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Original Article

The Relationship Between Keratoconus Stage and the Thickness of the Retinal Layers

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Abstract

Objectives: To examine the relationship between keratoconus (KC) stage and the thickness of the retinal layers.

Materials and Methods: Retinal layer thicknesses were compared between 85 eyes of 85 KC patients and 40 eyes of 40 controls similar in age, sex, and axial length. KC patients were staged as stage 1, 2, or 3 according to the Amsler-Krumeich staging system, and segmentation of the retinal layers was performed with spectral domain optical coherence tomography automatic segmentation program. The thickness of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) in the central 1 mm Early Treatment Diabetic Retinopathy Study subfield was analyzed.

Results: There was no significant difference between the control and KC groups in the segmentation of the RNFL, GCL, IPL, or OPL (p=0.306; p=0.661; p=0.893, p=0.664, respectively). The INL differed significantly between control and stage 2 KC, control and stage 3 KC, stage 1 and 2 KC, and stage 2 and 3 KC, increasing in thickness with higher stage (p=0.004; p=0.005: p=0.001; p=0.002, respectively). The RPE also differed significantly between control and stage 2 KC, control and stage 3 KC, stage 1 and 2 KC, and stage 2 and 3 KC, showing decreased thickness with higher stage (p=0.03; p=0.001; p=0.001; p<0.001, respectively). The ONL also thinned as stage increased, but the results were not statistically significant (p=0.051).

Conclusion: More advanced KC stage was associated with increased thickness of the INL layer, where the neuroglial cell bodies are located, and decreased thickness in the outer retinal layers, especially the RPE.

Keywords: Keratoconus, oxidative stress, optical coherence tomography, retinal layer thickness

Introduction

Keratoconus (KC) is a generally bilateral but asymmetrical corneal disease characterized by non-inflammatory stromal thinning, corneal protrusion, and irregular astigmatism.[1] The prevalence of KC is estimated to be 86 per 100,000 population. Although it can occur in all age groups, it is more common between the ages of 10 and 20 years.[2] KC can reduce visual acuity (VA) and quality to varying degrees depending on disease stage. VA can be improved with spectacles in the early stages of KC, whereas rigid gas-permeable contact lenses or corneal transplantation may be required to compensate for anterior corneal surface irregularity in the advanced stages.[3]

The current software of optical coherence tomography (OCT) imaging devices enables the objective measurement of macular thickness changes. These changes are helpful in the diagnosis and follow-up of various diseases such as diabetic retinopathy, macular degeneration, and retinal vascular occlusion.[4,5] OCT imaging can now be used to investigate the presence of accompanying macular pathologies, not only in posterior segment pathologies, but also in other ocular problems related to the anterior segment, such as myopia or KC. While there are studies in the literature

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showing that mean macular thickness did not change with refractive error,[6,7] others showed that mean macular volume and thickness decreased with higher myopia.[8] There are also a few studies in the literature on OCT imaging in patients with KC. Moschos et al.[9] reported that patients with KC may have macular changes undetectable by biomicroscopy. Another study showed that mean thickness in the central fovea, inner macula, and outer macula was significantly greater in patients with KC compared to a control group.[10] However, this study did not investigate the relationship between KC stage and thicknesses of the fovea or the individual retinal layers, or determine which retinal layer was responsible for the increase in thickness.

The present study aimed to evaluate whether macular layer segmentation differs in healthy volunteers and patients with KC and to evaluate the relationship between KC stage and retinal layer thicknesses.

Materials and Methods

Study Design

This observational clinical study was conducted in the Corneal and Retinal Units of the Kayseri Training and Research Hospital Ophthalmology Clinic in accordance with the principles of the Declaration of Helsinki after obtaining ethics committee approval (decision no: 00106647458). All participants were informed about the study and provided their written informed consent. The study included patients diagnosed with KC in our clinic and individuals without KC who presented to the outpatient clinic between January 2019 and December 2019.

