

Corneal Confocal Microscopy Reveals Neuroimmune Alterations in Drug-Naïve Patients With Obsessive–Compulsive Disorder: A Case-Control Study

Hatice Cansu Selvi

Gazi University

Burcu Atay

Gazi University

İrem Arslanyürek

Gazi University Medical School

Mehmet Cüneyt Özmen

Gazi University

İrem Ekmekci

iremekmekci@gazi.edu.tr

Gazi University

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Abstract

Background Obsessive–compulsive disorder (OCD) has been associated with inflammatory and immunological mechanisms. Ocular imaging provides a noninvasive approach of investigating peripheral and neuroinflammatory processes. This study aimed to evaluate ocular inflammatory biomarkers in OCD using enhanced-depth imaging optical coherence tomography (EDI-OCT) and corneal confocal microscopy (CCM).

Methods Twenty-nine drug-naïve patients with OCD and 28 age- and sex-matched healthy controls underwent comprehensive ophthalmic assessment. Subfoveal choroidal thickness and the choroidal vascularity index (CVI) were measured using EDI-OCT; while dendritic cell (DC) density and subbasal nerve plexus (SBNP) parameters were quantified using CCM. Between-group comparisons were performed using nonparametric tests, and correlations with clinical severity were assessed using Spearman's rho.

Results Subfoveal choroidal thickness did not differ between groups ($p=0.787$). CVI was higher in the OCD group ($p=0.044$), although the absolute difference was small. In contrast, CCM revealed marked corneal alterations: DC density was significantly increased (106.25 vs 32.29 cells/mm²; $p < 0.001$), and SBNP parameters—including fiber density, length, and branching—were all significantly reduced (all $p < 0.001$). No significant associations were observed between corneal parameters and overall symptom severity, whereas CVI showed a modest positive correlation with obsession scores.

Conclusions This study provides the first evidence of corneal neuroinflammatory alterations in OCD using CCM. Increased DC density and reduced nerve fiber parameters suggest that CCM-derived measures may represent potential markers of neuroinflammation, whereas choroidal parameters appear less informative. These findings warrant validation in larger, longitudinal studies.

Background

Obsessive-Compulsive Disorder (OCD) is a chronic psychiatric disorder characterized by recurrent obsessions and/or compulsions that cause significant anxiety and impair daily functioning (1). Although the exact etiology of OCD remains unclear, it is thought to involve complex, time-dependent interactions between genetic and environmental factors(2). The description of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) by Swedo et al. (3), along with accumulating evidence from subsequent studies, suggest that inflammatory processes may contribute to the pathophysiology of OCD. This association has been linked to mechanisms such as alterations in peripheral immune cell populations, changes in peripheral cytokine profiles, and neuroinflammatory processes (4-7).

Ophthalmological research in psychiatric disorders has a long-standing history. As the retina originates from neuroectodermal tissue, retinal alterations may reflect structural and functional changes in the brain(8). Choroidal thickness, which provides oxygen and nutrient support to the retina, has been shown

to be affected in neuroinflammatory conditions (9, 10). Although choroidal thickness is a known marker of inflammation in this context, it can be influenced by several factors including axial length, refractive error, intraocular pressure, and systolic blood pressure (11). More recently, the choroidal vascularity index (CVI) has been proposed as a more robust and reliable biomarker (12). CVI, defined as the ratio of the choroidal vascular area to the total choroidal area, has been investigated as a biomarker in various systemic and psychiatric disorders (13-15). While a limited number of studies in patients with OCD reported higher CVI values compared to controls (16), a recent study has found no significant differences between groups (17).

Another area of interest is corneal alterations. Corneal confocal microscopy (CCM), although not widely used in psychiatry, enables noninvasive, in vivo imaging of the cornea at the cellular level (18, 19). Corneal dendritic cells are antigen-presenting cells located on the anterior surface of the eye and play a key role in immune responses (20). Studies in neurodegenerative and autoimmune diseases have demonstrated increased dendritic cell density alongside reduced corneal nerve fiber density (20-24). In a study by Ponirakis and colleagues, a positive correlation was reported between corneal nerve fiber density and cingulate gyrus volume in patients with schizophrenia, suggesting that corneal nerve fiber loss detected by CCM may serve as a rapid and noninvasive marker of neurodegeneration (25). To date, however, no studies have investigated these parameters in patients with OCD.

