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RESEARCH ARTICLE

Evaluation of Macular and Choroidal Thickness in Patients with Subclinical Keratoconus

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ABSTRACT

Objective: To evaluate choroidal thickness (CT) and central macular thickness (CMT) in eyes with keratoconus and subclinical keratoconus (SKC), and in age- and sex-matched healthy controls.

Materials and Methods: This cross-sectional study included 18 patients with keratoconus in one eye and SKC in the other, and 18 controls. The CMT and CT measurements were obtained from all participants. Measurements were taken at the subfoveal CT, the CT at 750 µm nasal and temporal to the fovea, and the CT at 1500 µm nasal and temporal to the fovea.

Results: No significant difference was noted in the mean CMT values among the three groups ($p>0.05$). The mean subfoveal, N750, N1500, T750, and T1500 CT values in the keratoconus group were significantly higher than those in the SKC and control groups ($p<0.05$). However, there were no significant differences in the mean CT values of the subfoveal, N750, N1500, T750, and T1500 regions between the SKC and control groups ($p>0.05$).

Conclusion: Although we have shown that CT is increased in patients with keratoconus, the measurement of choroidal and macular thicknesses does not appear to be a useful technique to differentiate eyes with SKC from healthy eyes or to follow the progression of the disease.

Keywords: Keratoconus, choroidal thickness, macular thickness, subclinical keratoconus

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INTRODUCTION

Keratoconus, a degenerative corneal disease characterized by progressive corneal thinning, can be diagnosed with high accuracy based on clinical findings and corneal topographic analysis.[1] However, it is important to identify eyes with subclinical keratoconus (SKC) without clinical signs of keratoconus, which refers to the mildest form of topographic keratoconus with a normal clinical examination and visual acuity.[2,3] Most of the ectasias that develop after refractive surgery result from surgery performed in undiagnosed cases of SKC. In addition, detection of SKC in the preclinical stage is important, as it can be prevented by corneal collagen cross-linking therapy before progression to the clinical stage.[4]

Systemic disorders, such as Ehlers-Danlos syndrome and Leber's congenital amaurosis, have been reported to be associated with keratoconus and may lead to retinal degeneration.[5] In addition, several studies have reported that diseases, such as central serous chorioretinopathy and choroidal neovascularization, may accompany keratoconus.[6,7] These data suggest that keratoconus may be associated with retinal disorders or macular dysfunction. Therefore, a comprehensive retinal examination is appropriate for patients with keratoconus, especially before corneal transplantation.

Increased levels of local and systemic inflammatory cytokines in the corneal epithelium and tears of patients with keratoconus indicate that the disease has an inflammatory background.[8] Increased choroidal thickness (CT) is a common finding in inflammatory diseases, especially due to the infiltration of the vascular-rich choroidal tissue by proinflammatory mediators.[9] Certain studies present optical co-

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herence tomography (OCT) findings in patients with keratoconus.[10,11] In one such study of keratoconus cases, central macular thickness (CMT) was reported to be unchanged; however, it was shown that low visual acuity may be due to macular dysfunction as well as corneal abnormalities.[10]

Recently, it has been reported that CT is increased in patients with keratoconus, and this is interpreted as an inflammatory substructure of the disease.[12] The finding that some cytokines such as IL-6 and TNF-α were overexpressed in the tears of SKC and keratoconus eyes in patients diagnosed with unilateral keratoconus supported the role of inflammation in the pathophysiology of keratoconus.[13] Theories that claim a role for inflammation in the pathophysiology of keratoconus may help support the idea that inflammatory factors could potentially contribute to both the progression of keratoconus and an increase in CT.[14] From this point of view, in this study, we evaluated CT in keratoconus, SKC, and control groups and wanted to answer the question of whether CT could be a follow-up parameter in patients with SKC.

MATERIALS and METHODS

This cross-sectional observational study was approved by the Ethics Committee of Istanbul Atlas University (Number: E-22686390-050.99-34023, 25.10.2023) and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent after receiving information about the nature and possible outcomes of the study.

