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Original Article / *Özgün Araştırma*

Corneal Volume Measurements with Pentacam for Detection of Keratoconus and Subclinical Keratoconus

Keratokonus ve Subklinik Keratokonusun Tespit Edilmesi için Pentacamla Korneal Hacim Ölçümleri

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Summary

Purpose: To estimate the sensitivity and specificity of corneal volume (CV) measurements in discriminating keratoconus and subclinical keratoconus from normal corneas.

Material and Method: Clinical records and Pentacam measurements of ninety-four patients with keratoconus, 36 patients with subclinical keratoconus, and 166 refractive surgery candidates with normal corneas were evaluated retrospectively. CV within 3, 5, 7, and 10 mm circles around the central cornea was measured in one eye of each patient, using the Pentacam. CV measurements in keratoconus and subclinical keratoconus were compared with normal corneas. Receiver operating characteristic (ROC) curves were used to determine the test's overall predictive accuracy and to identify optimal CV cutoff points to maximize sensitivity and specificity in discriminating keratoconus and subclinical keratoconus from normal corneas.

Results: Mean CV within a 3.0 mm circle around the central cornea was statistically lower in keratoconus (3.4±0.2 mm^3, $p<0.001$) and subclinical keratoconus (3.6±0.2mm^3, $p<0.001$) versus normal corneas (3.8±0.3mm^3). ROC curve analysis showed high overall predictive accuracy of CV for keratoconus (area under the curve 0.92). Optimal cutoff points were 3.55 mm^3 for keratoconus and 3.65 mm^3 for subclinical keratoconus. These values provided sensitivity and specificity of 83% and 86%, respectively, for keratoconus, and 61% and 74% for subclinical keratoconus.

Discussion: CV within a 3.0 mm circle around the central cornea effectively discriminates keratoconus from normal corneas. However, its sensitivity and specificity are lower for subclinical keratoconus diagnosis. *(Turk J Ophthalmol 2013; 43: 77-82)*

Key Words: Corneal volume, keratoconus, pentacam, subclinical keratoconus

Özet

Amaç: Kornea hacmi (KH) ölçümlerinin keratokonus ve subklinik keratokonusu normal kornealardan ayırt etmedeki duyarlılık ve özgünlüğünün tespit edilmesi.

Gereç ve Yöntem: Doksan dört keratokonus hastası, 36 subklinik keratokonuslu hasta ve 166 refraktif cerrahi adayının klinik kayıtları ve Pentacam ölçümleri retrospektif olarak incelendi. Pentacam kullanarak her hastanın santral kornea etrafındaki 3, 5, 7 ve 10 mm lik dairelerdeki KH'sı ölçüldü. Keratokonus ve subklinik keratokonustaki KH ölçümleri normal kornealarla karşılaştırıldı. Testin tüm tahmini doğruluğunu test etmek ve keratokonus ve subklinik keratokonusu normal kornealardan ayırt etmekte duyarlılık ve özgünlüğü maksimuma çıkaran optimal kesim noktalarının tanımlamak için ROC (Receiver operating characteristic) eğrileri kullanıldı.

Sonuçlar: Santral kornea etrafındaki 3,0 mm'lik dairedeki KH; keratokonusta (3,4±0,2mm^3, $p<0,001$) ve subklinik keratokonusta (3,6±0,2mm^3, $p<0,001$) normal kornealara gore (3,8±0,3 mm^3) istatistiksel olarak düşüktü. ROC eğrisi analizi KH'nın keratokonus için yüksek toplam tahmini doğruluğunu gösterdi (eğri altında kalan alan 0,92). Optimal kesim noktaları keratokonus için 3,55 mm^3, subklinik keratokonus için ise 3,65 mm^3 idi. Bu değerler, keratokonus için 83% duyarlılık ve 86% özgünlük; subklinik keratokonus için 61% duyarlılık ve 74% özgünlük sağlıyordu.