In light of the growing evidence linking OCD to inflammatory and neuroimmune processes, and the limited and inconsistent findings from ocular imaging studies, the present study aimed to comprehensively investigate ocular inflammatory biomarkers in patients with OCD. Specifically, we evaluated subfoveal choroidal thickness and the CVI using EDI-OCT, and assessed DC density and SBNP parameters using CCM. We further sought to compare these parameters between patients and healthy controls and to explore their potential associations with clinical symptom severity.

Methods

2.1. Study design and patient recruitment

This study included 29 drug-naïve patients who presented to the psychiatric outpatient clinic of Gazi University Medical Faculty and were diagnosed with obsessive-compulsive disorder (OCD), as well as 28 age- and sex-matched healthy controls. The diagnosis of OCD was established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and symptom severity was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (26, 27).

Participants in the OCD group were required to be between 18 and 65 years of age, to meet DSM-5 criteria for OCD, and to provide informed consent. Only drug-naïve patients or those without psychotropic medication use in the past 6 months were included. Healthy controls (age- and sex-matched) were similarly required to be between 18 and 65 years of age, to have no current or past psychiatric diagnosis according to DSM-5, to have no history of psychotropic medication use within the past 6 months, and to provide informed consent.

A priori sample size estimation was conducted based on standard assumptions for between-group comparisons and correlation analyses. In the absence of prior studies evaluating corneal confocal microscopy (CCM) parameters in obsessive-compulsive disorder (OCD), effect sizes were estimated according to Cohen's widely accepted benchmarks ($d = 0.2$, 0.5 , and 0.8 representing small, medium, and large effects, respectively). Assuming a two-tailed alpha level of 0.05 and 80% statistical power, 26 participants per group would be sufficient to detect a large effect size ($d = 0.80$).

All participants underwent comprehensive ophthalmological examinations at the Gazi University Hospital Ophthalmology Outpatient Clinic, including assessments of uncorrected and corrected visual acuity, refraction measurements, detailed anterior and posterior segment examinations, and tear breakup time (TBUT) testing. Dry eye disease was evaluated using both subjective and objective measures. Subjective symptoms were assessed with the Ocular Surface Disease Index (OSDI), while objective assessment was performed using TBUT. Participants with an OSDI score greater than 12 and/or a TBUT of less than 10 seconds were excluded to minimize the confounding effects of ocular surface inflammation.

Exclusion criteria for both groups included:

- (i) any ocular condition that could affect optical coherence tomography (OCT) or corneal confocal microscopy (CCM) measurements (e.g., contact lens use, dry eye disease, glaucoma, cataract, macular disease, high refractive errors, uveitis, or choroidal disorders),
- (ii) comorbid psychiatric or neuropsychiatric disorders (for the OCD group),
- (iii) systemic conditions that may influence inflammatory parameters, including metabolic, neurological, allergic, rheumatologic, autoimmune, or chronic inflammatory diseases (e.g., diabetes mellitus, cancer),
- (iv) vascular diseases or use of medications affecting OCT results (e.g., calcium channel blockers, beta-blockers),
- (v) alcohol or substance use disorders, and
- (vi) inability to provide informed consent or complete study assessments.

The study was approved by the Gazi University Ethics Committee (17.01.2023/02), and written informed consent was obtained from all participants.

2.2. Enhanced Depth Imaging Optical Coherence Tomography

Images were recorded using the Spectralis OCT (Heidelberg Engineering, Germany) in EDI mode with an 840 ± 10 nm scanning diode laser. After mydriasis, horizontal EDI-OCT scans passing through the fovea were obtained from patients, focusing on the internal fixation light in the appropriate position. Choroidal thickness measurement was taken at the subfoveal choroid manually on the image that was obtained with EDI spectral-domain OCT from the outer edge of the retinal pigment epithelium (RPE) to the

choroidal-scleral junction. EDI-OCT images are opened in ImageJ software, and a region of interest, 1500 μm wide and centered on the fovea, is selected using the polygon tool. The upper boundary of this region is traced along the choroidal-RPE junction, while the lower boundary is traced along the sclerochoroidal junction to identify the total choroidal area (TCA). After converting the image to 8-bit, Niblack's autolocal thresholding method is applied to separate the luminal choroidal area (LCA) and the stromal choroidal area (SCA). Subsequently, the image is converted to red, green, and blue colors, and the color thresholding tool is used to select the dark pixels representing the LCA. Finally, the TCA and LCA are measured, and the SCA is found by subtracting the LCA from the TCA. The ratio between LCA and TCA is then calculated as choroidal vascularity index (CVI).(28, 29)

