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Original Article

Could Corneal Densitometry be a Progression Criterion for Subclinical Keratoconus?

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Abstract

Objectives: The objective of this study is to investigate the changes in topometry, tomography, and corneal densitometry in subclinical keratoconus (SK) at the 6-month interval.

Methods: The clinical keratoconus and SK groups included 25 eyes; the control group included 22 eyes from 22 patients. Corneal topographic, tomographic, topometric, and densitometric values obtained using the Pentacam HR imaging system were analyzed.

Results: Posterior elevation (PE), Keratoconus index (KI), index of height asymmetry (IHA), index of height decentration (IHD), Dp, Da, Final D, maximum pachymetric progression index (PPImax), and maximum Ambrósio relational thickness parameters showed significant changes between the baseline and the 6th-month follow-up in SK group ($p<0.05$ for all values). There were significant changes in all zones except a central layer of 6–10 zone, anterior, and central layer of 10–12 zone between the baseline and the 6th-month follow-up in the SK group ($p<0.05$, for all values). The changes in mean±standard deviation of KI, IHA, IHD, PPImax parameters, and corneal densitometry values of the posterior layer of 0–2 mm and 2–6 mm zones were significant in the SK group compared to the controls ($p<0.05$, for all values).

Conclusion: PE, KI, IHA, IHD, and PPImax parameters as well as increasing corneal light backscatter of the posterior central layer might be useful for follow-up of progression of SK. New multimeric parameters created by combinations of topometric, tomographic, and corneal densitometry parameters could be the future of SK follow-up.

Keywords: Densitometry, pentacam, subclinical keratoconus, tomography, topometry

Introduction

Keratoconus is the most prevalent ectatic corneal condition, defined by alterations in the stromal collagen matrix that result in a thinner stromal layer and uneven corneal protrusion (1). Keratoconus is usually bilateral; however, some patients show significant asymmetric presentation when the fellow has no topographic evidence of keratoconus. It is believed that the fellow eye that seems to be normal is already in the pre-clinical stages of the disease, which is known as subclinical keratoconus (SK) (2).

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Currently, early diagnosis of SK remains one of the most significant factors in preventing iatrogenic corneal ectasia following refractive surgery (3). In addition, vision loss can be averted with corneal collagen crosslinking if progression in keratoconus is recognized in its earliest pre-clinical phases (4). However, there is no definitive method or set of criteria for distinguishing SK from the normal cornea. Variable progression criteria, cutoff values, and follow-up frequency are reported (5-8).

The Pentacam HR (Oculus, Wetzlar, Germany) is thought to be the most sensitive instrument for identifying possible keratoconus using a variety of parameters (9). The Scheimpflug tomography system can now evaluate corneal transparency objectively and non-invasively (9). With the help of Pentacam HR, multiple studies that evaluated corneal topographic, topometric, tomographic, and aberrometric properties to distinguish SK from normal corneas were conducted. Too many progression parameters and cutoff values were reported for this purpose. Moreover, two studies of ours assessed the corneal densitometry for discrimination of SK from the normal cornea (3,5). However, corneal densitometry changes over a known period have not been studied for the progression of SK previously.

To test this theory, changes in corneal topographic, topometric, tomographic, as well as corneal densitometry were assessed in one eye with clinical keratoconus (CK) and the other eye with SK, and a control group using the Global Consensus definition of keratoconus and ectatic disease (2).

Methods

This longitudinal case–control study was carried out at the Cornea Department of Ulucanlar Eye Training and Research Hospital in accordance with the principles of the Helsinki Declaration. Informed consent was obtained from the participants or their legal guardians. After getting permission from the local ethics committee, patients who had CK on one side but SK on the other were identified by reviewing their medical records. CK was diagnosed with the following parameters: Inferior or central steeping at anterior sagittal curvature maps or an asymmetric bow tie pattern with or without skewed axes; an anterior stromal scar, Vogt striae, conical protrusion, or Fleischer ring at the biomicroscopic examination (2). The diagnosis of SK was determined by the presence of an inferior-superior difference of the average K value of <1.4 D, a central mean keratometry (K) value of <47.2 diopters (D), a keratoconus percentage index (KISA%) of <60%, normal topographic findings, the lack of clinical signs of keratoconus, and manifest keratoconus in the fellow eye (3,4).

