations and conducting comprehensive sensitivity analyses.

Materials and Methods

This retrospective cohort study received ethical approval from the Gaziantep Islamic University of Science and Technology Non-Interventional Clinical Research Ethics Committee (Date: 15.01.2025; Decision number: 519.42.24) and was conducted in accordance with the principles of the Declaration of Helsinki. As this study employs a retrospective design, it is exempt from the requirement for informed consent. Between October 2023 and April 2024, we systematically screened 142 consecutive patients presenting to our institution, ultimately enrolling 38 adults (18–65 years) with DSM-5-diagnosed generalized anxiety disorder confirmed by psychiatric evaluation, alongside 47 age- and sex-matched healthy controls.

Exclusion criteria addressed key confounders: significant ocular pathology (glaucoma, macular degeneration, diabetic retinopathy); systemic conditions affecting vasculature (uncontrolled hypertension, diabetes); spherical equivalent refractive error exceeding ±3.00 diopters; and for controls, any neurological disorders or psychotropic medication use. All participants underwent comprehensive ophthalmic evaluation including best-corrected visual acuity assessment (ETDRS chart), autorefractometry (Topcon KR-8900), Goldman applanation tonometry, and slit-lamp biomicroscopy. Anxiety severity was quantified using the Beck Anxiety Inventory and State-Trait Anxiety Inventory.

Spectral-domain OCT imaging was performed using the Heidelberg Engineering Spectralis® system under standardized mesopic conditions (luminance 3.4 cd/m²) following 30 minutes of dark adaptation. Macular cube scans (30° × 25°, 512 A-scans × 128 B-scans) and horizontal line scans through the fovea were acquired using eye-tracking and EDI modes, with quality control ensuring signal strength >7 and absence of motion artifacts. Central macular thickness was measured automatically within the 1 mm ETDRS grid using manufacturer software. For choroidal vascularity index quantification, single horizontal foveal B-scans were exported in uncompressed TIFF format (300 dpi resolution) and processed in ImageJ (v1.53t) using a standardized protocol: choroidal area delineation (1500 µm subfoveal width), Niblack auto-local thresholding (radius=15px; k=-0.2), and calculation of luminal area as total area minus stromal area, with CVI expressed as (luminal area / total choroidal area) × 100%. This protocol demonstrated excellent intergrader reliability (ICC=0.94) and intragrader consistency (ICC=0.97).

Statistical analyses employed SPSS v28.0 and R v4.2.1. Group comparisons utilized Welch's t-tests for continuous variables and chi-square tests with Yates' correction for categorical data. Sensitivity analyses examined medication-free anxiety patients (n=21) and non-smokers (n=28). Correlation analyses assessed relationships between anxiety metrics and OCT parameters using Pearson's r with Bonferroni correction. Effect sizes were calculated as Cohen's d with 95% confidence intervals, and post-hoc power analysis confirmed 85% power to detect effects >0.65.

Results

The final analytical cohort comprised 85 participants: 38 patients with confirmed generalized anxiety disorders and 47 demographically matched healthy controls. The demographic and clinical characteristics of both groups are presented in Table 1. Welch's t-tests revealed no significant age differences between groups. Similarly, chi-square analysis confirmed comparable sex distribution ($\chi^2(1) = 0.20$, $p = 0.659$), with females representing 57.9% of the anxiety group and 53.2% of controls. Intraocular pressure measurements were also equivalent between groups (13.3 ± 2.1 mmHg vs. 13.0 ± 2.7 mmHg; $t(82.3) = -0.72$, $p = 0.472$).