2.3. Corneal confocal microscopy:

In-vivo confocal microscopy was performed using the Rostock Cornea and Heidelberg Retina Tomograph 3®. The device captures images with a 670 nm wavelength diode laser source at a resolution of 400x400 μm and a 1 μm lateral resolution. After the application of a topical anesthetic (proparacaine hydrochloride), lubricant gel was applied to the microscope's anterior lens, and the cornea was brought closer to capture subbasal nerve plexus (SBNP) images. Among the 50-100 images obtained from the central cornea, the three best-focused images were selected by a masked observer. Two masked observers analyzed the corneal confocal microscopy (CCM) images in terms of dendritic cell density, as well as SBNP morphology as described in previous studies. (19, 30){Cruzat, 2011 #2662}

Dendritic cell density (cells/ mm^2) were measured using Image J (<https://imagej.nih.gov/ij/>). Briefly, cell density was manually counted, and data were expressed as cells/ mm^2 . Cell count tool in the manual mode was used to analyze the DC density per image. All complete DCs present in each image, as well as partial cells on the top and right borders of each frame were counted and included in the calculation of the average density of DCs. For each calculation, the mean of three images was used. (18, 30)

Corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve trunk density (CNTD), the total length of all nerve fibers and branches (corneal nerve fiber length; CNFL), corneal nerve branch length (CNBL) and corneal nerve trunk length (CNTL) were measured using Neuron J which is a semi-automated tracing program (a plugin for ImageJ) (<http://www.imagescience.org/meijering/software/neuronj/>). The whole frame was analyzed for the presence of main trunks, branches, and total nerves. Nerve density was assessed by measuring the number of the nerve fibers per mm^2 . Total number of main nerve trunks was counted in each image after analyzing anteriorly and posteriorly in order to confirm that main nerve trunks did not branch from other nerves. The number of total nerves measured was defined as the number of all nerves, including main nerve trunks and branches in one image. Nerve length was assessed by measuring the length of the nerve fibers in micrometers per mm^2 . All images were independently evaluated by two masked observers according to a predefined protocol. In cases where the discrepancy between observers exceeded 10%, a third masked observer performed an independent assessment, and the final value was calculated as the average of the three measurements.(18, 30)

2.4. Statistical Analysis

Data analysis was performed using SPSS 21.0. Descriptive statistics are presented as mean ($\pm$) standard deviation, frequency, percentage, and median (25–75% percentiles). Normality was assessed using histograms, probability plots, and Kolmogorov-Smirnov/Shapiro-Wilk tests. For non-normally distributed continuous variables, the Mann-Whitney U test was used, whereas the chi-square test was applied for categorical variables. The relationships between variables were analyzed using the Spearman correlation test.

Results

Sociodemographic data of the participants are presented in Table 1. No significant differences were found between the groups in terms of gender, age BMI, smoking status (all $p > 0.05$).

Table 1. Sociodemographic Characteristics of the Study Groups

	OCD Group	Control Group	P Value
Patients, n	29	28	
Age, y	34.07 $\pm$ 12.62 (M $\pm$ SD)	33.32 $\pm$ 11.74(M $\pm$ SD)	1.000
Gender (female/male)	21/8	21/7	0.825
BMI	24.1 $\pm$ 3.77 (M $\pm$ SD)	22.8 $\pm$ 3.12(M $\pm$ SD)	0.158
Smoking Status (Smoker / Non-Smoker)	6/23	8/20	0.490

**BMI: body-mass index*

Choroidal thickness and CVI values were compared between the groups (Table 2). A statistically significant difference was observed for CVI ($U = 246.5$, $p < 0.05$), whereas no significant difference was found for choroidal thickness. Although CVI was significantly higher in the OCD group in the unadjusted analysis ($p = 0.044$), this difference remained statistically significant after adjustment for age, sex, body mass index, and smoking status using ANCOVA

Table 2. Comparison of Groups Based on Choroidal Vascularity Index and Choroidal Thickness

	OCD Group (median [IQR])	Control Group (median [IQR])	p Value
CVI	0.65 (0.63-0.69)	0.64 (0.63-0.67)	0.044
Choroidal Thickness (μm)	354 (278.5-439.5)	358 (299.5-437)	0.787

**Values are reported as median (25th–75th percentiles)*

****CVI: Choroidal vascularity index**

Confocal microscopy revealed significant between-group differences across all subbasal nerve plexus parameters (Table 3). The OCD group showed reduced CNFD, CNFL, CNBL, CNBD, CNTD, and CNTL, alongside increased dendritic cell density compared with controls.