The study consisted of 3 groups: The CK group, the fellow eyes of CK patients (SK), and the control group. The individuals who made up the control group were all of the same age and had myopia of <5.0 diopters, myopic astigmatism of <3.0 diopters, normal results on topographic, topometric, and tomographic examinations, and no signs of ectasia after at least a year of monitoring. Solely, the right eye of each patient in the healthy control group was included in the study.

Patients with a history of ocular allergy/eye rubbing, ocular surface problems, ocular trauma, ocular surgery (even corneal crosslinking), topical eye drops, or significant corneal scarring that might potentially affect the outcomes were excluded. Following the removal of rigid gas-permeable and soft contact lenses, for 3 weeks and 1 week, respectively, all measurements were collected.

Corrected distance visual acuity (CDVA), refraction comprising spherical and cylindrical errors, assessments of intraocular pressure, and biomicroscopic evaluations of the anterior segment and fundus were all recorded for every case that met the inclusion criteria. Topographic, tomographic, topometric, and densitometric evaluations from the Pentacam HR database were also investigated. A single professional examiner took measurements using the Pentacam HR's 3D scanning mode of 50 images per second. Reviewing the image quality, only high-quality data were evaluated for each participant. Each participant's two consecutive measurements with a 6-month interval were analyzed retrospectively. Various parameters were derived from topographic, tomographic, topometric, and densitometry maps of Pentacam HR as described below:

Data from topographic maps: Q value (corneal asphericity) in the sagittal curvature map, K1 (flat K), Kmax (maximum K), and K2 (steep K) for the central 3.0 mm of the cornea, anterior and posterior elevation (AE, PE) at the thinnest corneal point (with best-fit sphere set to manual, float, sphere, diameter = 8 mm), and thinnest corneal thickness (TCT).

Data from BAD-III analysis: Deviation from the normality of the relational thickness (Da), deviation from the normality of the front elevation (Df), deviation from the normality of the pachymetric progression (Dp), deviation from the normality of the thinnest corneal point (Dt), deviation from the normality of the back elevation (Db), average and maximum pachymetric progression index (PPI) values, overall deviation from normality (final D), and Ambrósio relational thickness (ART).

Data from topometric maps: Index of height asymmetry (IHA), keratoconus index (KI), index of surface variance (ISV), central keratoconus index, index of height decentration (IHD), index of vertical asymmetry (IVA).

Finally, corneal densitometry values were recorded over a 12-mm diameter of the cornea using the Pentacam HR densitometry software. This examination provided densitometry readings of the cornea at three distinct depths: the anterior (120 µm thick; the section of the cornea that is closest to the surface of the eye), the central (between the anterior and posterior layers), and the posterior layers (60 µm thick; the innermost part of the cornea). This ocular region was then subdivided into four concentric zones for analysis. Zones 0–2, 2–6, 6–10, and 10–12 mm in diameter made up the first, second, third, and fourth annular areas, respectively. The densitometry data are given in gray scale units as the pixel brightness per unit volume in the Scheimpflug picture. According to the degree of light backscattering from the cornea, the readings varied from 0 (the maximum transparency) to 100 (a fully opaque cornea).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software version 22.0 for Windows was used to conduct the statistical analysis (SPSS Inc., Chicago, Illinois, USA). The Shapiro-Wilk test was used to determine whether the data were normal. The mean and standard deviation were used as descriptive statistics (SD). The categorical variables were analyzed using the Chi-square test. To see if the difference between two measures of the same eye was significant, paired t-tests were used. The one-way ANOVA test was used to compare the three groups with each other. When the overall ANOVA model was significant, the Bonferroni post hoc test was employed to compare pairwise significantly different means. The p-value for statistical significance was <0.05.

