Certain Anterior and Posterior Ocular Structure Measurements Acquired by Swept-Source Optical Coherence Tomography in Patients with Inflammatory Bowel Disease

İnflamatuar Bağırsak Hastalığı olan Hastalarda Swept-Source Optik Koherens Tomografi ile Elde Edilen Bazı Ön ve Arka Oküler Yapı Ölçümleri

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ABSTRACT

Objective: To measure some ocular parameters in inflammatory bowel disease and evaluate whether there are any differences between the measurements obtained from the patients and healthy subjects.
Methods: Thirteen patients with inflammatory bowel disease referred from the gastroenteroloji clinic and 14 control subjects selected from the individuals with minor complaints who admitted the ophthalmology outpatient clinic were included in the study. Average and segmental retinal nerve fiber layer thickness in four quadrant, average and sectoral ganglion cell inner plexiform layer thickness in in six guadrant, foveal and parafoveal vessel density in four quadrant, optic nerve head parameters, including rim area, disc area, horizontal cup-to-disc ratio, vertical cup-to-disc ratio, cup volume and additionally superficial/deep foveal avascular zone areas, choroid thickness, and central corneal thickness of the patients and controls were quantified using the swept-source optical coherence tomography.
Results: All measurements taken from the patients with inflammatory bowel disease and controls showed a great similarity and did not differ statistically.
Conclusion: Even though several inflammatory systemic diseases affect the eye and alter the particular structures, this study revealed that inflammatory bowel disease has no inluence on neural and vascular layers of the eye.

Key Words: inflammatory bowel disease; optical coherence tomography; choroid thickness; central corneal thickness

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ÖZET

Amaç: İnflamatuar bağırsak hastalığında göze ait bazı değerleri ölçmek ve hastalarla sağlıklı kişilerden elde edilen sonuçlar arasında fark olup olmadığını değerlendirmek.
Yöntemler: Gastroenteroloji kliniğinden sevk edilen 13 inflamatuar bağırsak hastası ile önemsiz bazı şikayetlerle göz polikliniğine muayeneye gelenlerden seçilen 14 sağlıklı kişi çalışma kapsamına alındı. Süpürücü kaynak optik koherens tomografi kullanarak hastaların ve kontrol grubunun ortalama ve dört kadrandaki sinir lifi tabakası kalınlığı, ortalama ve altı kadrandaki gangliyon hücre iç pleksiform tabaka kalınlığı, fovea ve fovea civarı dört kadranda damar yoğunluğu; rim alanı, disk alanı, yatay cup/disc oranı, dikey cup/disc oranı ve cup hacmi gibi optik sinir başı parametreleri, yüzeysel ve derin foveal damarsız bölge alanı, koroid kalınlığı ve merkezi kornea kalınlığı ölçüldü.
Bulgular: İnflamatuar bağırsak hastalığı olanlar ve kontrol grubunu oluşturanlardan elde edilen bütün ölçüm değerleri büyük benzerlik gösterdi ve istatistiksel olarak birbirlerinden farklı çıkmadı.
Sonuç: Bazı sistemik inflamatuar hastalıklar gözü etkilese ve belirli yapıları değiştirse de, bu çalışma inflamatuar bağırsak hastalığının gözün sinirsel ve damarsal yapıları üzerinde bir etkisi olmadığını ortaya koymuştur.

Anahtar Sözcükler: inflamatuar bağırsak hastalığı, optik koherens tomografi, koroid kalınlığı, merkezi kornea kalınlığı

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory gastrointestinal disease of unknown etiology (1,2). Though IBD is considered as a disease of intestinal tract, it is a systemic inflammatory disorder affecting multiple organs. Ulcerative colitis (UC) and Crohn's disease (CD) are the main types of IBD, with different pathophysiology and clinical features both characterized by episodes of recurrent acute attacks (3). Rectal bleeding, diarrhea, abdominal pain, weight loss and low-grade fewer are the symptoms of IBD. Similar clinical presentations can frequently make it difficult to differentiate between these two entities. UC affects the colon and rectum, while CD can influence any part of the gastrointestinal tract. In UC, lesions are continuous and involve only superficial layers of the bowel wall such as mucosa and submucosa. In CD, lesions are often discontinuous and tend to involve all layers of the wall. Multiple factors such as infection, genetics and environmental conditions may interfere in the etiology (4). IBD has been noted to occur within families, which suggests the theory that genetics may play an important role in its pathogenesis. Historically, the disease has been considered that it might be infectious in origin but this has yet to be supported by the isolation of consistent specific agents. The most significant factor in IBD pathogenesis is likely immune dysregulation, particularly increased secretion of cytokines such as tumor necrosis factor. Extraintestinal manifestations (EIM) of IBD most commonly arise from the skin, joint, eyes and hepatobiliary system (5).