All participants underwent a thorough ophthalmological examination including manifest refraction measurement, VA evaluated with Snellen chart, slit-lamp biomicroscopy and anterior segment evaluation, intraocular pressure measurement, and dilated fundus examination. Corneal topography (Pentacam TM, Oculus Inc., Lynnwood, WA, USA) was used to diagnose and stage KC, spectral domain-OCT (SD-OCT) (Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany) was used to obtain segmentation of the macular layers, and non-contact partial coherence interferometry (IOL Master, Zeiss, Jena, Germany) was used to measure axial length. KC patients were classified as stage 1, stage 2, or stage 3 according to the Amsler-Krumeich Classification.[11]

Of the patients with KC confirmed by clinical examination and corneal topography in at least one eye and the healthy controls, those with complete ophthalmological examination records including axial length measurement, corneal topography, and SD-OCT imaging were included in the study. Topographic findings in favor of KC were the presence of focal steepening greater than 47 diopters (D) and more than 1.4 D asymmetry between the midperipheral and inferior/superior corneal regions on the topographic map.[12] Exclusion criteria included the presence of non-KC corneal pathology such as corneal degeneration and keratectasia in either eye, any retinal pathology such as age-related macular degeneration or retinal vascular occlusion, age less than 18 or over 40 years, myopia greater than -6 diopters, axial length longer than 26 mm, any systemic disease, and optic nerve diseases (optic neuritis, optic atrophy). In addition, patients with severe corneal problems (e.g., corneal scarring, previous corneal surgery) that precluded SD-OCT or Pentacam imaging and participants with vitreoretinal interface pathology (e.g., vitreoretinal traction, retinoschisis, epiretinal membrane, and lamellar macular hole) that could affect segmentation in SD-OCT scans were excluded from the study. Patients who had undergone corneal cross-linking (CXL) were also excluded due to its potential effects on the retinal layers. Therefore, 2 patients with inadequate image quality due to advanced KC, 21 patients with history of CXL, 5 patients with myopia greater than -6 diopters, 1 patient with collagen tissue disease, and 4 patients younger than 18 years of age were excluded from the study.

Corneal Topography and Screening Analysis

A Pentacam corneal topographer was used to evaluate anterior segment parameters. All images were acquired by an experienced nurse (G.C.) at the same time of day (between 9 and 10 a.m.) and evaluated by an experienced refractive surgeon (Y.Y.).

All participants were screened with the SD-OCT Fast Macular Thickness program to show the macular structure and analyze the thickness of the individual retinal layers. Signal-to-noise ratio was maximized using automatic real-time averaging mode. OCT image was classified according to signal strength ranging from 0 (low-quality image) to 40 (high-quality image) and patients with SD-OCT image quality lower than 20 were excluded from the study. One eye of each KC patient was randomly selected using randomization software (http://random-allocation-software.software.informer.com/2.0/) for comparison with the right eyes of the healthy controls. All OCT scans were performed by the same experienced nurse (S.E.) at the same time of day and the automated OCT segmentation (Segmentation Technology; Heidelberg Engineering, Inc) was validated by an experienced retinal specialist (C.O.). After imaging, all images were checked to ensure that the foveal depression was evident in the center of the scan. The segmentation application automatically divided the retina into 7 separate layers with a single horizontal foveal scan of the retinal layers and calculated the average thickness of each layer. Patients with severe corneal distortions due to advanced KC were advised to wear contact lenses during image acquisition; images that were not suitable despite this were not included in the analysis. The mean thickness values of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) within the central 1 mm Early Treatment Diabetic Retinopathy Study subregion as determined by automatic segmentation were analyzed.

Outcome Measures

The primary outcome measures were differences in retinal layer thicknesses in the central macular region between patients with KC and healthy volunteers. The secondary outcome

measures were correlations between keratometric and clinical values and retinal layer thickness.

Statistical Analysis

All analyses were performed using SPSS version 22.0 for Windows software package (IBM Corp, Armonk, NY). Distribution of the variables was assessed using Kolmogorov-Smirnov test. Descriptive data were expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used for parametric data and Kruskal-Wallis H test for non-parametric data. Spearman correlation analysis was performed to evaluate relationships between non-parametric variables and Pearson correlation analysis for parametric variables. Chi-square test was used to analyze quantitative data. P values less than 0.05 were accepted as statistically significant.