Results

The CK and SK groups included 25 eyes, whereas the control group included 22 eyes from 22 patients. Table 1 displays the demographic features of all participants. The groups were similar in regard to gender and age (p=0.311 and p=0.802, respectively). In all groups, CDVA did not differ substantially during the 6-month interval (p>0.05 for all values). However, CDVA was better in SK and control groups compared to the CK group (p=0.041 and 0.021, respectively).

Table 2 shows the changes in topographical and topometric indices, as well as enhanced ectasia display indicators, in all groups during the 6-month follow-up. In the CK group, K1, K2, TCT, AE, PE, KI, IHA, IHD, Df, Dt, Dp, Da, ARTmax, and PPImax exhibited statistically significant changes from beginning to 6-month follow-up (p>0.05, for each). In the SK group, TCT, PE, KI, IHA, IHD, Dp, Da, PPImax, ARTmax, and final D values changed considerably from baseline to 6th-month follow-up (p>0.05, for each). On the other hand, there were no meaningful alterations in the control group for any parameter (p>0.05, for each).

Table 3 provides a summary of the changes in corneal densitometry measurements during the 6-month follow-up for all groups. There were significant changes in all zones except the anterior, central layer of 0–2 zone during the 6-month interval in the CK group (p>0.05, for each). There were significant changes in all zones except the central layer of the 6–10 zone, and the anterior, central layer of the 10–12 zone measurements during the 6-month follow-up in the SK group (p>0.05, for each). However, no significant changes were seen in the control group (p>0.05, for each).

Table 4 summarizes the changes in mean values of topographic, topometric, and Belin–Ambrosio ectasia display indices across all groups. There were substantial differences in the changes of K1, K2, Kmax, AE, PE, KI, Da, IHA, IHD, and PPImax parameters between groups (p>0.05, for each). The Bonferroni corrections revealed that the changes of K1, K2, Kmax, AE, PE, Da, IHA, IHD, and PPImax parameters showed significant differences in the CK group compared to the SK and control groups (p>0.05, for each). The changes in K2, Kmax, PE, IHA, IHD, and PPImax parameters were also significant in the SK group compared to the controls (p>0.05, for each).

The changes in mean corneal densitometry values of all groups are summarized in Table 5. Changes in corneal densitometry were not significantly different between the CK and SK groups (p>0.05, for each). The changes in corneal den-

Table 1. Demographic variables of groups

	CK group (n=25)	SK group (n=25)	Control (n=22)	p
Age (years)	25.84±6.45	25.84±6.45	23.18±13.70	0.311*
Gender (F/M)	10/15	10/15	7/15	0.802¥
CDVA (logMAR) Baseline/ 6th-Month follow-up/p#	0.15/0.16/0.12	0.03/0.03/0.97	0.02/0.02/0.98	0.035*, 0.041[a], 0.021[b], 0.125[c]

CK: Clinical keratoconus; SK: Subclinical keratoconus; CDVA: Corrected distance visual acuity; *One-way ANOVA test, with Bonferroni correction. [a]: CK versus SK; [b]: CK versus control; [c]: SK versus control; ¥Pearson Chi-square test; #Paired samples t-test, Bold values indicate p<0.05.

Table 2. Topographic parameters, topometric indices, and enhanced ectasia display indices at baseline and 6th months follow-up in all groups

