Research Square

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Investigation of corneal sub-basal nerve plexus and dendritic cell density by in vivo confocal microscopy in thyroid-associated ophthalmopathy patients

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Abstract

Purpose

To investigate corneal sub-basal nerve plexus (SBP) and dendritic cell (DC) density by in vivo confocal microscopy (IVCM) and the association between corneal involvement and clinical features in thyroid-associated ophthalmopathy patients.

Methods

Thirty-three patients diagnosed with TAO and thirty-six age- and sex-matched healthy controls were included. Central corneal sub-basal nerve fibers and DC were evaluated with in vivo laser scanning confocal microscopy and analyzed using NeuronJ, a semi-automated ImageJ software and ImageJ's Cell Counter.

Results

Corneal nerve fiber length (CNFL), corneal nerve fiber density (CNFD), and corneal nerve branch density (CNBD) were significantly reduced in TAO patients compared to healthy controls. The DC density was significantly increased in TAO patients compared to healthy controls (Table 3) (Figs. 1 and 2). No correlation was found between IVCM parameters and thyroid-stimulating hormone (TSH), Graves' disease duration, The Clinical Activity Score (CAS), and thyroid receptor antibody (Trab) level. There are significant negative correlations between DC density and corneal SBP IVCM parameters, including CNFL, CNFD, and CNBD.

Conclusion

Decreased sub-basal corneal nerve fibers correlated with increased corneal DC density, indicating corneal nerve loss associated with corneal inflammation in TAO patients. However, elucidation of the exact underlying mechanisms warrants further study.

Introduction

Thyroid-associated ophthalmopathy (TAO), also known as von Basedow disease, is a chronic inflammatory autoimmune condition that is seen in 8.97 persons out of 10,000 [1, 2]. It is a multifactorial disease, influenced by immunological, genetic, epigenetic, and environmental factors [3, 4]. It is the most frequent extrathyroidal symptom of Graves' disease, affecting 25% of patients among which with Graves' hyperthyroidism are more likely to develop, although those with euthyroid or hypothyroid state can also be effected [5, 6].

The underlying pathophysiology is the increased production of hydrophilic glycosaminoglycans (GAGs) as well as the orbital changes (expansion of the fibroadipose tissue, swelling of the extraocular muscles), that contribute most of the clinical features of TAO such as soft tissue changes, exophthalmos, diplopia, and compressive dysthyroid optic neuropathy [3]. TAO patients may also develop ocular surface findings such as conjunctival hyperemia and chemosis, dry eye, superficial punctate keratopathy, exposure keratopathy, and corneal ulcers at any stage of the disease [3, 7–9]. When severe, the ocular surface symptoms can result in blindness and decrease in the quality of life.

Cornea is innervated by ophthalmic division of trigeminal nerve (cranial nerve V) which is responsible for the sensation of cornea, blink reflex, as well as corneal epithelial integrity, and tearing, which all together regulate ocular homeostasis [10, 11]. In addition, neurotrophic factors released from the corneal nerves contribute to maintain cornea healthy and modulation of wound repair [12]. While TAO cause inflammation-mediated corneal symptoms, a decrease or change in corneal nerve fiber layer itself throughout the disease course can also lead to a series of ocular surface problems, such as dry eye, persistent corneal epithelial defects, and keratopathy [12]. The corneal neural impairment can be evaluated with in vivo confocal microscopy (IVCM) which is a non-invasive ophthalmic imaging technique to detect the corneal sub-basal nerve plexus (SBP) at a cellular level [13].

In our study, we aim to assess structural changes of corneal SBP and differences in corneal DC density, and the relationship between them in TAO patients by IVCM. The association between those changes and the clinical severity of the disease will also be investigated.