MATERIALS and METHODS

Subjects

Patients with IBD and controls were recruited in the study in accordance with the tenets of Declaration of Helsinki and written consents were obtained from all of the patients and controls. The study protocol was reviewed and approved by the Ethic Committee of Keçiören Training and Research Hospital before starting to study. Patients were between 21 and 70 and control subjects were between 25 and 66 years of age and signed an informed consent. Thirteen IBD patients were referred from the gastroenterology clinic and 14 healthy controls were selected from the individuals who admitted to ophthalmology department for refraction examination or minor complaints. Control subjects were deemed to be normal if any previous history of systemic or ocular disease was absent or a normal appearance of retina and optic disc in clinical examination was present. Randomly selected eyes of the patients and controls were assessed in the study. Both normal individuals and patients who were eligible for the study underwent a complete ophthalmologic examination consisting of the best corrected visual acuity level, slit-lamp biomicroscopy and dilated funduscopy.

Exclusion criteria were history or clinical evidence of retinal disease, presence of macular edema, diabetic retinopathy, previous ocular surgery or laser photocoagulation and medications known to affect retina or choroid. Eyes with quality images less than 50 due to segmentation algorithm failures, motion artifacts or poorly focusing were excluded from the analysis. The data of the patients and controls, including ages, spherical equivalent refractive error, best-corrected visual acuity, gonioscopy, slit-lamp microscopy, intraocular pressure with Goldmann applanation tonometer were recorded. Peripapillary retinal nerve fiber layer (RNFL), macular ganglion cell inner plexiform layer (GCIPL), optic nerve head (ONH) parameters, central corneal thickness (CCT), choroid thickness (CT), vessel density (VD) in macula, as well as the deep and superficial foveal avascular zone (FAZ) areas were quantified by the swept-source optical coherence tomography (OCT).

Optical Coherence Tomography

Images were obtained through the undilated pupils using swept-source OCT. This deep range imaging OCT (DRI OCT, Topcon, Tokyo, Japan) device uses a swept laser with a wavelength of 1050 nm and the wide angle (12x9 mm) scan centered on the posterior pole. This longer wavelength allows a deeper penetration into the tissue and it is therefore possible to obtain images of the macula and optic nerve head in a single scan. The 12x9 mm scan comprises 256 B-scans, each consists of 512 A-scans. For a wide angle scan, SS-OCT obtaines 100.000 A-scans per second with an axial resolution of 8 µm and lateral resolution of 20 µm in tissue. All the anterior and posterior segmental parameters were measured automatically using the built-in segmentation software algorithms.

To measure average or sectoral GCIPL thickness, a circle of 6 mm in diameter is automatically centered on the fovea. GCIPL thickness is the distance from the interface between the nerve fiber layer and ganglion cell layer to the interface between the inner plexiform layer and inner nuclear layer.

Nerve fiber layer is the thickness between the internal limiting membrane and the interface between the nerve fiber layer and ganglion cell layer. For the measurements of RNFL and ONH parameters, a peripapillary circle of 3.4 mm in diameter is automatically centered on the optic disc. Topcon swept-source OCT is equipped with the anterior segment analysis mode, which was used in this study for corneal imaging and CCT.

Topcon OCT angiography allows visualisation of superficial capillary plexus, deep capillary plexus and choriocapillaris. The superficial network extends from 3 µm below the internal limiting membrane to 15 µm below the inner plexiform layer. The deep capillary network is the distance from 15 to 70 µm beneath the inner plexiform layer. In this study, OCT images of the superficial and deep capillary networks were generated separately using the automated software algorithm of the machine. The borderline of the foveal avascular zone was outlined manually and the foveal avascular zone area was then calculated by the built-in analysis software. Vascular density is defined as the percentage of the area occupied by the vessels within the total measured area. The percentage of vessels calculated in parafoveal superior, inferior, nasal and temporal sectors and at the fovea center is automatically determined by the embedded software. The inner and outer rings with a diameter of 1 and 2.5 mm around the fovea are considered for evaluation. Angio analytics software evaluates the relative density of flow as a percentage of the total area.

Statistical Analysis

Statistical analysis was performed using the statistical package for the social science, SPSS version 22 (SPSS, Inc., Chicago, IL). The normality of distribution of the quantitative variables was determined with the Shapiro-Wilk test. For distributed variables and median, mean and standard deviation were used as descriptive statistics. To compare variables between two independent groups, the Mann-Whitney U test was used for non-normally distributed variables. Normally distributed average or quadrant RNFL thickness, average or sectoral GCIPL thickness, ONH parameters, CT, CCT, foveal and parafoveal VDs, superficial and deep FAZ areas were compared between the patients with IBD and control eyes using the independent sample t test. $P < 0.05$ was considered statistically significant.