Parameters Mean±SD	CK Group (n=25)			SK group (n=25)			Control group (n=22)		
	Baseline	6th month follow up	p*	Baseline	6th month follow up	p*	Baseline	6th month follow up	p*
K_1, (D)	42.34±2.41	43.28±2.28	0.01	41.91±1.57	41.91±1.49	0.73	42.38±1.55	42.78±2.87	0.32
K_2, (D)	46.53±2.31	47.27±2.15	0.03	43.01±1.53	43.19±1.63	0.23	43.20±1.60	43.20±1.67	0.89
K_{max}, (D)	50.05±3.80	50.81±3.22	0.08	43.53±1.70	44.00±1.90	0.65	43.57±1.59	43.65±1.78	0.47
TCT, µm	492.36±32.64	481.88±48.69	0.04	535.04±23.92	529.84±25.16	0.02	543.68±32.45	544.50±30.00	0.79
AE, µ	11.68±7.11	14.84±6.88	0.01	2.72±1.02	3.76±2.90	0.06	2.77±1.50	2.50±1.43	0.24
PE, µ	36.40±13.63	42.60±16.57	0.04	7.44±3.34	10.84±8.07	0.02	6.63±5.53	6.18±2.90	0.62
ISV	54.84±23.58	57.60±24.79	0.25	16.64±3.70	19.52±7.80	0.05	15.77±3.66	15.86±3.75	0.81
IVA	0.52±0.33	0.55±0.34	0.21	0.11±0.04	0.14±0.10	0.11	0.10±0.04	0.10±0.05	0.44
KI	1.11±0.06	1.14±0.07	0.04	1.01±0.01	1.02±0.02	0.03	1.01±0.01	1.02±0.01	0.62
CKI	1.03±0.03	1.04±0.03	0.11	1.00±0.06	1.00±0.09	0.64	1.00±0.01	1.00±0.01	0.66
IHA	20.84±18.39	28.20±20.80	0.04	4.37±3.72	8.20±9.19	0.04	3.33±2.12	4.14±3.51	0.29
IHD	0.06±0.03	0.08±0.04	0.04	0.009±0.005	0.017±0.020	0.04	0.008±0.004	0.079±0.005	0.77
Df	4.40±3.45	5.94±3.84	0.02	0.21±0.68	0.45±1.15	0.28	0.37±0.86	0.68±0.15	0.32
Db	5.17±3.22	5.69±4.17	0.08	0.10±0.52	0.21±0.94	0.08	-0.23±0.71	-0.29±0.61	0.52
Dp	5.33±2.67	7.34±6.91	0.03	0.75±0.59	1.18±1.00	0.04	0.68±0.99	0.74±0.83	0.65
Dt	1.50±1.20	1.99±2.10	0.04	0.13±0.70	0.26±0.75	0.05	-0.10±0.95	-0.14±0.86	0.66
Da	2.20±0.55	2.63±0.08	0.04	0.75±0.41	1.02±0.63	0.02	0.40±0.73	0.60±0.75	0.17
Final D	5.84±2.13	6.04±2.97	0.43	1.16±0.31	1.53±0.97	0.04	0.94±0.77	0.95±0.65	0.90
Average PPI	1.69±3.91	1.99±1.02	0.06	1.02±0.98	1.07±0.14	0.07	1.00±0.14	1.01±0.12	0.68
Maximum PPI	2.45±0.70	2.90±1.49	0.04	1.33±1.14	1.45±0.26	0.03	1.25±0.20	1.34±0.27	0.21
Maximum ART	216.16±61.05	190.80±91.90	0.03	403.84±48.06	375.52±69.78	0.04	443.27±80.66	421.40±83.1	0.17

Kmax: Maximum keratometry, D: Diopters, SD: Standard deviation, AE: Anterior elevation, PE: Posterior elevation, TCT: Thinnest corneal thickness, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Center keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, ARTmax: Maximum Ambrósio relational thickness indice, PPImax: Maximum pachymetric progression index, Df: Deviation of normality of the front elevation, Db: Deviation of normality of the back elevation, Dp: Deviation of normality of pachymetric progression, Dt: Deviation of normality of corneal thinnest point, Da: Deviation of normality of relational thickness, D: Overall deviation of normality, µm: micrometer, SD: Standard deviation, *Paired samples t-test. Bold values indicate P<0.05.

sitometry values in the posterior layer of 0–2 mm zone, all layers of 2–6 mm, and 6–10 mm zones, and a posterior layer of 10–12 mm zone showed significant alterations between the CK and control groups (p>0.05, for each). Only changes in corneal densitometry values of the posterior layer of 0–2 mm and 2–6 mm zones showed significant alterations between the SK and control groups (p>0.05, for each).