This study was undertaken between October 2023 and March 2024 and included 18 patients with keratoconus in one eye and SKC in the other eye, and 18 controls. A comprehensive ocular examination and topographic and keratometric measurements of the cornea were performed. Keratoconus was diagnosed based on clinical evaluation. In addition to prominent keratoconus-specific topographic findings (an asymmetric bowtie pattern with or without a skewed radial axis or inferior or central steepening on anterior sagittal curvature maps), at least one of the following findings was required for the diagnosis of keratoconus: scissor reflex on retinoscopy, a Fleischer ring, Vogt striae, corneal thinning, and Munson's and Rizutti's sign.[5] The criteria used to define the diagnosis of SKC were a central mean keratometry (K) value less than 47.2 dioptres (D), an asymmetry of less than 1.2 D for the mean K value between the inferior and superior corneal curvature, normal topographic findings, absence of any clinical signs of keratoconus, and the presence of significant keratoconus in the fellow eye.[15] Exclusion criteria were the presence of any systemic or metabolic disorder, ocular abnormality other than keratoconus, a long or short axial length (>25.0 mm or <22.0 mm, respectively), history of refractive surgery, use of vasoactive medications or hormone replacement treatment, and coffee consumption on the day of the examination.

The control group participants were selected from volunteers with myopia or myopic astigmatism (spherical <6.00 D; cylindrical <3.00 D) but with normal corneal topography and OCT imaging. Eyes without an ocular pathology, previous ocular surgery, or irregular corneal patterns were considered normal. Only one eye of each participant was randomly selected and evaluated.

The participants underwent a complete ophthalmological examination, including refraction, visual acuity, and slit-lamp examinations. Corneal topography imaging (Pentacam, Oculus Inc., Wetzlar, Germany) and OCT imaging were performed.

OCT Screening Protocol

OCT (software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany) was used in enhanced depth imaging mode using a previously reported method.[16] This device has a wavelength of 870 nm and acquires 40,000 A-scans per second. The resolutions obtained by the device in axial and horizontal sections are 7 and 14 µm, respectively. In the horizontal scanning mode centered on the fovea, an average of 100 scans was obtained for each slice, covering an area of 1×30°. The CT was calculated by measuring the vertical distance between the inner surface of the choroidal-scleral junction and the outer edge of the hyperreflective retinal pigment epithelium. CT was performed manually by the same ophthalmologist in all the cases. Measurements were taken at the subfoveal CT, the CT at 750 µm nasal and temporal to the fovea, and the CT at 1500 µm nasal and temporal to the fovea. In addition, CMT, defined as the distance between the vitreoretinal interface and anterior surface of the retinal pigment epithelium at the central fovea, was automatically calculated. Only high-quality images were used in this study. To avoid daily fluctuations in the CT images, all measurements were performed between 09:00 and 12:00.

Statistical Analysis

SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Descriptive statistics are presented as mean±standard deviation. Qualitative data were analyzed using chi-square tests. The Kruskal-Wallis test was used to determine whether there was a statistically significant difference among the three groups, and Mann - Whitney U test was used to analyze the groups separately. The significance level was set at $p<0.05$.

Table 1. Demographic variables of the participants

	Keratoconus (n=18)	Subclinical keratoconus (n=18)	Control (n=18)	p*
Age, years	24.9±4.9	24.8±5.0	24.7±6.8	0.990* 0.999[a], 0.998[b], 0.998[c]
Gender, n (%)				
Female	8 (44)	8 (44)	9 (50)	0.928[¥]
Male	10 (56)	10 (56)	9 (50)	1.0[¥], 0.738[¥], 0.738[¥]
BCVA, logMAR	0.40±0.10	0.05±0.05	0.01±0.01	**<0.001*** **<0.001[a], <0.001[b], 0.01[c]**
SE, (D)	-5.99±1.84	-1.79±0.66	-1.38±0.67	**<0.001*** **<0.001[a], <0.001[b]**, 0.194[c]
K max, (D)	51.9±5.4	44.9±3.3	44.1±2.6	**<0.001*** **<0.001[a], <0.001[b]**, 0.842[c]
K min, (D)	46.7±6.2	43.5±2.7	42.7±1.8	**0.013*** 0.165[a], 0.052[b], 0.698[c]
TCT, µm	442.0±51.1	525.7±32.8	543.5±15.1	**<0.001*** **<0.001[a], <0.001[b]**, 0.135[c]