Table 3. Comparison of Parameters Obtained from the Subbasal Nerve Plexus (SBNP) Layer Evaluated by Confocal Microscopy Across Groups

	OCD Group (median [IQR])	Control Group (median [IQR])	P Value
CNFD (n/mm ²)	58.33 (45.83-65.62)	81.25 (68.75-95.83)	0.001
CNFL (mm/mm ²)	14.37 (11.45-15.79)	18.92 (16.96-20.4)	0.001
CNBL (mm/mm ²)	5.12 (4.43-6.23)	7.84 (6.63-7.84)	0.001
CNBD (n/mm ²)	35.42 (28.12-42.71)	52.08 (41.67-63.54)	0.001
CNTD (n/mm ²)	20.83 (15.62-25)	27.08 (26.04-31.25)	0.001
CNTL (mm/mm ²)	8.52 (5.91-9.91)	11.12 (10.56-12.17)	0.001
Dendritic cell density, cells/mm²	106.25 (58.33-182.29)	32.29 (17.19-62.5)	0.001

*Values are reported as median (25th–75th percentiles)

****** Corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve trunk density (CNTD), Corneal nerve fiber length (CNFL), corneal nerve branch length (CNBL), Corneal nerve trunk length (CNTL)

The IVCM images of the representative cases in each group are in Fig.1

Figure 1. Comparison of dendritic cell density and corneal nerve fiber density between patients with OCD and healthy controls.

Dendritic cell density (cells/mm²) was significantly higher in the OCD group than in controls, whereas total corneal nerve fiber density (fibers/mm²) was significantly lower in the OCD group compared with controls. Representative CCM images from a healthy control and a patient with OCD are shown in Fig. 2.

In the OCD group, correlations between ocular inflammatory parameters and clinical scale scores are summarized in Table 4. CVI showed a significant positive correlation with Y-BOCS obsession scores ($r = 0.405$, $p < 0.05$).

Table 4. Relationship Between Clinical Scale Scores and Ocular Inflammatory Parameters in the OCD Group

	Y-BOCS obsession	Y-BOCS compulsion	Y-BOCS total
CVI	0.405*	0.197	0.303
Choroidal Thickness (micrometer (μm))	-0.140	0.093	-0.012
CNFD (n/mm ²)	-0.221	-0.139	-0.185
CNFL (mm/mm ²)	-0.158	-0.154	-0.167
CNBL (mm/mm ²)	-0.042	0.054	0.008
CNBD (n/mm ²)	-0.185	-0.061	-0.125
CNTD (n/mm ²)	-0.105	-0.175	-0.161
CNTL (mm/mm ²)	-0.250	-0.263	-0.265
Dendritic cell density, cells/mm2	0.065	-0.010	0.005

Figure 2. Representative corneal confocal microscopy (CCM) images from a patient with obsessive–compulsive disorder (OCD) (A) and a healthy control (B).

The OCD image demonstrates reduced subbasal nerve plexus density along with increased dendritic cell density compared with the control.

Discussion

This study aimed to investigate the potential role of inflammatory and immunological mechanisms in the pathophysiology of OCD by comparing ocular inflammatory parameters between patients with OCD and healthy controls. To our knowledge, this is the first study to quantitatively evaluate corneal nerve parameters and dendritic cell density using CCM in patients with OCD.

With regard to choroidal parameters, no significant difference was observed in subfoveal choroidal thickness between groups, and no association was found with disease severity. Choroidal thickness has been proposed as a potential marker of inflammation in systemic diseases, with increased thickness reported during inflammatory activity and even in subclinical stages (31, 32). In psychiatric populations, the first study to assess choroidal thickness in OCD was conducted by Özen et al., who reported significant thickening in patients compared with controls(33), consistent with findings in schizophrenia and major depression (34, 35). However, subsequent studies have yielded inconsistent results. For example, Topcu-Yılmaz et al. found no significant differences in choroidal thickness between patients with schizophrenia and healthy controls across multiple retinal regions(36), and a recent study in first-episode psychosis similarly reported no group differences (15).