Materials and Methods

Patients and controls

Thirty-three patients diagnosed with TAO and thirty-six age- and sex-matched healthy controls were included in this cross-sectional study. The patients are diagnosed, treated and followed-up according to criteria defined by the 2016 American Thyroid Association Guideline by Koç University Hospital, Endocrinology and Metabolism Department, Turkey [14]. This study was approved by the local ethics committees of Koç University (Protocol number: 2021.246.IRB1.079) and each conduct in the study adhered to the tenets of the Declaration of Helsinki. After obtaining a written informed consent from participants, detailed history of disease including duration of the disease, extrathyroidal symptoms are recorded, and laboratory parameters concerning disease and antibody status are documented. Healthy controls were recruited from volunteers. Then, all participants were referred to Koç University Hospital, Ophthalmology Department, Turkey to undergo full ophthalmological examination including visual acuity testing, slit lamp biomicroscope, tonometer (Canon TX-20P, Japan), autorefractometer (Topcon KR-800, Japan), The Schirmer I and II test, ocular surface disease index (OSDI), Noninvasive first breakup time (NIF-BUT) and noninvasive average breakup time (NIAvg-BUT) (Sirius System CSO, Italian) and in vivo confocal microscopy (Heidelberg Retinal Tomography 3 Rostock Cornea Module, Heidelberg Engineering GmbH, Heidelberg, Germany). The recruited TAO patients are evaluated by means of Clinical Activity

Score (CAS) to classify clinical severity of orbital involvement of Graves' disease was evaluated by an experienced ophthalmologist for each patient. The Clinical Activity Score (CAS) is a grading system to evaluate clinical severity of TAO in both inflammatory progressive and noninflammatory stationary states which is described by Mourits et al in 1989 (Table 1) [15]. This scoring system has a range from 0 to 7, in which a higher score indicates worse orbital morbidity. Exclusion criteria were a history of any other autoimmune disease, diabetes mellitus, glaucoma, ocular surface disorders, contact lens use, history of ocular surgery, dry-eye syndrome, meibomian gland dysfunction, allergic ocular surface disease, pterygium, corneal dystrophy, and uveitis or had received either systemic or local treatment that might affect ocular surface parameters.

Table 1
Clinical Activity Score (CAS) [15].

For initial assessment of patients	Score
Spontaneous retrobulbar pain in last 4 weeks	1
Pain on attempted up- or down gaze	1
Moderate to severe eyelid erythema	1
Moderate to severe eyelid edema	1
Conjunctival hyperemia	1
Chemosis	1
Redness and swelling of the lacrimal caruncle and/or plica	1
Follow-up assessment of patients	
Increase in proptosis > 2mm	1
Decrease in uniocular movement in any direction ≥ 5°	1
Decrease in visual acuity ≥ 1 on Snellen chart	1

In vivo Corneal confocal microscopy (IVCM)

All of the subjects had their central corneas scanned using IVCM (Heidelberg Retinal Tomography 3 Rostock Cornea Module, Heidelberg Engineering GmbH, Heidelberg, Germany) in section mode. The corneal parameters including corneal nerve fiber length (CNFL), density (CNFD), and corneal nerve branch density (CNBD), as well as DC density, were measured using IVCM. Two drops of topical anesthetic (0.5% proparacaine hydrochloride) and lubricating gel (carbomer-containing gel 2 mg/g) were given to both eyes prior to the inspection and a single experienced examiner blinded by the subject's disability status. For each eye, the inspection lasted about 5 minutes. An experienced blinded ophthalmologist (AS) from Koç University Hospital selected three best quality non-overlapping representative IVCM frames per eye and analyzed 414 images in total using NeuronJ, a semi-automated ImageJ software plug-in. DCs exist in immature and mature forms. A network of long membrane processes resembling dendrites extends

from the nucleated cell body of mature DCs [16]. Only mature DC are considered, and their number was counted using ImageJ's Cell Counter plug-in, followed by a calculation of DC density in cells/ mm². All visible nerve fibers were traced, and their length and density were estimated as mm/mm² and fibers/ mm² (image area = 0.16033585 mm²). The entire length of main nerves in millimeters per square millimeter was measured; the total number of major nerves per square millimeter was measured; and the number of branches per square millimeter was measured.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 24.0. Basic descriptive statistics were calculated on all the data and data distribution and homogeneity were analyzed. Normally distributed quantitative variables were expressed as the mean ± standard deviation and analyzed using the student's t test and others as median (IQR), analyzed using the Mann Whitney-U test. Demographic features of NMOSD group and control were analyzed using a non-parametric Mann Whitney-U test for age and Yates` Continuity correction test for sex. For the correlation analysis between clinical parameters, IVCM values, Spearman's correlation coefficient correlation (r) was used. Additionally, receiver operating characteristics (ROC) calculated to compare diagnostic abilities of IVCM measurements. A two- sided p-value lower than 0.05 was considered statistically significant.