Discussion

Corneal topography is an important tool for detecting keratoconus as well as the progression of the disease. Even though corneal topography can detect intermediate and advanced stages of keratoconus, diagnosing keratoconus in its early subclinical phases is more difficult. With tomographic and topometric methods, SK can be detected early. Despite their excellent sensitivity, tomographic devices are unable to detect all cases of keratoconus. The tomographic and biomechanical index, which was devised by Ambrósio et al., (9) is efficient when detecting SK in eyes that have normal topography. Despite many studies focused on the discrimination of SK, the progression of SK eyes over a known period has not been extensively evaluated. To help with the detection of progression in SK eyes, we evaluated topographic, topometric, tomographic, and corneal densitometry parameters in SK eyes at 6-month intervals.

Table 3. Corneal densitometry values at baseline and 6th months follow-up in all groups

Parameters Mean±SD	CK Group (n=25)			SK group (n=25)			Control group (n=22)		
	Baseline	6th month follow up	p*	Baseline	6th month follow up	p*	Baseline	6th month follow up	p*
0–2 mm zone									
Anterior	21.48±5.10	22.55±3.63	0.302	18.80±2.20	20.36±2.25	0.009	16.39±1.17	16.60±0.84	0.481
Central	12.91±2.63	13.85±1.66	0.096	12.08±1.43	12.89±1.32	0.015	10.98±0.90	11.03±0.53	0.852
Posterior	8.40±1.67	10.20±1.48	0.001	8.69±0.95	10.00±1.47	0.001	8.43±1.10	8.45±0.62	0.947
Total	14.26±2.93	15.52±2.11	0.057	13.18±1.46	14.43±1.60	0.003	11.94±0.98	12.00±0.57	0.800
2–6 mm zone									
Anterior	17.55±1.89	19.50±3.05	0.003	16.68±2.08	18.20±2.14	0.008	14.75±1.21	14.90±0.72	0.618
Central	10.89±0.99	12.14±1.28	0.000	10.82±1.37	11.53±1.20	0.024	9.93±0.92	9.92±0.54	0.970
Posterior	8.40±0.92	10.02±1.54	0.000	8.11±1.00	9.23±1.35	0.003	7.81±1.11	7.79±0.54	0.931
Total	12.28±1.16	13.90±1.82	0.000	11.87±1.42	12.98±1.50	0.005	10.84±1.04	10.91±0.47	0.793
6–10 mm zone									
Anterior	14.23±1.43	16.15±2.42	0.001	15.21±2.54	16.36±2.61	0.022	13.70±1.97	13.45±2.24	0.490
Central	9.63±0.86	10.82±1.49	0.000	10.09±1.16	10.8±1.54	0.061	9.51±1.37	9.51±1.46	0.999
Posterior	8.04±0.77	9.54±1.59	0.001	8.37±1.32	9.33±1.51	0.005	8.32±1.30	8.24±1.13	0.782
Total	10.64±0.95	12.18±1.80	0.000	11.22±1.78	12.12±1.82	0.016	10.51±1.47	10.56±1.55	0.880
10–12 mm zone									
Anterior	21.89±5.68	23.76±6.57	0.119	26.12±6.65	25.76±6.35	0.640	25.52±6.25	25.38±6.86	0.815
Central	13.41±2.33	14.86±3.15	0.002	14.71±2.75	15.28±2.65	0.184	14.41±2.42	15.00±2.95	0.263
Posterior	10.87±1.82	12.57±2.89	0.000	10.89±1.98	11.99±2.57	0.014	10.84±1.60	10.91±2.06	0.835
Total	15.40±2.86	17.06±3.70	0.008	17.25±3.45	17.68±3.24	0.376	17.00±2.93	17.10±3.69	0.817
Total									
Anterior	17.82±1.88	19.64±2.54	0.000	18.13±2.44	19.22±2.44	0.022	16.48±1.38	16.60±1.68	0.715
Central	11.22±0.96	12.41±1.43	0.000	11.45±1.53	12.11±1.35	0.037	10.76±0.89	10.82±1.00	0.826
Posterior	8.69±0.72	10.30±1.53	0.000	8.76±1.16	9.86±1.45	0.003	8.58±0.80	8.59±1.03	0.960
Total	12.58±1.07	14.13±1.75	0.000	12.71±1.67	13.73±1.62	0.015	11.94±0.97	12.00±1.06	0.843

*Paired t test Bold values indicate P<0.05.