Results

Participant Characteristics

This study included 85 eyes of 85 KC patients and 40 eyes of 40 non-KC controls. The mean age of the control group was 26.25±7.14 years and the female/male distribution was 21/19. According to the Amsler-Krumeich staging system, there were 40 stage 1 KC patients (mean age: 27.32±7.43, female/male distribution: 14/26), 27 stage 2 KC patients (mean age: 28.18±8.25, female/male distribution: 14/13), and 18 stage 3 KC patients (mean age: 29.94±10.34, female/male distribution: 9/9). The groups had statistically similar demographic characteristics, axial length values, and SD-OCT image quality scores. The demographic and descriptive data of the groups are shown in Table 1.

Retinal Segmentation Results

Table 2 shows the comparison of retinal segmentation results between the groups. There were no significant differences in RNFL, GCL, IPL, or OPL between the control and KC groups (p=0.306; p=0.661; p=0.893; p=0.664, respectively). INL thickness increased with higher KC stage and differed significantly between the control and stage 2 KC groups (p=0.004), control and stage 3 KC groups (p=0.005), stage 1 and 2 KC groups (p=0.001), and stage 1 and 3 KC groups (p=0.002) (Figure 1a, b).

RPE thickness decreased with higher KC stage and differed significantly between the control and stage 2 KC groups (p=0.03), control and stage 3 KC groups (p=0.001), stage 1 and 2 KC groups (p=0.001), and stage 1 and 3 KC groups (p<0.001) (Figure 2a,b).

Mean thickness of the ONL also showed a marked decrease as KC stage increased, but the result narrowly missed statistical significance (p=0.051).

Correlation Analysis

Correlation analysis was performed between all retinal layers and mean keratometric value (Kmean), maximum keratometric value (Kmax), thinnest corneal thickness, topographic cylinder, axial length, age, and gender (Table 3). Kmean was positively correlated with INL thickness (r=0.305, p=0.001) and negatively correlated with RPE thickness (r=-0.386, p<0.001).

Topographic cylinder also correlated positively with INL thickness (r=0.244, p=0.006) and negatively with RPE thickness (r=-0.270, p=0.002).

Similar correlations were detected in the analysis of relationships between Kmax and retinal layer thicknesses. There were no significant correlations between the retinal layers and age, axial length, or thinnest corneal thickness values.

Discussion

KC is a degenerative corneal disorder characterized by defects in Bowman's layer and ectasia associated with iron deposits in the form of Fleischer rings in the epithelial basal membrane.[13] Environmental, genetic, and mechanical factors such as oxidative ultraviolet (UV) radiation, genetic susceptibility, contact lens use, atopy, and eye rubbing play an important role in the pathogenesis and progression of KC.[14,15] Compared to normal corneal specimens, human corneas with KC were found to have high levels of nitrotyrosine, a marker of superoxide and peroxynitrite production, and increased endothelial nitric oxide synthesis (eNOS) at sites of breaks in Bowman's layer.[16] The formation of increased reactive oxygen species (ROS) leads to oxidative stress, resulting in mitochondrial DNA (mtDNA) degradation in KC corneas.[14] In KC corneas, increased mtDNA damage affects the protein-encoding mtDNA regions

Table 1. Demographic and descriptive data

	Control n=40	Stage 1 n=40	Stage 2 n=27	Stage 3 n=18	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	26.25±7.14	27.32±7.43	28.18±8.25	29.94±10.34	0.592
Axial length (mm)*	23.72±1.02	23.34±0.61	23.66±0.65	23.48±0.85	0.581
Kmean (diopters)	43.74±1.56	44.77±1.70	49.47±1.18	54.49±2.79	<0.001
Thinnest corneal thickness (µm)*	525.85±37.21	450.17±69.33	421.81±60.89	387.16±55.03	<0.001
Topographic cylinder (diopters)	1.20±0.77	2.71±1.54	3.68±1.98	5.98±3.13	<0.001
Sex (M/F)α	19/21	26/14	13/14	9/9	0.376
Image quality score	25.61±3.52	24.80±2.29	23.72±2.53	22.91±1.37	0.310