Results

Demographic and Clinical Status

Demographic data and clinical features are shown in Table 2. There were no significant differences between the two groups in terms of gender and age. Thyroid-stimulating hormone (TSH) receptor antibody (Trab) was positive in 93.9% of the patients and the mean ± SD value was 15.01 ± 4.98 (Table 2).

Table 2
Demographic and clinical features of TAO patients and control subjects

	TAO patients	Control subjects	P value
Number of subjects, n	33	36	
Female to male ratio (F:M)	26:7	28:8	1.00
Age (mean ± standard deviation (SD), year)	42.79 ± 12.29	43.14 ± 12.01	.971
Duration of disease (mean ± SD, months)	8.59 ± 7.7		
Clinical Activity Score (CAS)			
• 0	48.5% (16)		
• 1	30.3% (10)		
• 2	15.2% (5)		
• 3	6.1% (2)		
• 4	0		
• 5	0		
• 6	0		
• 7	0		
Disease State			
• Overt hyperthyroidism, (n)	66.7% (22)		
• Subclinical hypothyroidism, (n)	3.0% (1)		
• Subclinical hyperthyroidism, (n)	15.2% (5)		
• Euthyroid, (n)	15.2% (5)		
TSH (mean + SD)	0.33 ± 0.15		
• T3 (mean + SD)	10.19 ± 1.49		
• T4 (mean + SD)	3.10 ± 0.48		
• TSH receptor antibody (mean + SD)	15.01 ± 4.98		
Smoker, (n)	33.3% (11)		
Non-smoker, (n)	66.7% (22)		
Medication			

	TAO patients	Control subjects	P value
• Methimazole, (n)	81.82% (27)		
• Propylthiouracil, (n)	15.15% (5)		
• Propranolol, (n)	3.03% (1)		

In Vivo Corneal Confocal Microscopy (IVCM)

TAO patients had significantly reduced CNFL, CNFD, and CNBD compared to control. The DC density was increased significantly in TAO compared to healthy control (Table 3) (Figs. 1 and 2). When diagnostic ability of CNFD, CNBD, CNFL, DD values are compared via ROC curve, CNBD shows significantly higher sensitivity and specificity (AUC = 0.853, P < 0.001) (Fig. 3 and Table 4). There was a significant negative correlation between CNFL, CNFD, CNBD and age of the patients, while no correlation was found between those IVCM parameters and TSH, Graves' disease duration, CAS, and thyroid receptor antibody level (Table 5). Smoking behavior had no effect on IVCM parameters of TAO patients (p = 0,5). There are significant negative correlations between DC density and corneal sub-basal nerve plexus IVCM parameters, including CNFL, CNFD, and CNBD (Table 6).

Table 3
In vivo corneal confocal microscopy (IVCM) results in thyroid-associated ophthalmopathy (TAO) patients and control subjects.

IVCM parameters	TAO patients	Control subjects	P value
CNFL (mm/ mm²)	12.57 (7.75)	19.71 (5.75)	< .001
CNFD (fibers/mm²)	20.95 (10.70)	25.17 (11.03)	.006
CNBD (fibers/ mm²)	27.24 (23.57)	79.67 (38.59)	< .001
DC density (cells/mm²)	20.97 (30.42)	12.58 (13.84)	< .001
Corneal nerve fiber length (CNFL), density (CNFD), and corneal nerve branch density (CNBD), dendritic cell (DC).			

Table 4
Area under the curve (AUC) for each in vivo corneal confocal microscopy (IVCM) parameter as a predictor thyroid-associated ophthalmopathy (TAO).

Factor	AUC (95%)	Cut off	Sensitivity (%)	Specifity(%)
CNFD	.301 (.176-.425)	23.25	.364	.389
CNBD	.853 (.746–960)	38.52	.848	.833
CNFL	.839 (.737-.941)	14.42	.758	.75
DC density	.768 (.651-.885)	16.58	.636	.583
Corneal nerve fiber length (CNFL), density (CNFD), and corneal nerve branch density (CNBD), dendritic cell (DC).				