Table 1. Demographic and Clinical Characteristics

Characteristic	Anxiety Group (n=38)	Control Group (n=47)	p-value	Statistical Test
Age (years), mean ± SD	40.2 ± 9.2	38.8 ± 10.2	0.492	Independent t-test
Female, n (%)	22 (57.9)	25 (53.2)	0.659	Chi-square test
IOP (mmHg), mean ± SD	13.3 ± 2.1	13.0 ± 2.7	0.472	Welch's t-test*
Smokers, n (%)	10 (26.3)	12 (25.5)	0.937	Chi-square test
Medication Use, n (%)	17 (44.7)	0 (0)	<0.001	Chi-square test
BAI Score, mean ± SD	32.4 ± 14.1	N/A†	-	-
STAI-State, mean ± SD	54.6 ± 11.3	N/A†	-	-

**Welch's t-test applied due to unequal variances (Levene's test: F=4.32, p=0.041)*

†N/A = Not Applicable (anxiety assessment scales not administered to control group)

IOP = Intraocular pressure; BAI = Beck Anxiety Inventory; STAI = State-Trait Anxiety Inventory; SD = Standard Deviation

Optical coherence tomography analysis demonstrated no significant differences in posterior segment parameters between groups (Table 2). Central macular thickness measurements were comparable between anxiety patients (249.4 ± 20.5 µm) and controls (246.0 ± 32.5 µm; t(72.7) = 0.55, p = 0.582), with a negligible effect size (Cohen's d = 0.12; 95% CI: -0.31 to 0.55). Similarly, choroidal vascularity index values showed no significant intergroup difference (70.3 ± 3.3% vs. 70.5 ± 3.6%; t(83) = -0.27, p = 0.787), with a trivial effect size (Cohen's d = -0.06; 95% CI: -0.49 to 0.37).

Sensitivity analyses confirmed the robustness of these null findings. In the medication-free anxiety subgroup (n=21), CMT (251.2 ± 18.7 µm vs. 246.0 ± 32.5 µm; t(66) = 0.81, p = 0.421) and CVI (70.6 ± 3.1% vs. 70.5 ± 3.6%; t(66) = -0.08, p = 0.934) remained statistically indistinguishable from controls. Similarly, analysis of non-smokers in the anxiety group (n=28) showed no significant differences in CMT (247.8 ± 22.3 µm; t(73) = 0.50, p = 0.615) or CVI (70.5 ± 3.4%; t(73) = -0.24, p = 0.812) compared to the full control group.

Correlational analyses within the anxiety group revealed no significant associations between anxiety severity metrics and OCT parameters. Beck Anxiety Inventory scores showed negligible correlation with CMT (r(36) = 0.11, p = 0.519) and CVI (r(36) = -0.09, p = 0.602). Similarly, State-Trait Anxiety Inventory (STAI-State) scores demonstrated no meaningful relationship with CMT (r(36) = 0.07, p = 0.687) or CVI (r(36) = -0.14, p = 0.402). Disease duration also showed no significant correlation with either OCT parameter (CMT: r(36) = -0.06, p = 0.724; CVI: r(36) = -0.09, p = 0.612).

Table 2. OCT Parameters Comparison

Parameter	Anxiety Group (n=38)	Control Group (n=47)	p-value	Effect Size (95% CI)	Statistical Test
CMT (µm), mean ± SD	249.4 ± 20.5	246.0 ± 32.5	0.582	d = 0.12 (-0.31, 0.55)	Independent t-test*
CVI (%), mean ± SD	70.3 ± 3.3	70.5 ± 3.6	0.787	d = -0.06 (-0.49, 0.37)	Independent t-test

**Welch's t-test applied for CMT due to unequal variances (Levene's test: F=8.94, p=0.004)*

CMT = Central Macular Thickness; CVI = Choroidal Vascularity Index; SD = Standard Deviation; CI = Confidence Interval

Discussion

In contrast to our initial hypothesis, this methodologically standardized investigation demonstrated no significant structural alterations in central macular thickness or choroidal vascularity index among generalized anxiety disorder patients. These robust null findings persisted across medication-free subgroups and non-smokers, challenging prevailing assumptions about anxiety-induced structural remodeling of the posterior segment. The observed choroidal structural stability may result from several protective mechanisms: its remarkable autoregulatory capacity maintains hemodynamic stability across perfusion pressures (50–180 mmHg) through myogenic control and metabolic regulation (11), while specialized adrenergic receptor distribution—with choroidal vessels exhibiting lower α1-adrenergic density (2.7 fmol/mg protein) than systemic vasculature (15.2 fmol/mg)—buffers sympathetic hyperactivity (13,14). Additionally, enzymatic protection via 11β-hydroxysteroid dehydrogenase type 2, which inactivates 80–90% of cortisol (6), may prevent glucocorticoid-mediated vascular changes.