RESULTS

A randomly selected eye of the patients and controls met the inclusion criteria and was enrolled in the study. The mean ages of 13 patients with IBD (6 males and 7 females) and 14 controls (6 males and 8 females) were 44.73±16.57 and 45.36±12.18, respectively, (P=0.91). Both the patients and controls had no systemic disease, including diabetes mellitus, hypertension and cardiovascular disease. Patients did not use ocular antihypertensive medication or any other drug affecting the eye at the time of OCT imaging. In this study, OCT images of the neural and vascular structures and corneal thickness were generated separately by the swept-source OCT. Average and sectoral RNFL, ONH parameters such as rim area, disc area, vertical cup-to-disc ratio, horizontal cup-to-disc ratio and cup volume, average and sectoral macular GCIPL and CCT were quantified automatically by the software algorithm of Topcon device. After the choroid layer and superficial/deep capillary networks were established by the built-in analysis software, the borderline of superficial and deep capillary FAZ areas was outlined and CT between the pigment epithelium and choroid-sclera junction was measured using the caliper tool provided by the software.

When multiple ocular parameters were evaluated by OCT, mean and quadrant RNFL and ONH parameters did not differ between the patients and controls (Table 1). The differences between the superficial/ deep capillary FAZ areas, CT, foveal/parafoveal VDs, CCT of the patients and controls were not statistically significant (Table 2). Average and sectoral GCIPL thickness also showed no difference between the groups (Table 3). Figure 1 illustrates the appearance of normal fundus and sectoral thickness map of GCIPL in an IBD patient whereas the corneal thickness and FAZ area of superficial capillary plexus are demonstrated in Figure 2.

Table1. Retinal nerve fiber layer and optic nerve head parameters of patients and controls

RNFL	**Patient eye** [Mean±SD (µm)]	**Control eye** [Mean±SD (µm)]	**P**	**Lower limit** (95% CI)	**Upper limit** (95% CI)
Average	112.45±15.88	110.79±11.05	0.75	-9.47	12.81
Superior	142.64±21.92	137.14±15.01	0.46	-9.79	20.78
Inferior	144.09±23.17	143.71±18.23	0.96	-16.73	17.48
Nasal	86.82±13.73	80.07±10.31	0.17	-3.19	16.69
Temporal	75.64±11.12	81.21±10.72	0.21	-14.66	3.51
ONH					
Rim area	1.37±0.55	1.45±0.43	0.68	-0.49	0.32
Disc area	2.18±0.26	2.11±0.33	0.53	-0.17	0.33
HCDR	0.57±0.21	0.59±0.18	0.79	-0.18	0.14
VCDR	0.55±0.13	0.55±0.13	0.98	-0.13	0.13
Volume	0.21±0.21	0.13±0.14	0.27	-0.06	0.22

SD: standard deviation, RNFL: retinal nerve fiber layer, ONH: optic nerve head
HCDR: horizontal cup-to-disc ratio, VCDR: vertical cup-to-disc ratio

Table 2. Posterior segment vascular parameters and central corneal thickness

FAZ area	**Patient eye** [Mean±SD (µm)]	**Control eye** [Mean±SD (µm)]	**P**	**Lower limit (**95% CI)	**Upper limit (**95% CI)
Superficial	282.25±102.78	297.95±136.37	0.75	-118.14	86.72
Deep	416.11±161.55	439.47±227.31	0.77	-191.20	144.49
Vessel density					
Fovea	21.08±3.22	20.71±3.73	0.74	-2.46	3.40
Superior	50.87±2.52	49.49±2.88	0.22	-12.90	3.65
Inferior	49.70±3.68	49.11±3.16	0.67	-2.24	3.41
Nasal	44.26±2.01	43.92±4.76	0.82	-2.83	3.52
Temporal	47.43±2.01	46.51±2.40	0.31	-0.94	2.74
CT	355.45±85.19	310.93±95.13	0.23	-31.27	120.32
CCT	524.00±38.85	526.15±31.20	0.88	-32.50	28.19

SD: standard deviation, FAZ: foveal avascular zone, CT: choroid thickness, CCT: central corneal thickness

Table 3. Ganglion cell inner plexiform layer thickness in IBD patients and controls