Table 5. Correlation between in vivo corneal confocal microscopy (IVCM) and clinical parameters.

Clinical parameters / IVCM parameters	Age	*TSH*	Disease duration (mo)	Clinical activity score (CAS)	Thyroid receptor antibody (Trab)
CNFL (mm/ mm²)	r= -.426 p=<.001	r= .065 p=.614	r=.138 p=.285	r=.110 p=.394	r=-.198 p=.123
CNFD (fibers/ mm²)	r= -.432 p=<.001	r= .188 p=.144	r=.207 p=.106	r=.009 p=.944	r=-.144 p=.264
CNBD (fibers/ mm²)	r= -.360 p=.003	r= .043 p=.742	r=.126 p=.327	r=.197 p=.126	r=-.165 p=.199
DC density (cells/ mm²)	r= -.012 p=.929	r= .044 p=.733	r=-0.76 p=.557	r=-.348 p=.06	r=-.142 p=.270

Spearman rank correlation coefficients (r value), p: P value, corneal nerve fiber length (CNFL), density (CNFD), and corneal nerve branch density (CNBD), dendritic cell (DC).

Table 6
Correlation between dendritic cell (DC) density and corneal subbasal nerve parameters.

	CNFL (mm/ mm²)	CNFD (fibers/ mm²)	CNBD (fibers/ mm²)
DC density (cells/ mm²)	r = − .415 p = < .05	r = − .353 p = < .05	r = − .342 p = < .05

Corneal nerve fiber length (CNFL), density (CNFD), and corneal nerve branch density (CNBD), dendritic cell (DC).

Discussion

In this study, we showed a decrease in IVCM SBP parameters and an increase in DC density in TAO patients compared to the control group. We found a correlation between the decrease in IVCM SBP parameters and the increase in DC density. Our results may provide evidence that corneal inflammation contributes to SBP damage in TAO patients. To our knowledge, our study is the first to investigate the relationship between and corneal sub-basal plexus and DC density by IVCM in a single study.

TAO may cause lid retraction, proptosis and ocular surface problems including conjunctival chemosis, conjunctival hyperemia, superficial punctate keratopathy, exposure keratopathy, dry eye, superior limbic

keratoconjunctivitis and corneal ulcer [7, 17–19]. The corneal nerve plexus plays a role in regulating ocular surface homeostasis [10, 12]. The corneal nerve plexus damage will affect the homeostasis of the ocular surface, leading to ocular surface disorders including dry eye syndrome, neurotrophic keratopathy, and corneal ulcers.

Few IVCM studies have reported the corneal sub-basal nerve changes in TAO [8, 20–22]. All previous reported and current studies showed decreased IVCM SBP parameters (including CNFD, CNFL and CNBD) in TAO patients compared to control subjects [8, 20–22]. This suggests that ocular surface symptoms in TAO patients may result from corneal nerve plexus damage. To evaluate the diagnostic validity of IVCM measurements for TAO, we used ROC curve analysis to obtain optimal cut off points, sensitivities, and specificities. CNBD showed acceptable diagnostic performance compared with other IVCM parameters.

The ocular surface inflammation may cause corneal nerve plexus damage in TAO patients. Huang et al. reported tumor necrosis factor – a (TNF-a) concentration in tears was significantly higher in both active and inactive TAO compared with the controls [23]. Xu et al. presented tear inflammatory cytokines and vascular endothelial growth factor (VEGF) concentrations were significantly higher in TAO than in the control. They reported decreased inflammatory cytokines and improvement in clinical parameters after steroid treatment [24]. DCs stimulate naïve T cells and initiate primary immune responses. They can induce primary immune responses and permitting establishment of immunological memory. The presence of antigen - presenting cells, including DCs, in the cornea has important implications for a variety of pathological and immunoinflammatory responses in the ocular anterior segment [25]. Previous IVCM studies have demonstrated the changes in corneal Langerhans cells (LCs) in TAO patients [26, 27]. They found LC density increased in TAO compared to control. In current study, we evaluated The DC density, and it was significantly higher in TAO compared to healthy control. We can say that it provides evidence of corneal inflammation in TAO. Based on this, we investigated the relationship between DC and SBP parameters to determine the role of corneal inflammation in corneal SBP damage in TAO. We revealed correlation between increased DC density and decreased CFND, CNFL, and CNBD. This may show us that corneal inflammation plays an active role in corneal SBP damage.