Reconciling our null findings with previously reported positive associations necessitates careful examination of methodological differences across studies. Ayyildiz et al.'s (9) report of choroidal thickening in pediatric anxiety employed manual segmentation without medication control, while Wang et al.'s (15) finding of reduced CVI used manual binarization. Technical factors significantly influence outcomes: automated versus manual CVI quantification yields differences exceeding 7% (16), bin width selection alters calculations by 4–12% (17), and instrument choice (EDI-OCT vs. SS-OCT) causes choroidal thickness variations of 18±6 µm (18). Our standardized protocol with automated analysis, fixed imaging windows, and confounder-adjusted sensitivity analyses provides a more controlled assessment.

From a clinical perspective, while anxiety disorders may not

directly modify choroidal architecture, they substantially exacerbate comorbid ocular pathologies through shared inflammatory and autonomic pathways. The 2.3-fold higher anxiety prevalence in dry eye disease patients (19), reflects common inflammatory mechanisms (elevated IL-6, MMP-9), with SSRIs further disrupting tear film stability via muscarinic antagonism (20). In glaucoma, anxiety amplifies intraocular pressure fluctuations through catecholamine-mediated trabecular meshwork contraction (21). Our findings suggest static OCT metrics may overlook transient stress responses, as acute mental stress induces choroidal thickening (ΔCT = +22.4±8.7 μm) within 15 minutes (13).

Several methodological limitations warrant acknowledgment, including the cross-sectional design that precludes establishment of temporal relationships and absence of molecular biomarkers. Future research should implement provocation paradigms (e.g., Trier Social Stress Test with serial OCT), integrate autonomic phenotyping through heart-rate variability stratification, and combine multimodal assessments: OCT-angiography for microvascular perfusion dynamics, electroretinography for retinal ganglion cell function, and aqueous humor analysis for local stress biomarkers. Longitudinal designs monitoring choroidal changes during cognitive behavioral therapy or tracking anxiety patients developing central serous chorioretinopathy would provide valuable insights.

We propose a triphasic model of choroidal stress adaptation: 1) Acute phase (minutes-hours) with transient thickening and increased permeability; 2) Adaptive phase (weeks-months) featuring autoregulatory normalization and 11β-HSD2 upregulation; 3) Exhaustion phase (years) involving structural remodeling. This framework explains why our cohort—characterized by moderate anxiety severity (mean duration 4.2±3.1 years)—exhibited no structural changes, residing in the adaptive phase where protective mechanisms maintain homeostasis.

Conclusion

This methodologically standardized analysis provides compelling evidence for choroidal structural stability in generalized anxiety disorder, challenging simplistic models of stress-induced ocular pathology. The absence of CMT or CVI alterations underscores the choroid's sophisticated autoregulatory capacity against chronic psychological stress. These findings suggest that static OCT parameters (CMT and CVI) should not be considered primary diagnostic biomarkers for psychological stress manifestations in ophthalmology, directing clinical attention toward more dynamic assessment approaches and established ocular pathologies where anxiety disorders demonstrate clear exacerbating effects. Future research should prioritize dynamic assessments, autonomic phenotyping, and molecular correlation to identify state-dependent biomarkers, advancing our understanding of the nuanced interplay between mental health and ocular vasculature.

Acknowledgment

Ophthalmology technicians at Gaziantep Hospital for imaging support.

Ethical Approval: Approval for this study was received from the Gaziantep Islamic University of Science and Technology Non-Interventional Clinical Research Ethics Committee (Date: 15.01.2025; Decision number: 519.42.24).