To discriminate SK eyes from normal eyes, topographic, topometric, and tomographic parameters were evaluated before. Bae et al. (10) found significant differences in IVA, IHD, and final D values in SK patients compared to the control. Hashemi et al. (11) found that all topometric indices, except for IHA, increased in SK patients. Huseynli et al. (12) reported that KI, IHD, ISV, and IVA were significantly higher in SK patients compared to controls. Another recent study found that IHD and IVA were the most reliable topometric indices to diagnose keratoconus at an early stage (13). According to the findings of Vázquez et al., (14) both ART and PPI were found to have a high degree of sensitivity in the process of diagnosing SK. In the study of Koc et al., (4) final D and PPI were discovered to be especially sensitive in discriminating eyes with SK from normal eyes. Research conducted by Thulasidas and Teotia (15). suggests that the final D value and PPI could be helpful in diagnosing the first stages of SK. In addition, they emphasized that a single metric by itself is insufficient to recognize early changes; rather, a variety of data must be combined to differentiate SK. Even though there have been numerous studies on this issue published in the literature, the results are inconsistent, and there are no universally recognized diagnostic criteria for SK. These differences in the results of topometric and tomographic studies might be mainly due to the definition of SK and the inclusion criteria. In our study, TCT, PE, KI, IHA, IHD, Dp,

Table 4. Changes in mean±standard deviation values of topographic parameters, topometric indices, and enhanced ectasia display indices in all groups

Parameters Mean±SD	CK Group (n=25)	SK group (n=25)	Control group (n=22)	p*
K_1, (D)	0.93±1.74	0.02±0.40	0.04±0.63	0.003, 0.003[a], 0.005[b], 0.15[c]
K_2, (D)	0.74±1.63	0.17±0.72	0.01±0.32	0.008, 0.010[a], 0.005[b], 0.015[c]
K_{max}, (D)	0.76±2.14	0.41±1.07	0.07±0.46	0.015, 0.015[a], 0.006[b], 0.006[c]
TCT, µm	-10.48±24.77	-5.20±10.71	-0.81±14.74	0.104
AE, µ	3.16±5.99	1.04±2.65	-0.27±1.07	0.001, 0.041[a], 0.001[b], 0.160[c]
PE, µ	6.20±9.78	3.40±6.96	0.45±4.27	0.021, 0.038[a], 0.001[b], 0.004[c]
ISV	2.76±11.92	2.88±7.24	0.09±1.82	0.062
IVA	0.03±0.12	0.03±0.09	-0.005±0.03	0.069
KI	0.03±0.03	0.008±0.19	0.01±0.008	0.013, 0.011[a], 0.199[b], 0.901[c]
CKI	0.01±0.03	0.008±0.008	0.001±0.004	0.081
IHA	7.36±13.94	3.83±9.00	0.80±3.52	0.023, 0.032[a], 0.001[b], 0.012[c]
IHD	0.02±0.019	0.008±0.018	-0.001±0.002	0.016, 0.014[a], 0.013[b], 0.005[c]
Df	1.53±3.12	0.24±1.10	0.31±0.41	0.161
Db	0.52±1.46	0.31±0.86	0.05±0.41	0.157
Dp	2.01±5.19	0.42±0.97	0.06±0.62	0.077
Dt	0.49±1.21	0.12±0.31	0.03±0.41	0.058
Da	0.43±0.51	0.27±0.57	0.20±0.67	0.021, 0.041[a], 0.022[b], 0.180[c]
Final D	0.20±1.26	0.36±0.87	0.008±0.33	0.420
Average PPI	0.29±0.76	0.53±0.14	0.008±0.09	0.071
Maximum PPI	0.45±1.03	0.11±0.26	0.008±0.29	0.001, 0.012[a], 0.000[b], 0.001[c]
Maximum ART	-25.36±56.57	-28.32±65.99	-21.86±73.61	0.447