Kmean: Mean keratometry value, M: Male, F: Female; Kruskal-Wallis Test, *One-way ANOVA, αChi-square test

and disrupts mitochondrial oxidative phosphorylation, thereby causing deviations in the expression of oxidative phosphorylation proteins, incorrect ATP synthesis, increased ROS formation, and more oxidative damage. Reduced antioxidant defenses in KC corneas also result in keratocyte apoptosis and adverse changes in the extracellular matrix, leading to corneal thinning and deformation. In addition to accelerating keratocyte apoptosis in the anterior segment, oxidative stress may also have important effects on the lens tissue and the retina in the posterior segment.[17]

Oxidative stress in the lens tissue occurs not only due to oxidant-antioxidant imbalance but also as the result of an imbalanced redox state in the lens epithelial cells. Lens

Table 2. Retinal segmentation results of the control group and the KC group according to stage

	Control n=40[a]	Stage 1 n=40[b]	Stage 2 n=27[c]	Stage 3 n=18[d]	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Total retina (µm)*	271.17±22.19	265.55±23.66	273.11±23.92	270.77±29.24	0.615
RNFL (µm)	12.87±2.31	12.12±2.30	13.48±3.27	12.77±4.03	0.306
GCL (µm)	17.37±8.45	15.72±6.56	17.14±6.59	16.27±7.62	0.661
IPL (µm)	21.10±5.02	20.15±3.86	20.81±4.50	20.44±5.57	0.893
INL (µm)	19.07±5.65	18.37±5.85	23.11±6.06	25.50±9.19	**<0.001**
OPL (µm)	26.60±8.07	25.62±6.78	27.59±6.19	27.88±9.13	0.664
ONL (µm)*	86.85±10.10	86.80±11.87	78.50±12.22	77.52±17.59	0.051
RPE (µm)	16.95±1.86	17.70±2.51	15.85±1.83	15.11±1.87	**<0.001**

RNFL: Retinal nerve fiber layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer, OPL: Outer plexiform layer, ONL: Outer nuclear layer, RPE: Retinal pigment epithelium; Kruskal-Wallis Test, *One-way ANOVA; INL p: [a-c]: 0.004, [a-d]: 0.005, [b-c]: 0.001, [b-d]: 0.002, RPE p: [a-c]: 0.030, [a-d]: 0.001, [b-c]: 0.001, [b-d]: <0.001