In both our study and previous published studies, several alterations were observed on the correlation between SBP IVCM parameters and CAS [8, 20, 21]. Villani et al. reported that the sub-basal nerve number analyzed with slit-scanning confocal microscopy was significantly decreased in TAO compared to control [8]. They evaluated corneal inflammation with activated keratocytes instead of dendritic cells, due to the use of a white-light confocal microscope. They found a difference between the patients with GO and the control group in terms of activated keratocytes. However, there was no difference in IVCM parameters except activated keratocyte between active and inactive TAO patients in that study [8]. We also found we also did not find correlation between the increased CAS, Trab level, disease duration and decreased SBP parameters values. For this reason, directly relating SBP damage to CAS may be misleading. It is conceivable that there may be other factors other than corneal inflammation in the mechanism underlying SPB damage, or that corneal inflammation may not be directly related to Graves' disease. The corneal SBP loss and corneal inflammation may develop due to other reasons such as exophthalmos,

eyelid retraction and orbital compartment rather than Graves-related inflammation. On the other hand, two published studies reported correlations between some SBP IVCM data and CAS [20, 21]. In addition, Kocabeyoglu et al. showed SBP changes were also present in newly diagnosed Graves' disease before the onset of TAO [22]. However, they did not evaluate DC.

One of the limitations of this study is not including Graves's disease patients without TAO. Besides, although our results support the role of corneal inflammation due to chronic inflammatory process in SBP damage, longer follow-up of the ocular surface with a large patient population and studies at the molecular level would be beneficial. This will help explore the exact mechanisms responsible for the ocular surface changes in TAO.

In conclusion, IVCM is useful in detecting structural changes of the cornea in TAO patients. IVCM revealed decreased corneal sub-basal nerve density and length, and increased corneal DC density in TAO patients and they were correlated. These results demonstrated corneal sub-basal nerve loss is related with corneal inflammation in TAO patients. However, elucidation of the exact underlying mechanisms warrants further study.

Declarations

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Data availability statement

All data related to the study are included in the article.

Competing Interests

The authors declare no competing interests.