Data is given as mean±standard deviation. Mann - Whitney U test. [a]: Group 1 vs Group 2; [b]: Group 1 vs Group 3; [c]: Group 2 vs Group 3.*: Kruskal-Wallis test; [¥]: Chi-square test. BCVA: Best Corrected Visual Acuity; logMAR: Logarithm of the minimum angle of resolution; SE: Spherical equivalent; TCT: Thinnest corneal thickness

Table 2. Central macular thickness (CMT) and choroidal thickness (CT) in different locations at each group

	Keratoconus (n=18)	Subclinical Keratoconus (n=18)	Control (n=18)	p*
CMT	251.55±21.65	249.94±12.36	246.16±16.14	0.629 0.990[a], 0.782[b], 0.816[c]
Subfoveal	373.33±29.11	314.38±28.65	305.88±29.64	**<0.001** **<0.001[a], <0.001[b]**, 0.765[c]
N750	352.83±28.05	308.16±37.05	292.77±34.69	**<0.001** **0.001[a], <0.001[b]**, 0.494[c]
N1500	347.66±27.54	304.27±29.02	286.77±37.35	**<0.001** **<0.001[a], <0.001[b]**, 0.327[c]
T750	357.22±31.80	311.94±24.48	299.11±24.70	**<0.001** **<0.001[a], <0.001[b],** 0.328[c]
T1500	355.94±30.08	308.61±30.24	296.55±33.62	**<0.001** **<0.001[a], <0.001[b],** 0.597[c]

Data is given as mean±standard deviation. *: Kruskal-Wallis test. Mann - Whitney U test. [a]: Group 1 vs Group 2; [b]: Group 1 vs Group 3; [c]: Group 2 vs Group 3. Measurements undertaken at subfoveal, nasal 750 µm (N750), nasal 1500 µm (N1500), temporal 750 µm (T750), and temporal 1500 µm (T1500).

RESULTS

Eighteen patients and 18 healthy controls were included in the study (Table 1). Age and sex distributions did not differ significantly between the two groups (p>0.05). The best-corrected visual acuity (BCVA) and keratometry values of eyes with keratoconus were significantly different from those of the other two groups (p<0.05).

The results of the CT and CMT measurements in the groups are presented in Table 2. The mean CMT was not significantly different between the groups (p>0.05). In post hoc

analyses, the keratoconus group had higher subfoveal, N750, N1500, T750, and T1500 CT values than the other two groups ($p<0.05$). No significant differences were found between eyes with SKC and healthy eyes in terms of subfoveal, N750, N1500, T750, or T1500 CT values ($p>0.05$).

DISCUSSION

Keratoconus is a bilaterally asymmetrical corneal disease involving structural changes that are thought to be non-inflammatory. In contrast, SKC is defined as a condition in which the disease does not show clinical symptoms, but has the potential to progress. It is of great importance to determine the progression of SKC. Recently, an increase in CT scans reported in patients with keratoconus suggested that the disease may be inflammatory.[17] The hypothesis that inflammation might play a role in the pathophysiology of keratoconus and SKC supports the idea that inflammatory factors could potentially contribute to both the progression of keratoconus and the increase in CT.[13,14] In the current study, we aimed to determine whether CT could be used as a follow-up parameter in patients with SKC. Thus, we compared the groups by performing CT measurements from five different points in the keratoconus, SKC, and control groups. The findings of this study revealed that while the mean CT values of eyes with keratoconus were significantly higher than those of eyes with SKC and the control group, there was no significant difference in the mean CT values between the SKC and control groups. Although we have shown that CT is increased in patients with keratoconus, evaluation of choroidal thickness does not appear to be a useful technique for differentiating eyes with SKC from healthy eyes or following the progression of the disease.