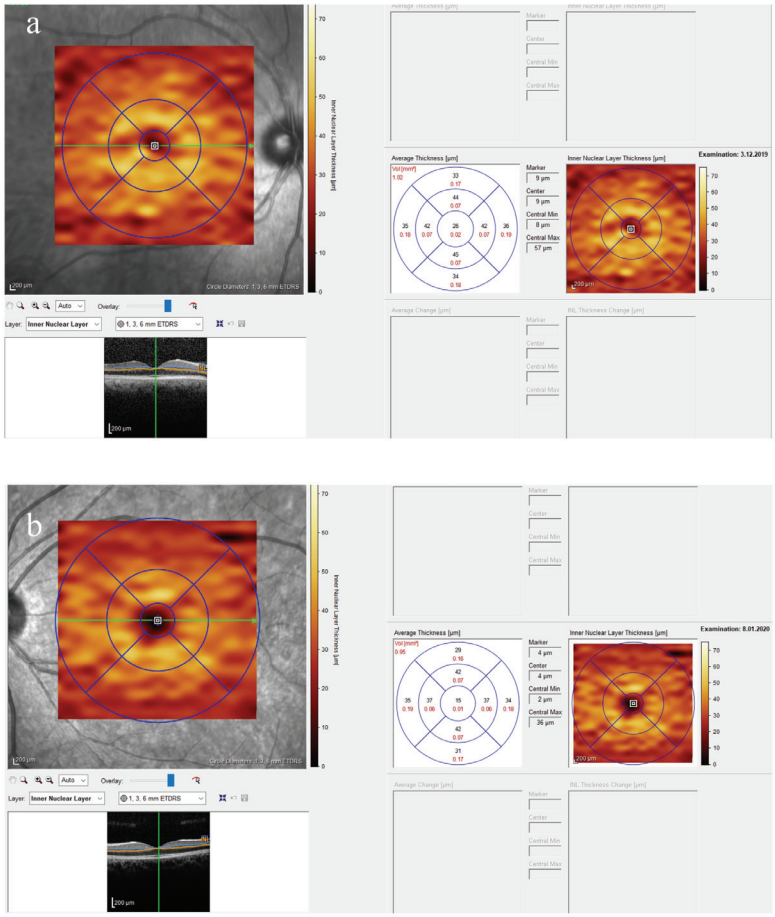

Figure 1. Automatic segmentation showing that the inner nuclear layer tends to be thicker in a patient with advanced keratoconus (a) compared to the control group (b)

epithelial cells contain abundant mitochondria, consume 90% of the oxygen entering the lens, are major sources of endogenous ROS, converting 1-5% of uptaken oxygen into ROS, and their oxidative damage plays an important role in cataractogenesis.[18] Therefore, the mitochondrial dysfunction and ROS imbalance that can be present in patients with KC may also play a role in the pathogenesis of cataract development by inducing oxidative damage of cellular components.

ROS reduces levels of brain-induced neurotrophic factor (BDNF), which regulates axonal growth, synaptic activity, and neuron survival. Synaptic transmitter damage and neurotrophic factor inhibition by excessive ROS levels lead to neuronal apoptosis, visual impairment, and impaired vision quality.[19] It has been reported that central macular thickness showed no difference between pediatric KC patients and a control group.[20] However, the thickness of the individual retinal layers was not evaluated, and no detailed study to determine whether retinal layer segmentation differs in adult KC patients compared to a control group has been conducted to date. Uzunel et al.[21] evaluated peripapillary RNFL measurement, ganglion cell analysis, and total macular thickness and reported that all parameters decreased compared to the control group as KC stage increased. However, they did not analyze the individual retinal layers in the central macular area. Cankaya et al.[22] similarly reported that RNFL thickness values were more comparable than optic nerve head parameters. The present study also aimed to investigate whether factors involved in the pathogenesis and progression of KC lead to posterior segment changes in addition to problems affecting the anterior segment. Müller cells provide architectural support to the retina and are known to play a key role in the retinal physiology. However, macroglia stimulated by oxidative stress indirectly contribute to retinal excitotoxicity by increasing glial fibrillary acidic

Table 3. Correlation analysis

	r	p
Kmean		
INL	0.305	0.001
RPE	-0.386	<0.001
Topographic cylinder		
INL	0.244	0.006
RPE	-0.270	0.002

Kmean: Mean keratometry value, INL: Inner nuclear layer, RPE: Retinal pigment epithelium