Kmax: Maximum keratometry, D: Diopters, SD: Standard deviation, AE: Anterior elevation, PE: Posterior elevation, TCT: Thinnest corneal thickness, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Center keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, ARTmax: Maximum Ambrósio relational thickness indice, PPImax: Maximum pachymetric progression index, Df: Deviation of normality of the front elevation, Db: Deviation of normality of the back elevation, Dp: Deviation of normality of pachymetric progression, Dt: Deviation of normality of corneal thinnest point, Da: deviation of normality of relational thickness, D: Overall deviation of normality, µm: micrometer, SD: Standard deviation, *One-way ANOVA, Bonferroni correction: [a]CK versus SK, [b]CK versus control, [c]SK versus control, Bold values indicate P<0.05.

Da, ARTmax, PPImax, and Final D parameters showed significant changes during 6-month intervals in the SK group. However, there were no differences in tomographic and topometric indices in the control group over the 6-month period. Moreover, the changes in mean±standard deviation values of PE, IHA, IHD, and PPImax parameters were also significant in the SK group compared to the controls. As these values were found to be significant in the diagnosis of SK in previous studies, the significant change in these values in SK eyes over 6 months may be considered in the follow-up of SK progression.

Corneal densitometry, which is an indirect evaluation of corneal transparency, could also be used for the discrimination of SK from normal eyes. It has been demonstrated that CK is responsible for an increase in densitometry in the 0–2 and 2–6 mm zones, most noticeably in the anterior layer (16,17). Ozkan et al. (5) discovered that the corneal densitometry values in all layers of the 0–2 mm and 2–6 mm annular areas were considerably greater in SK eyes when compared to the values found in the control group. Similar to this study, Koc et al. (3) also looked at SK with normal topometric values and discovered that the SK group showed corneal densitometry values that were significantly greater than those of the control group in all layers of the 0–2 mm zone, as well as in the anterior and central layers of the 2–6 mm zone. According to the findings of ROC analysis, densitometry of the anterior layer of the 0–2 mm zone had the greatest level of specificity and sensitivity in differentiating SK eyes from normal eyes in both studies (3,5). These findings could be attributed to more noticeable alterations

Table 5. Changes in mean±Standard deviation values of corneal densitometry values of all groups

Parameters Mean±SD	CK Group (n=25)	SK group (n=25)	Control group (n:22)	p*
0–2 mm zone				
Anterior	1.06±4.61	1.56±2.73	0.20±1.33	0.355
Central	0.93±2.44	0.81±1.55	0.04±1.15	0.222
Posterior	1.80±2.09	1.31±1.81	0.01±1.29	0.005, 0.999[a], 0.005[b], 0.049[c]
Total	1.26±2.86	1.24±1.89	0.06±1.18	0.105
2–6 mm zone				
Anterior	1.94±2.67	1.52±2.62	0.14±1.33	0.036, 0.899[a], 0.043[b], 0.149[c]
Central	1.25±1.18	0.70±1.46	-0.01±1.16	0.009, 0.479[a], 0.007[b], 0.196[c]
Posterior	1.62±1.72	1.12±1.66	-0.02±1.23	0.004, 0.840[a], 0.003[b], 0.048[c]
Total	1.61±1.74	1.11±1.81	0.07±1.22	0.010, 0.893[a], 0.009[b], 0.105[c]
6–10 mm zone				
Anterior	1.91±2.13	1.15±2.34	-0.25±1.64	0.004, 0.652[a], 0.004[b], 0.078[c]
Central	1.18±1.23	0.58±1.48	0.00±1.25	0.021, 0.403[a], 0.017[b], 0.437[c]
Posterior	1.50±1.71	0.96±1.57	-0.07±1.24	0.005, 0.709[a], 0.004[b], 0.074[c]
Total	1.54±1.69	0.90±1.73	0.04±1.42	0.016, 0.563[a], 0.013[b], 0.247[c]
10–12 mm zone				
Anterior	1.86±5.25	-0.36±3.80	-0.14±2.76	0.144
Central	1.44±1.81	0.57±2.08	0.59±2.36	0.301
Posterior	1.70±1.64	1.10±2.08	0.07±1.65	0.018, 0.812[a], 0.016[b], 0.188[c]
Total	1.66±2.58	0.42±2.37	0.10±1.95	0.077
Total				
Anterior	1.81±1.92	1.09±2.23	0.12±1.53	0.023, 0.647[a], 0.019[b], 0.286[c]
Central	1.19±1.08	0.66±1.49	0.06±1.27	0.024, 0.513[a], 0.020[b], 0.380[c]
Posterior	1.61±1.63	1.10±1.65	0.01±1.27	0.003, 0.775[a], 0.003[b], 0.051[c]
Total	1.55±1.51	1.01±1.93	0.05±1.30	0.014, 0.813[a], 0.013[b], 0.154[c]