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Figures

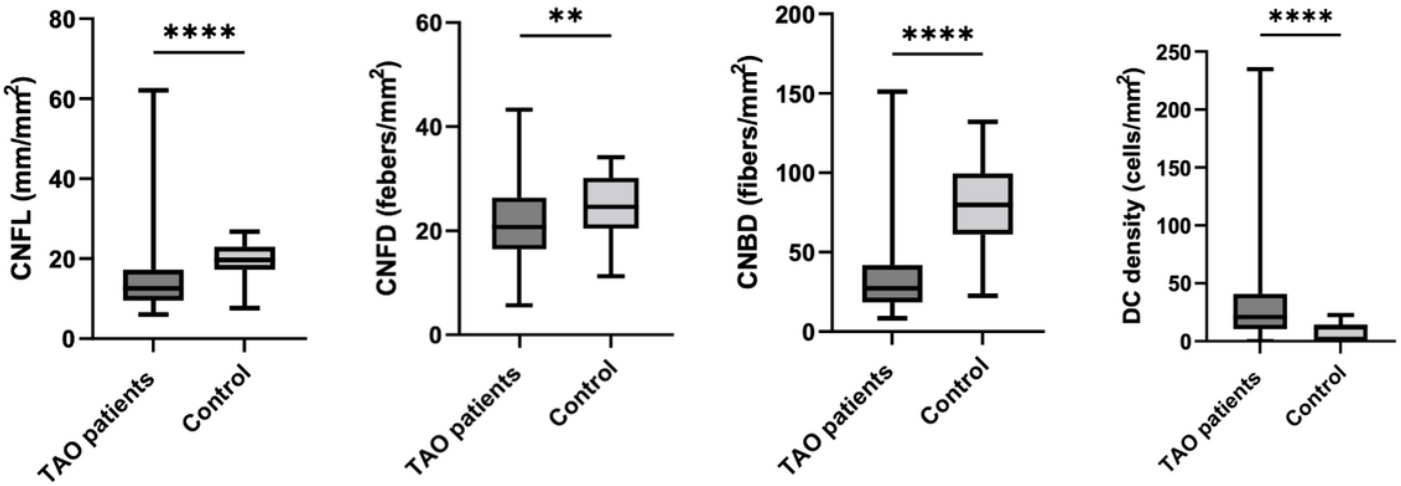


Figure 1

In vivo corneal confocal microscopy results in TAO patients and control subjects. Dendritic density ****p<0.0001, ***p=0.0002, **p=0.0021, *p=0.0332. Corneal nerve fiber length (CNFL), corneal nerve fiber density (CNFD), and corneal nerve branch density (CNBD), dendritic cell (DC).

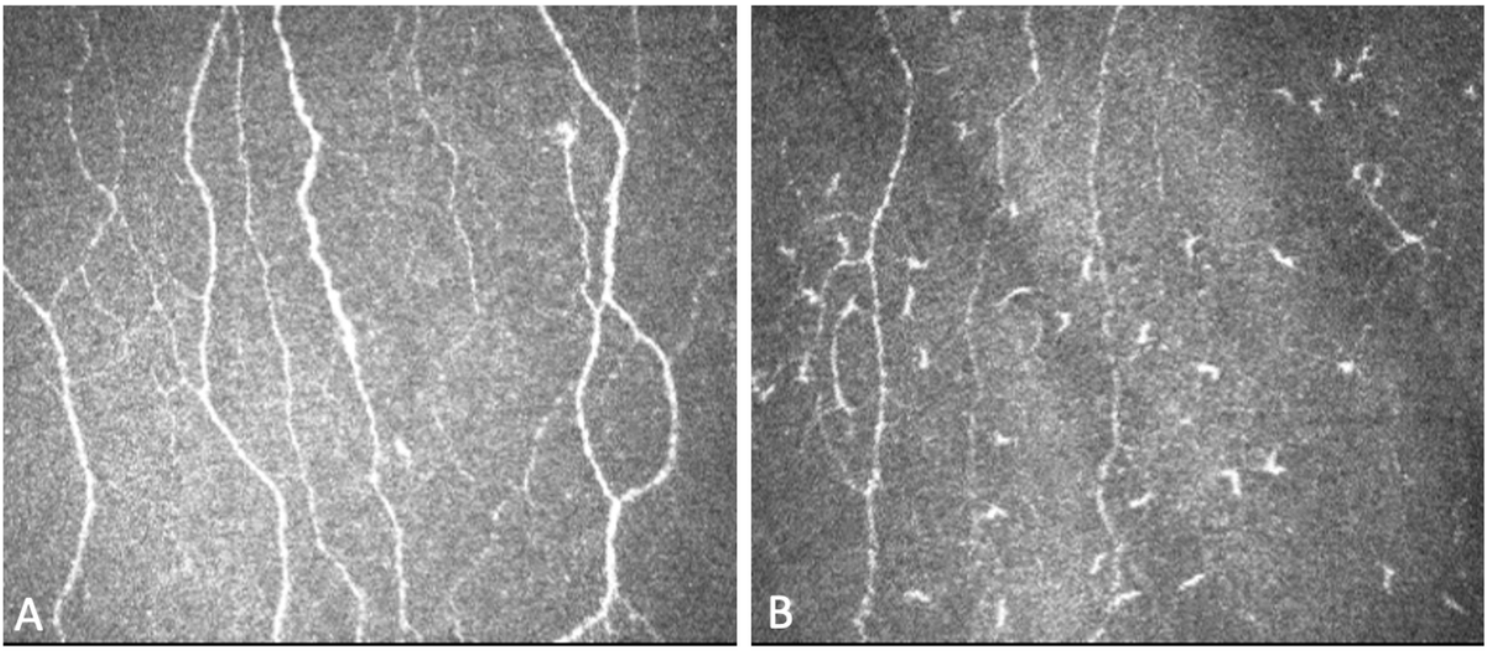


Figure 2

A. In vivo corneal confocal microscopic image (IVCM) of central cornea in a control subject. B. An IVCM image of a TAO patient showing reduced corneal nerve fibers and increased dendritic cells (DC) compared to control subject.