In line with these heterogeneous findings, our results do not support a consistent alteration in choroidal thickness in OCD. This may indicate that choroidal thickness is not a sufficiently sensitive marker of neuroinflammatory processes in this population, or that any potential changes are subtle and influenced by multiple physiological and methodological factors.

These inconsistencies have led to the increasing use of the choroidal vascularity index (CVI) as a potentially more robust parameter. CVI is considered more stable, as it separately quantifies the vascular and stromal components of the choroid and is less affected by physiological variability (12).

In the present study, CVI was evaluated alongside choroidal thickness to enhance the reliability of the assessment. Although CVI values were higher in the OCD group, the magnitude of this difference was small and should be interpreted cautiously. Despite reaching statistical significance, its clinical relevance appears limited. Interestingly, CVI demonstrated a modest but significant positive correlation with Y-BOCS obsession scores, which may point to a link between choroidal vascular alterations and specific symptom dimensions rather than overall disease severity. However, this finding highlights a lack of comparable evidence in the literature, as previous OCD studies have not assessed the association between CVI and symptom dimensions using similar methodologies (37).

Previous studies examining CVI in psychiatric disorders have reported inconsistent findings. Lower CVI values have been reported in bipolar disorder, albeit without statistical significance (14), whereas higher values have been observed in first-episode psychosis (15).

Only two studies have evaluated CVI in OCD. Gediz et al. reported higher CVI values in patients with OCD (16). whereas a subsequent study found no significant difference between patients and controls (17).

Consistent with the latter, our findings suggest that CVI may reflect subtle variations in choroidal vascular structure; however, its utility as a clinically meaningful or standalone biomarker in OCD appears limited. Variability across studies may be attributable to methodological differences, including medication status and illness characteristics.

A more consistent pattern of alterations was observed in corneal confocal microscopy (CCM) findings compared with choroidal parameters. Previous studies in systemic and neuroinflammatory conditions have demonstrated that increased corneal dendritic cell density, often accompanied by reductions in corneal nerve fiber parameters, is associated with inflammatory processes and corneal nerve alterations. Similar patterns have been reported in conditions such as multiple sclerosis, obesity-related inflammation, and COVID-19, supporting a potential link between immune activation and corneal nerve changes (22, 23, 38, 39).

Studies using CCM in psychiatric patients remain limited. Significant reductions in corneal nerve fiber parameters have been reported in individuals with mild cognitive impairment and dementia, suggesting that CCM may capture neurobiological alterations (24, 40). In schizophrenia, CCM has been used to investigate neurodevelopmental and neurodegenerative processes, with findings demonstrating reduced corneal nerve fiber parameters alongside lower cognitive performance and reduced cingulate gyrus volume. Notably, corneal nerve fiber loss was not associated with metabolic syndrome or diabetes mellitus, supporting a potential central rather than peripheral metabolic mechanism (25).

In line with these findings, our study demonstrated increased dendritic cell density and reduced corneal nerve fiber parameters in patients with OCD. The coexistence of these alterations may indicate a potential interaction between immune activation and corneal nerve integrity. However, no significant associations were observed between corneal parameters and disease severity, suggesting that these changes may not represent markers of current symptom severity. Instead, they may reflect relatively stable trait-like biological characteristics associated with OCD vulnerability, chronic low-grade immune activation, or long-standing neuroimmune alterations. However, this interpretation remains speculative and requires confirmation in longitudinal studies.

Previous studies have reported an inverse relationship between corneal nerve fiber parameters and subbasal immune cell density(18, 30), further supporting a link between immune activation and nerve alterations. To minimize potential confounding, individuals with a history of contact lens wear—known to be associated with increased dendritic cell density—were excluded from the present study (41). Furthermore, no significant between-group differences were observed in OSDI scores or TBUT measurements, suggesting that residual confounding related to ocular surface symptoms was unlikely to account for the observed CCM findings.

While these findings provide insight into potential peripheral neuroinflammatory changes in OCD, several limitations should be considered. The relatively small sample size, cross-sectional design, and lack of longitudinal follow-up limit the generalizability of the results and preclude causal inferences.