GCIPL	**Patient eye** Mean±SD (µm)	**Control eye** Mean±SD (µm)	**P**	**Lower limit (**95% CI)	**Upper limit (**95% CI)
Superior	71.00±7.02	71.57±6.23	0.83	-6.06	4.92
Superonasal	73.36±7.32	76.21±5.05	0.26	-7.97	2.27
Inferonasal	74.06±5.68	75.50±4.95	0.41	0.58	0.74
Inferior	72.82±7.11	75.21±3.94	0.29	7.02	2.22
Inferotemporal	72.91±6.13	75.21±4.50	0.29	-6.70	2.09
Superotemporal	70.45±4.92	73.43±5.33	0.16	-7.27	1.32
Average	71.73±6.21	73.57±4.51	0.39	-6.28	2.59

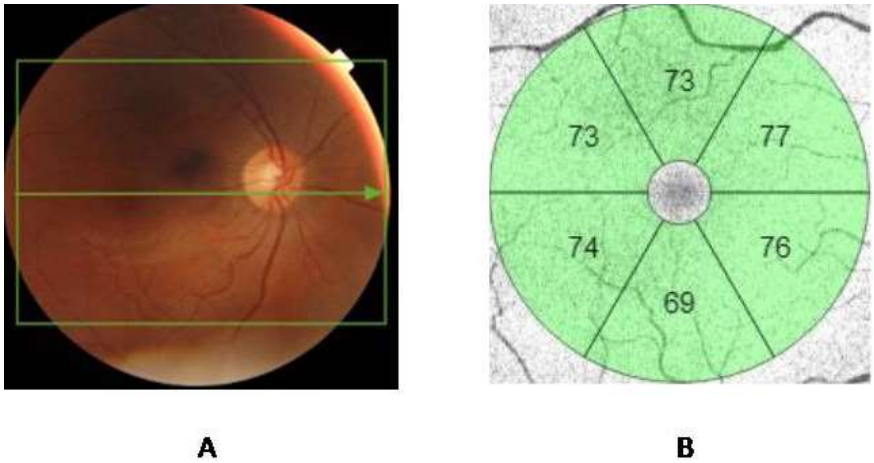

Figure 1. A) Colored fundus photo of a patient with inflammatory bowel disease, B) Sectoral thickness map of ganglion cell inner plexiform layer

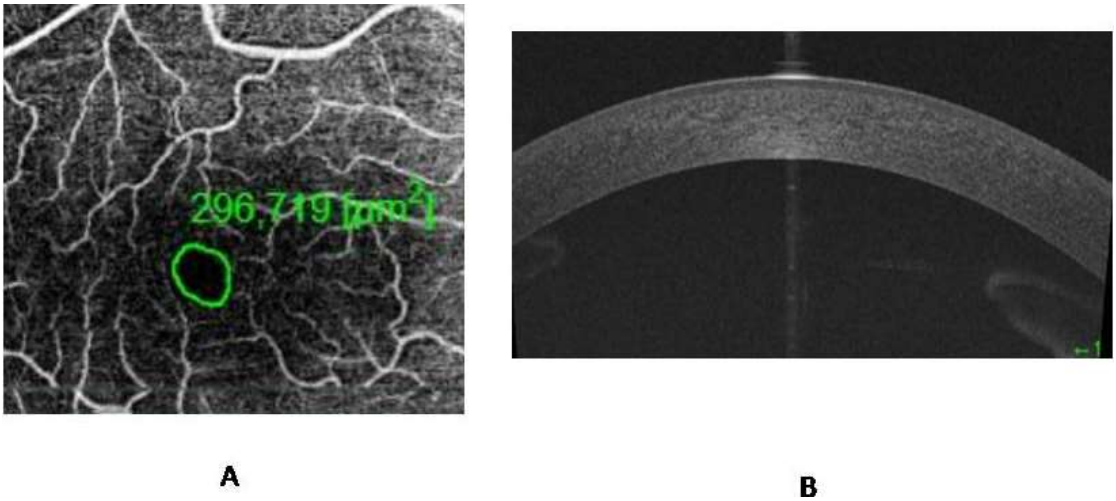

Figure2. A) Foveal avascular zone area at the level of superficial vascular plexus, B) Central corneal thickness