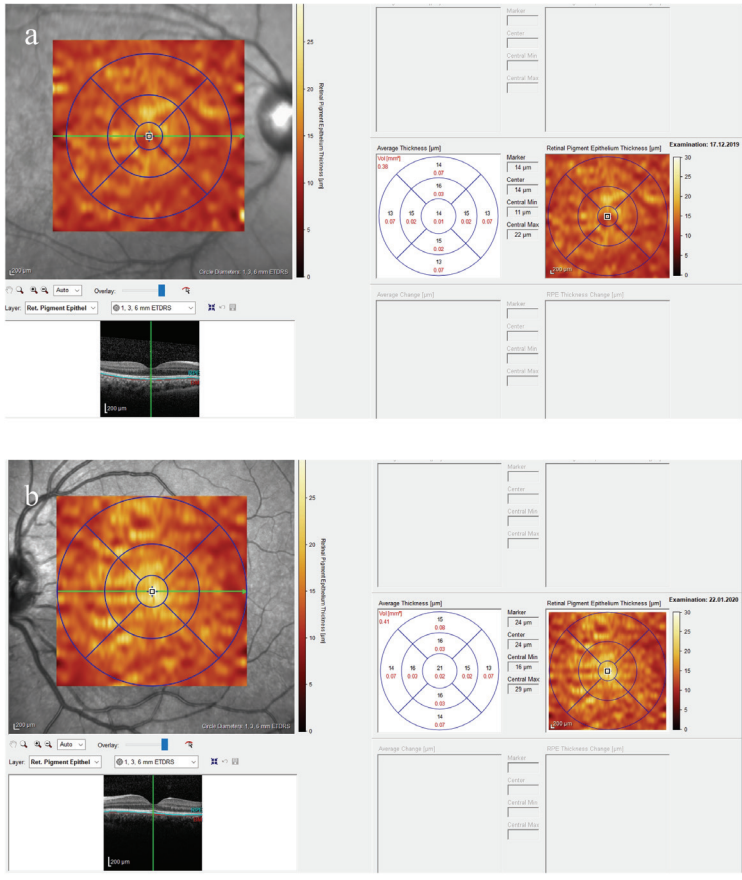

Figure 2. Automatic segmentation showing that the retinal pigment epithelium layer tends to be thinner in a patient with advanced keratoconus (a) compared to the control group (b)

protein expression, nitric oxide production, and glutamate synthesis.[23] The INL is known to contain Müller cells, bipolar cells, and the bodies of horizontal and amacrine cells. We believe that the increase in INL thickness with more advanced KC stage observed in the present study is likely due to the response from Müller cells that are present in higher numbers and activated as a result of increased oxidative stress. To the best of our knowledge, there are no previous reports on this subject in the literature.

Increased ROS levels and reduced antioxidant cell defense systems cause damage to photoreceptors and RPE cells through apoptosis.[24] As KC progresses, it can be expected that the adverse effects on the outer retinal layers will also increase, because these layers are more susceptible to UV radiation and blue light, which are involved in the pathogenesis and progression of KC. As the cell membranes of photoreceptors are rich in polyunsaturated fatty acids that are easily oxidized, this is one of the reasons why they are more susceptible to oxidative damage. In our study, we observed that the ONL, which comprises the nuclei of photoreceptor cells, thinned as KC stage advanced. However, the difference did not reach statistical significance, probably due to the small number of patients. Photoreceptors are cells that have high metabolic activity and high oxygen and nutrient demand. Due to their high oxygen consumption, any mitochondrial dysfunction results in a high rate of ROS production. Photoreceptors and RPE cells, which are postmitotic cells with high metabolic activity, show a reduction in number and thickness in the presence of increased oxidative stress.[25] In the present study, we observed significant thinning of the RPE layer in eyes with KC compared to the control group and in the advanced stages of KC. We believe that this difference between groups with similar central macular thickness is also clinically significant.

When examining retinal layer thickness in patients with KC, other common factors besides the oxidative stress mechanism that could affect the anterior and posterior ocular structures should also be investigated. KC is a complex, multifactorial pathology whose etiology involves both genetic and environmental factors. Currently, genetic risk factors that may play a role in the development of KC are mostly being investigated by analyzing genes identified as important in other complex eye diseases. In a genotyping study of DNA extracted from the blood or saliva samples of 248 KC and 366 control patients, single nucleotide polymorphisms in two gene loci that have been implicated in AMD, rs6795735 (*ADAMTS9*) and rs5749482 (*TIMP3*), were significantly associated with KC and were reported to potentially play a role in the pathogenesis of KC.[26] Another study reported that these two genes encoded enzymes involved in proteoglycan and extracellular matrix metabolism and were expressed at a lower rate in KC patients compared to the control group.[27] Determining the relationship between this genetic relationship and the RPE layer thinning observed in this study, especially in patients with advanced KC, and whether it causes a clinical predisposition to atrophy at a younger age than expected remains to be clarified in future studies.