Although increased dendritic cell density and reduced corneal nerve fiber parameters may be compatible with neuroimmune or inflammatory mechanisms, these findings should not be interpreted as direct evidence of neuroinflammation. Corneal immune and neural alterations may be influenced by multiple factors, including stress-related physiological responses, autonomic nervous system activity, sleep disturbances, and lifestyle-related factors.

Another limitation is the absence of direct measures of central nervous system inflammation or neuroimmune activity. The study did not include neuroimaging, cerebrospinal fluid biomarkers, or systemic inflammatory markers that could establish a direct relationship between corneal findings and central neuroinflammatory processes.

Conclusion

Despite these limitations, the study has notable strengths. To our knowledge, this is the first study to apply CCM in patients with OCD and to demonstrate corneal alterations in this population. Furthermore, the inclusion of drug-naïve participants and the absence of significant differences between groups in variables such as age, sex, smoking status, and body mass index reduce potential confounding and allow for a more independent evaluation of the findings. In addition, the exclusion of potential ocular, psychiatric, and systemic confounders affecting inflammatory and imaging parameters enhances the specificity and interpretability of the results.

Taken together, these results indicate that CCM reveals consistent corneal alterations in patients with OCD, which may reflect peripheral neuroinflammatory changes associated with the disorder. Future studies with larger samples and longitudinal designs are warranted to validate these findings and to further elucidate the clinical relevance of ocular biomarkers in OCD.

Declarations

Ethics approval and consent to participate: The study was approved by the Gazi University Ethics Committee (17.01.2023/02), and written informed consent was obtained from all participants. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication: Not Applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' Contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Hatice Cansu Selvi, Burcu Atay. Data analysis was performed by Hatice Cansu Selvi, Mehmet Cüneyt Özmen and İrem Ekmekci. The first draft of the manuscript was written by Hatice Cansu Selvi and İrem Ekmekci all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