New theories on the pathophysiology of keratoconus point to a possible inflammatory component that may explain the increase in CT in eyes with keratoconus compared to that in a healthy population.[12,18] Numerous studies have found increased levels of proinflammatory cells, cytokines, and other inflammatory mediators in the tears of patients with keratoconus, whereas agents that suppress the inflammatory response are decreased.[18,19] Inflammatory mediators, such as MMP-9, TNF-α, IL-1 and IL-6, have been found to be increased in the tears of patients with keratoconus.[19] These inflammatory mediators are active on the ocular surface, and may be crucial factors in the pathogenesis of keratoconus.[18] In addition to local inflammatory activation, there are studies suggesting that systemic oxidative stress and inflammatory alterations may potentially have an impact on the corneal microenvironment in keratoconus.[19,20]

Detection of SKC and whether it will progress are of great importance in terms of preventing refractive, postsurgical iatrogenic ectasia that may occur if these patients cannot be detected, and vision loss with corneal crosslinking treatment to be administered to these patients. Therefore, corneal topographic parameters were evaluated to distinguish eyes with SKC from normal eyes. Although many studies have reported that many parameters obtained using corneal topography can be used to differentiate normal eyes from eyes with SKC and to follow the progression of SKC, it has been emphasized that no single parameter is sufficient.[21,22] No universally accepted standards exist for the follow-up of SKC because the results are highly variable. The inflammatory component implicated in the pathophysiology of keratoconus suggests that an increase in CT during disease progression may be a useful monitoring parameter in eyes with SKC. Therefore, we measured CT at five different points in the keratoconus, SKC, and control groups and performed intergroup comparisons.

The association between changes in the choroidal structures of patients with keratoconus and disease progression has been evaluated previously. It has been reported that CT is increased in keratoconus patients, and it has been suggested that CT may be a possible indicator of progression in keratoconus patients.[23] However, Pinheiro-Costa et al.[24] evaluated CT in patients with progressive and non-progressive keratoconus and concluded that the evaluation of the choroidal profile does not seem to be an efficient method to detect disease progression. In the present study, we also evaluated CT findings as possible markers of disease activity in patients with SKC. No difference was found between the patients with SKC and controls in terms of CT. These findings do not rule out higher CT as a risk factor for keratoconus development. However, a prospective controlled investigation of a pediatric population with keratoconus is needed to determine whether distinct choroidal patterns are associated with varying degrees of disease progression. This could be a significant finding in the follow-up of patients with keratoconus.

Oxidative stress-stimulated macroglia (such as astrocytes and Müller cells) increase the synthesis of glutamate, nitric oxide, and glial fibrillary acidic proteins, which indirectly contribute to retinal excitotoxicity.[25] A recent study showed an increase in inner nuclear layer thickness with advanced keratoconus stages and suggested that this was probably due to the activation of Müller cells in response to increased oxidative stress.[26] Uzunel et al.[27] evaluated peripapillary retinal nerve fibre layer, ganglion cell and macular thickness and they reported that all parameters decreased with increasing keratoconus stage compared to the control group. Different results have been reported in studies comparing patients with keratoconus with control groups in terms of CMT.[10,28] In the present study, no significant difference was found in terms of

CMT between the eyes with keratoconus and controls. Moreover, there was no significant difference in the mean CMT between eyes with keratoconus and those with SKC.

Our study is the first to evaluate CT values in patients with SKC. In addition, patients who had previously undergone corneal collagen cross-linking and corneal intraocular ring implantation, or in whom CT may have been affected, were not included. Nonetheless, this study had certain limitations. First, our study was cross-sectional in design, which precludes the determination of a causal link between changes in CT and the progression of keratoconus. Second, only horizontal OCT images were used to calculate the CT images, and not vertical OCT images. Finally, the small sample pool size and restricted ethnicity of the participants meant that the findings cannot be extrapolated to the entire population.

CONCLUSION

In conclusion, the choroidal layer was thicker in patients with keratoconus than in patients with SKC and healthy eyes. However, the mean CT values in the eyes with SKC were similar to those in the controls. Mean CMT values were not significantly different among the three groups. Although we have shown that CT is increased in patients with keratoconus, evaluation of choroidal and macular thickness does not appear to be a useful technique in differentiating eyes with SKC from healthy eyes or to follow the progression of the disease. Prospective studies with larger numbers of participants will provide a more accurate evaluation of patients with SKC and reveal the relationship between functional and structural parameters.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Atlas University Clinical Research Ethics Committee (No: E-22686390-050.99-34023, Date: 25/10/2023).

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