DISCUSSION

Considering the underlying disease, prevalence of EIM ranges between 12% to 35% in UC, 25% to 70% in CD (5). The pathogenesis of the EIM of IBD is not well understood. Inflammation causing damage to intestinal mucosal epithelium may allow protein and microorganisms to pass through the intestinal barrier and lead to lymphoid tissue response. This in turn results in antibody production or antigen-antibody complexes that circulate in the body and cause systemic inflammation (6,7). Patients with EIM of CD have a higher prevalence of HLA-B27 type of leukocytes than the normal population (8). Most studies show a higher frequency of EIMs in CD patients, while some report similar frequencies in both disease. EIM may occur before an IBD diagnosis or even before recurrent intestinal episodes. The diagnosis of IBD in those under 40 years old and of female sex are considered risk factors for the development of EI (9). Among EIMs, musculoskeletal conditions are the most common, followed by mucocutaneous and ophthalmic involvement. However, almost any organ, including those of dermatologic, hepatobiliary, renal and pulmonary systems can be involved (10). Most IBD patients have active colon inflammation, although they can occur prior to or after the onset of colonic symptoms. Early recognition of EIM is important as they may characterize subclinical inflammation in IBD patients with a possible increased risk of morbidity and mortality (11).

The ocular system can be affected by several immune systemic diseases, including IBD (12-16). Since Crohn (17) published the first report of ocular involvement in IBD in 1925, many ocular complications have been determined related to inflammatory manifestations (18). It has been demonstrated that there is a greater tendency of ocular inflammation in CD patients. The prevalence of ophthalmic inflammatory disorders ranges from 0.3% to 13% among all IBD patients (19). Considering the risk factors for developing ocular manifestations in IBD, an association has been reported with female sex (7). A positive correlation has been identified between smoking and ocular manifestation in UC patients (20).

The ocular findings include dry eye, conjunctivitis, episcleritis, scleritis, keratitis, anterior uveitis, retinitis, retinal vascular occlusive disease, optic neuritis and orbital inflammation (21-24).

Ocular involvement may either precede or follow the IBD diagnosis. Ocular complications are categorized as primary, secondary and coincidental. Primary complications are associated with IBD exacerbations and tend to resolve with systemic treatment of the intestinal inflammation. These are keratopathy, episcleritis and scleritis. Secondary complications arise from primary complications. There are in this group cataract formation due to treatment with corticosteroid, scleromalacia due to scleritis and dry eye due to hypovitaminosis-A following gut resection. Coincidental complications, including conjunctivitis or corneal ulcer commonly occur in population and cannot be correlated to IBD alone.

The most common ocular manifestations related to IBD are episcleritis(2%-5%) and uveitis (0.5%-3.5%) (7,10). Mild to moderate pain and mild tenderness to palpation are typical in episcleritis (11). It is associated active CD and can be considered as an indicator of active bowel disease, its resolution occurs with effective treatment of the intestinal disease. Scleritis presents with deep scleral injection and a more sever deep pain, unlike episcleritis is not always associated with active CD (11,22). In addition to major ocular symptoms in IBD such as episcleritis and uveitis, other sporadic ocular complications, including lacrimal gland inflammation, orbital inflammation, central serous chorioretinopathy, choroidal neovascularization, central retinal vein occlusion, central retinal artey occlusion or optic perineuritis were also reported (25-31).

Variations in some ocular parameters, including corneal thickness and CT have previously been reported in systemic autoimmune diseases such as rheumatoid arthritis. Corneal thickness may change in IBD due to the alterations in structure of the tear film layer because dry eye is one of the most common ocular symptoms. Choroid thickness may be supposed to change due to posterior scleritis and vascular events occurring in choroid and and deep retinal layer. The chronic process of this long-term inflammatory disease might allow the variations in anterior and posterior segments of the eye. Therefore, certain ocular parameters were measured using swept-source OCT and compared with those of normal eyes. Önal et al (32) measured the CT with OCT and found no change between the patient and normal eyes and their study was the only one regarding OCT in IBD.

To our knowledge, our study was the first in terms of its scope. In the current study, central corneal thickness, retinal nerve fiber layer thickness, optic nerve head parameters, ganglion cell inner plexiform layer thickness, choroid thickness, foveal avascular zone area and macular vessel density were quantified and analyzed. However, any significant difference could not be detected between the parameters of patient and healthy eyes.

This study presents certain limitations. Our study population included only 13 IBD patients and 14 control subjects. Patients were entirely normal and any of the ocular manifestations, including uveitis, episcleritis, scleritis or chorioretinitis were not present in the patients. Thus, the effects of these entities on ocular parameters were not researched. The small sample size in this study prevented the further subgroup analysis of IBD patients with different disease severities. The restricted sample size might explain the lack of statistically significant differences in different ocular parameters between IBD and healthy eyes. Although they are important factors, age and sex were not analysed in the study due to small sample size. Finally, since this is a cross-sectional study, it is difficult to comment on the effect of IBD in structurel ophthalmic changes. Longitudinal studies will help understand the relationships between IBD and ocular manifestations.

Conflict of interest

No conflict of interest was declared by the authors.

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