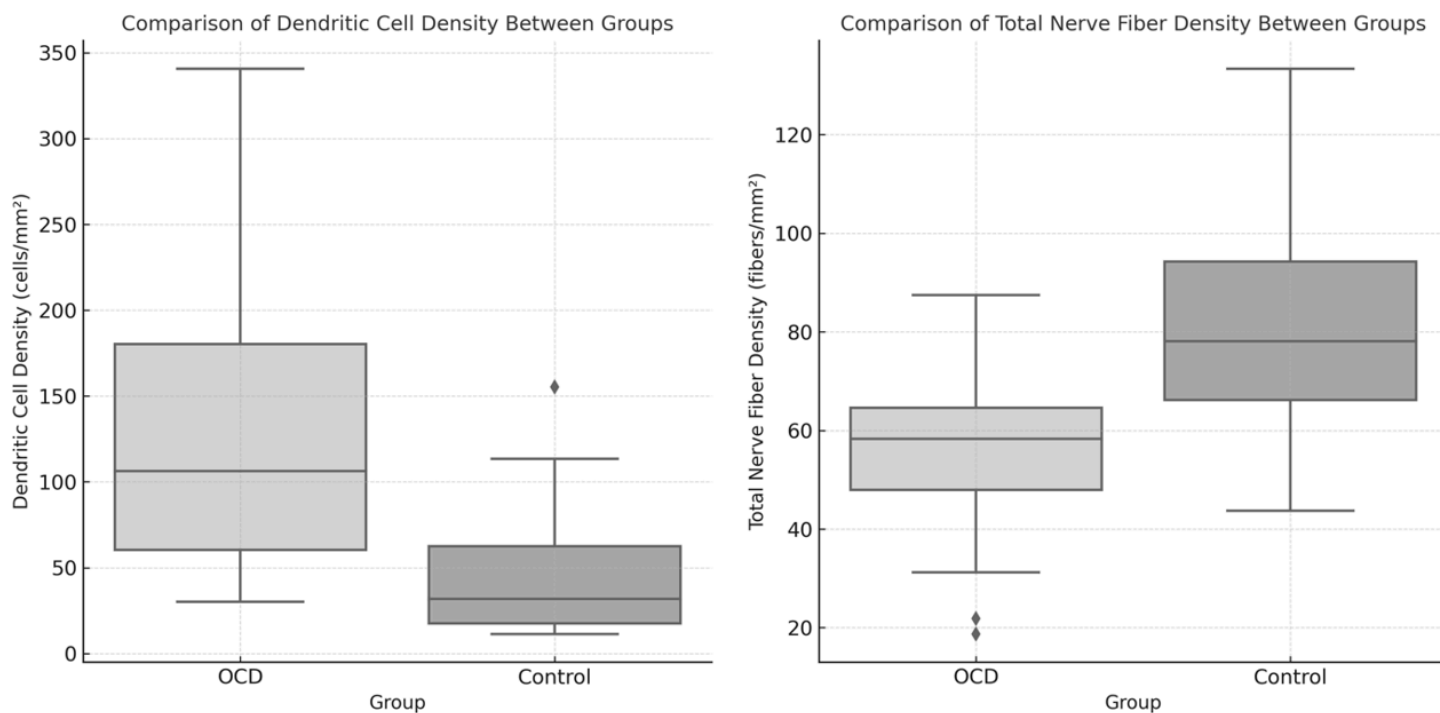


Figure 1

Comparison of dendritic cell density and corneal nerve fiber density between patients with OCD and healthy controls.

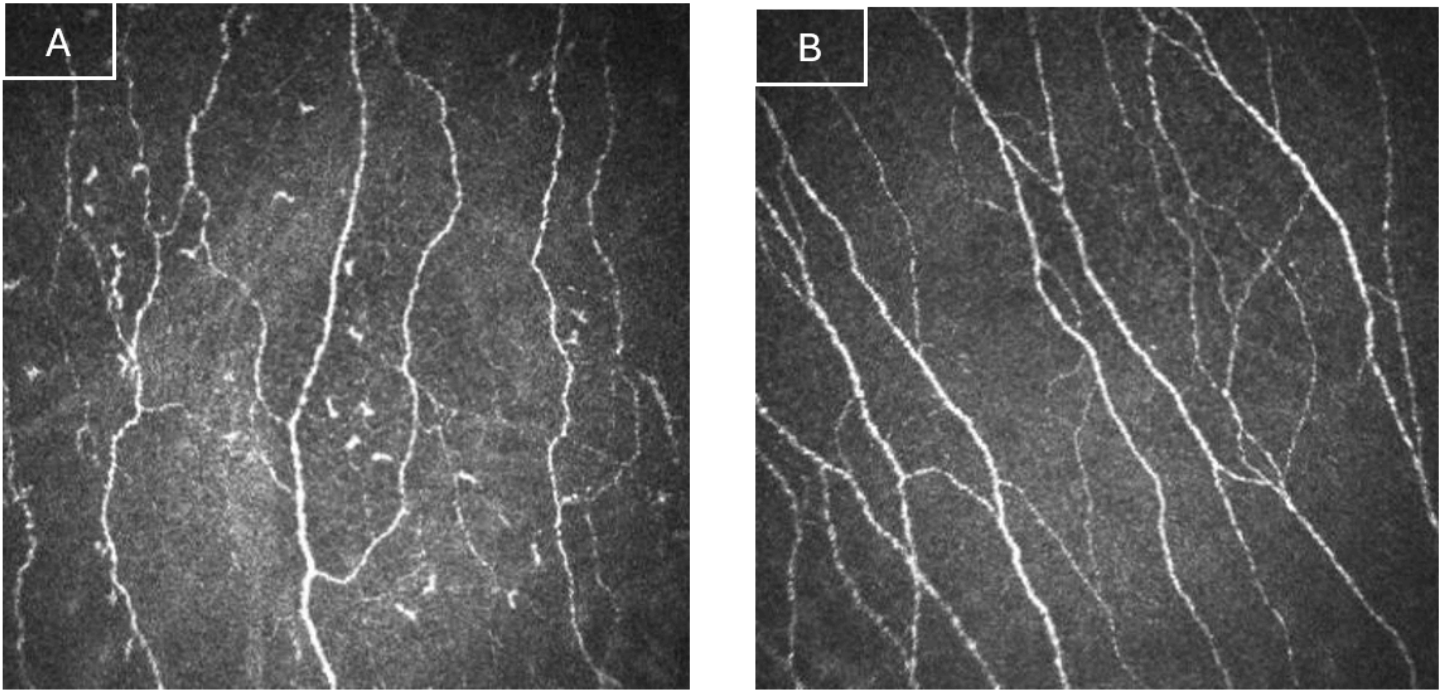


Figure 2

Representative corneal confocal microscopy (CCM) images from a patient with obsessive–compulsive disorder (OCD) (A) and a healthy control (B).