When conducting retinal layer segmentation, it is also necessary to evaluate for distortions and artifacts that may lead to possible errors. Increasing astigmatism as KC progresses can lead to artifacts in different parts of the retina. Langenbucher et al.[28] reported that high astigmatism may lead to changes in peripapillary RNFL measurements due to elliptical distortion of the retinal image in different quadrants and that image size may vary according to meridian. They also stated that increased scanning distance from the optic disc could affect RNFL measurements around the optic disc head. Similarly, Hwang et al.[29] reported that RNFL measurements in the superior/inferior peripapillary regions and those obtained from the nasal/temporal areas may be affected differently. Leonard et al.[30] investigated objective scattering index and retinal image quality in KC patients using point spread function analysis. They reported that image quality was close to normal in mild to moderate KC patients, while in advanced KC the retinal image could assume an ellipsoid shape, resulting in lower image quality. The authors concluded that the use of this objective analysis in the clinic may be effective in the early diagnosis of patients with KC and in treatment decision-making during preoperative management.[30] As mentioned above, Uzunel et al.[21] reported that peripapillary RNFL measurements decreased as KC stage advanced, but their study did not include macular measurements. Similarly, Cankaya et al.[22] reported that RNFL thickness measurements obtained by OCT in KC and normal individuals were more comparable than optic nerve head parameters obtained by scanner laser ophthalmoscope. Furthermore, other studies in the literature suggested that astigmatism had no significant effect on macular thickness measurements.[31,32] Finally, in a meta-analysis examining the reliability of retinal layer thickness measurements performed with different OCT devices in patients with different demographic characteristics (e.g., refractive error, age), it was reported that segmentation measurements obtained within the central 6 mm zone were highly reliable and that the OCT devices could be used in clinical research.[33] Based on this information, we believe that a possible artifact would not significantly affect the results of our automatic segmentation of the central macular region in a similar meridian.

Another important parameter to keep in mind when evaluating the retinal layers is axial length. Studies evaluating the effect of axial length on macular layer analysis have yielded different results. In some of these studies, macular thickness parameters measured by OCT were reported to decrease with increased axial length.[34,35] Xie et al.[35] reported that the mean macular thickness was significantly thinner in the myopia group compared to the emmetropia group. Lim et al.[7] reported that the mean macular thickness did not change with myopia, while the parafovea was thinner and the fovea was thicker. Choi et al.[36] reported that longer axial length was associated with increased foveal thickness. In our study, the similarity between the groups in terms of other clinical parameters such as axial length, age, and sex ensured that the potential effects on the retinal layers were also similar.

There are also studies in the literature examining the relationship between KC and other posterior ocular structures. Akkaya and Küçük[37] found that the lamina cribrosa was significantly thinner in patients with KC compared to the control group and suggested that the structural features of the cornea may be associated with the sclera and optic nerve. In another study, subfoveal choroidal thickness was reported to be significantly higher in KC patients than controls, and this change was attributed to the natural course of the disease.[38] Considering our findings of different effects on the retinal layers, the relationship between KC and the posterior ocular structures and the possible underlying mechanisms are an important subject for future research.

Study Limitations

This study has certain limitations. Further studies with more advanced KC cases are needed to determine whether changes in macular parameters consistently follow these patterns and to confirm the current findings. It has been reported in the literature that astigmatism may affect peripapillary RNFL measurements but does not change the signal strength of macular parameters measured with SD-OCT devices.[22,31] However, the correlation between astigmatism severity and peripapillary RNFL and thickness analyses in the macular region must be confirmed in future studies. The strength of our study is that it is the first study showing that potential factors involved in the progression of KC, such as UV radiation, oxidative stress, and genetic predisposition, may also have different effects on the retinal layers.

Conclusion

Another important question worth investigating through long-term follow-up is whether patients with advanced KC are predisposed to AMD due to RPE dysfunction. Further studies at the molecular level could reveal that KC may also be accompanied by retinal pathologies that can affect vision level and quality.

Ethics

Ethics Committee Approval: Kayseri City Training and Research Hospital (ethics committee decision approval: 00106647458)

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., Y.Y., Concept: C.Ö., Design: C.Ö., Data Collection or Processing: Y.Y., Analysis or Interpretation: Y.Y., Literature Search: C.Ö., Writing: C.Ö.

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

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