*One-way ANOVA, Bonferroni correction: [a]CK versus SK, [b]CK versus control, [c]SK versus control, Bold values indicate P<0.05.

in the keratoconus-related stromal collagen composition in these certain layers of the cornea (18,19). In addition, studies utilizing Fourier optical coherence tomography and very high-frequency ultrasound have demonstrated that epithelium thinning can occur prior to topographic findings (20,21). As a result, alterations in the epithelial structure of the keratoconic cornea, in addition to the degradation of the corneal stromal collagen composition, may be linked to changes in the anterior layers of the keratoconic cornea.

In our study, there were significant changes in all zones except the central layer of the 6–10 zone, and the anterior, central layer of the 10–12 zone during the 6-month follow-up in the SK group. The control group demonstrated no significant alterations. The mean values of corneal densitometry alterations did not significantly differ between the CK and SK groups. Only changes in corneal densitometry values of the posterior layer of 0–2 mm and 2–6 mm zones showed a significant difference between SK and the control group. Mercatelli et al. (22) used a harmonic generation microscope to demonstrate that in the early stages of keratoconus, the formation of collagen lamella in the corneal stroma is disrupted. Therefore, differences in corneal densitometry values at 6-month intervals may be a result of disruption of corneal stromal collagen. Moreover, as the changes in the posterior layer of 0–2 mm and 2–6 mm zones are meaningful, it can be proposed that changes in the posterior corneal stroma may occur early period of keratoconus. Because keratoconus first affects the posterior corneal surface, topography methods have been ineffective in detecting the disease early (5). On the other hand, the examination of densitometry has the potential to forecast degradation in the corneal stromal collagen composition as well as early ectatic alterations

at the ultrastructural level. Further studies will be needed to address these results. Moreover, corneal densitometry, which indirectly shows changes in the corneal stromal collagen formation, could be used in diagnosis as well as follow-up of the progression of SK.

Our research had several limitations. Measurements could not have been conducted at the same time of day due to the retrospective nature of the study. Densitometry measurements may have been influenced by the diurnal variability of corneal hydration (23). Another significant limitation of our study was the limited sample size, which may have an impact on the validity of our findings. Our findings may also be limited in their applicability because the control group included primarily of those with myopia and myopic astigmatism. Moreover, as the main aim of the study was to test corneal densitometry changes as a potential progression criterion, this study particularly focused on densitometry values. However, a comparative analysis between stable and progressive keratoconus forms would be beneficial to demonstrate whether progression was properly detected by densitometry measurement or by "state-of-the-art" Pentacam measurement. In future prospective studies with extended follow-up, these topics might be studied in more depth.

Conclusion

PE, KI, IHA, IHD, and PPImax parameters might be useful for follow-up of the progression of SK. Moreover, increasing corneal light backscatter of the posterior central layer may also be a sensitive way to detect the progression of SK. We feel that these parameters are insufficient on their own. However, new multimeric parameters created by combinations of topometric, tomographic, and corneal densitometry parameters can be more sensitive for precise detection of progression. Given the relatively small sample size of our research, prospective studies with a larger number of patients are needed to further investigate the use of these indices in the assessment of progression, their validation, and cutoff values.

Disclosures

Ethics Committee Approval: This study was approved by Ankara Numune Training and Research Hospital Ethics Committee (Date: 19.10.2020, Number: E-16-1073).

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