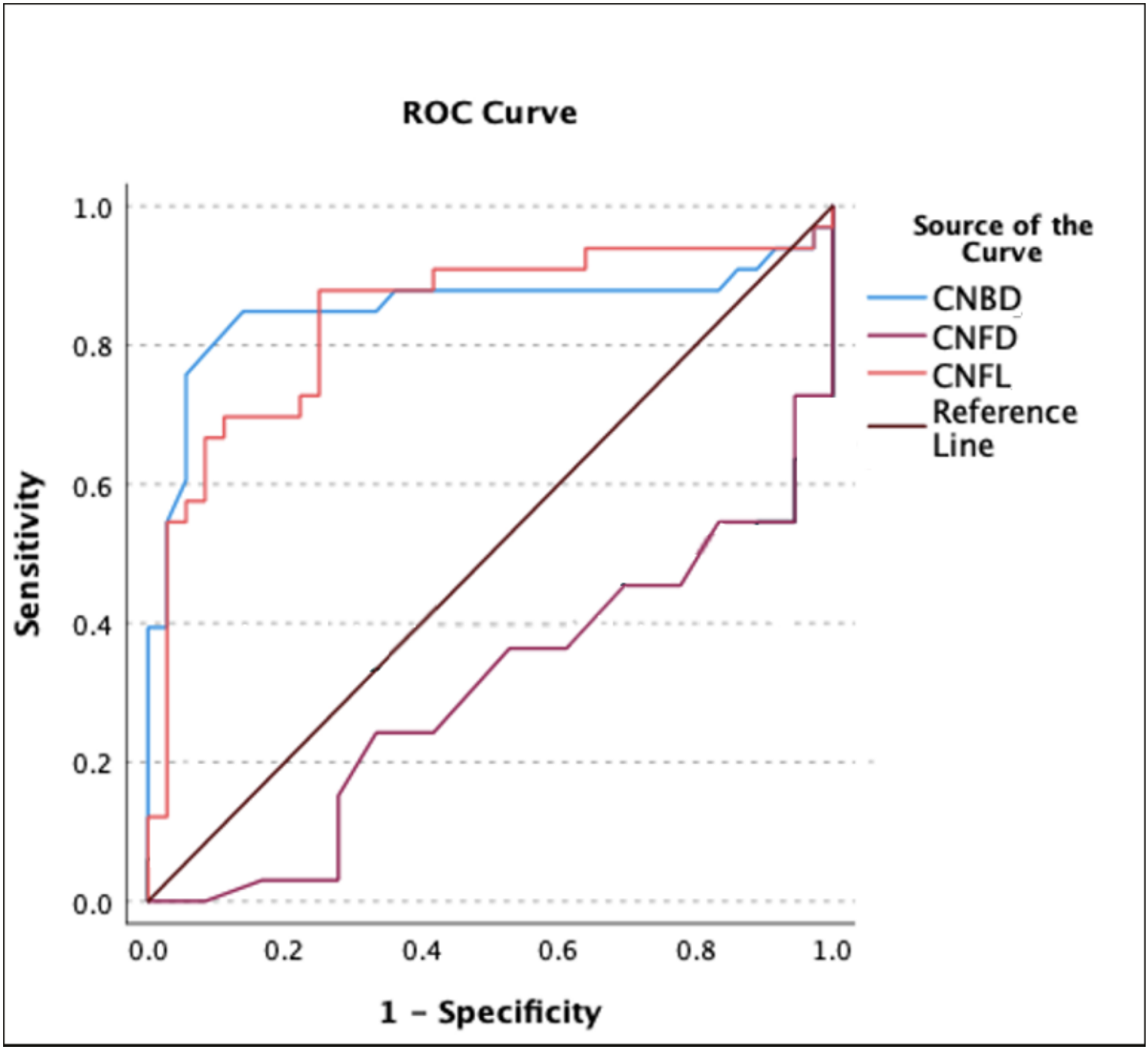


Figure 3

Receiver-operated characteristic (ROC) curves, based on the analysis of corneal nerve fiber length (CNFL), corneal nerve fiber density (CNFD), and corneal nerve branch density (CNBD).