Author Contributions:
Concept: İ.E.Y., M.B., N.Y.G.
Literature Review: İ.E.Y., A.H.R.
Design : İ.E.Y., A.H.R.
Data acquisition: İ.E.Y., M.B., N.S.T., N.Y.G.
Analysis and interpretation: İ.E:Y., M.B., G.G.S., A.H.R.
Writing manuscript: İ.E.Y., N.S.T., G.G.S., M.B.
Critical revision of manuscript: İ.E.Y., N.S.t., G.G.S., A.H.R., M.B., N.Y.G.
Conflict of Interest: *The authors have no conflicts of interest to declare.*
Financial Disclosure: *Authors declared no financial support.*

References

1. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: A systematic review and meta-regression. Psychol Med. 2013;43(5):897-910.
2. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374-81
3. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012; 9:360–70. Available from: https://pubmed.ncbi.nlm.nih.gov/22473079/
4. Nickla DL, Wallman J. The multifunctional choroid. Prog Retin Eye Res. 2010;29(2):144-68.
5. Kiel JW. Choroidal myogenic autoregulation and intraocular pressure. Exp Eye Res. 1994;58(5):529-43..
6. Harvey DH, Sugali CK, Mao W. Glucocorticoid-Induced Ocular Hypertension and Glaucoma. Clin Ophthalmol. 2024;18:481-505.
7. Agrawal R, Gupta P, Tan KA, Cheung CM, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: Measurements in healthy eyes from a population-based study. Sci Rep. 2016;6:21090.
8. London A, Benhar I, Schwartz M. The retina as a window to the brain-from eye research to CNS disorders. Nat Rev Neurol. 2013;9(1):44-53.
9. Ayyildiz D, Ayyildiz T. Central choroidal thickness in children and adolescents with anxiety disorders: enhanced depth imaging optical coherence tomography findings. Int J Ophthalmol. 2020;13(10):1580-1585.
10. Acan D, Baykan H, Karahan E. Evaluation of retinal and choroidal vascular structures in patients with anxiety disorder. Eur J Ophthalmol 2024; 34:1211–6.
11. Ozisik GG, Kiraz S. Evaluation of retinal thickness measured by optical coherence tomography in patients with generalized anxiety disorder. Photodiagnosis Photodyn Ther 2023; 44:103766.
12. Baykara S, Kazğan A, Yıldırım H, Tabara MF, Kaşıkcı HÖ, Danacı Keleş D. Retinal changes in generalized anxiety disorder patients. Int J Psychiatry Med 2024; 59:270–86.
13. Lin J, Han Y, Liu M, Wang X. Effects of Acute Mental Stress on Choroidal Thickness. Bioengineering 2024; 11:684.
14. Schmetterer L, Polak K. Role of nitric oxide in the control of ocular blood flow. Prog Retin Eye Res 2001;20:823–47.
15. Wang Y, Liu L, Li C, Yang Y, He X, Jiang M, et al. Choroidal vessel density in major depressive disorder using swept-source optical coherence tomography angiography. J Affect Disord 2024; 344:79–85.
16. Tan KA, Laude A, Yip V, Loo E, Wong EP, Agrawal R. Choroidal vascularity index – a novel optical coherence tomography parameter for disease monitoring in diabetes mellitus? Acta Ophthalmol. 2016; 94:e612–6.
17. Yang TK, Huang XG, Yao JY. Effects of Cigarette Smoking on Retinal and Choroidal Thickness: A Systematic Review and Meta-Analysis. J Ophthalmol 2019; 2019:8079127.
18. Ikuno Y, Maruko I, Yasuno Y, Miura M, Sekiryu T, Nishida K, et al.

Reproducibility of retinal and choroidal thickness measurements in enhanced depth imaging and high-penetration optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:5536–40.
19. Galor A, Felix ER, Feuer W, Shalabi N, Martin ER, Margolis TP, et al. Dry eye symptoms align more closely to non-ocular conditions than to tear film parameters. Br J Ophthalmol. 2015;99(8):1126-9.
20. Alkozi HA. Ocular Surface Health in Connection with Anxiety and Depression: a Review. J Multidiscip Healthc 2024; 17:2671-2676.
21. Jesus J, Ambrósio J, Meira D, Rodriguez-Uña I, Beirão JM. Blinded by the Mind: Exploring the Hidden Psychiatric Burden in Glaucoma Patients. Biomedicines 2025;13(1):116.