Tartışma: Santral korneanın çevresindeki 3.00mm'lik dairedeki KH keratokonusu normal kornealardan etkin bir biçimde ayırmasına karşın subklinik keratokonus tanısındaki duyarlılık ve özgünlüğü düşüktür. *(Turk J Ophthalmol 2013; 43: 77-82)*

Anahtar Kelimeler: Kornea hacmi, pentacam, keratokonus, subklinik keratokonus

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Introduction

Keratoconus is a non-inflammatory ectatic dystrophy which is characterized by progressive thinning, steepening, and apical protrusion of the cornea.[1] These changes in corneal shape lead to irregular astigmatism and myopic shift, causing gradual deterioration of vision. Clinical diagnosis of moderate to advanced keratoconus does not pose a great difficulty. Presence of marked irregular astigmatism and the development of classical retinoscopic and biomicroscopic signs such as localized corneal thinning, Fleischer's corneal epithelial iron ring, Rizzuti's sign, and Vogt's striae are adequate to reach a diagnosis in these cases. On the other hand, the identification of subclinical forms of keratoconus, especially in patients with normal best spectacle-corrected visual acuity in presence of minimum or no clinical signs may not be easy and may become complicated.

The identification of very early forms of keratoconus or forme fruste keratoconus, described by Amsler in 1946,[2] is important for evaluating and following patients considered to have asymmetric or unilateral keratoconus[3,4] and for studying family members of patients with the disease.[5] In addition, the preoperative identification of forme fruste keratoconus is crucial in evaluation of candidates for refractive surgery.[6] Laser in situ keratomileusis (LASIK) and photorefractive keratectomy may result in poor outcomes and progressive ectasia in patients with keratoconus or other forms of ectasia.[7-9] Placido disk–based corneal topography has been used extensively to diagnose corneal ectasia, and this test has been accepted as the most sensitive method to detect ectatic corneal disorders such as keratoconus and pellucid marginal degeneration.[4,5,10,11] Topographic analysis can point to characteristic clues of these diseases before the development of clinical signs or symptoms.[11,12] Up to date, a lot of indices and differentiation methods, such as the Rabinowitz-McDonnell test,[13] the Klyce-Maeda-Smolek Expert System,[14] KISA% index,[15] and the corneal navigator[16] have been developed to assist ophthalmologist with keratoconus diagnosis. Although these indices were reported to have a high degree of sensitivity and specificity to detect keratoconus, they did not have this high degree of sensitivity and specificity in discrimination between normal and subclinical keratoconus cases.[14-16] In addition, false negatives could occur in cases of pellucid marginal degeneration because most of the systems were calibrated for keratoconus.[17]

Corneal tomography provides 3-dimensional reconstruction of the cornea, enabling evaluation of the anterior and posterior corneal surfaces and creation of a pachymetric map. Corneal tomography has been proposed to help identify forme fruste keratoconus at an earlier stage.[18-20] Corneal thickness spatial profile, corneal volume (CV) distribution, percentage increase in thickness, and percentage increase in volume were studied, and it was reported that these parameters could serve as indices to diagnose keratoconus and screen refractive candidates.[21] Although these measurements have high specificity and sensitivity in differentiation of keratoconic and normal corneas, subclinical keratoconus diagnosis still impose difficulties. We aimed to determine how CV measurements changed in different diameters of corneal tissue, starting from central 3 mm to 10 mm in keratoconic, subclinical keratoconic, and normal corneas. We also tried to find whether these volume measurements can differentiate among keratoconus, subclinical keratoconus and normal.

Material and Methods

One eye of 94 patients with keratoconus, 36 patients with subclinical keratoconus, and 166 candidates for refractive surgery with normal corneas were analyzed using the Pentacam rotating Scheimpflug camera. Pentacam software data (version 1.16r04) for each examination were used for retrospective evaluation. An eye was diagnosed as having keratoconus if there were a scissoring reflex on retinoscopy and central or paracentral steepening of the cornea on topography with at least one of the following clinical slitlamp findings: stromal thinning, anterior bulging or conicity, Vogt striae, Fleischer ring, Descemet's breaks, apical scars, and subepithelial fibrosis. Patients who had worn a contact lens within the past 6 months, eyes with ocular surgical anamnesis, and eyes with other pathology or corneal scarring were excluded from the study.

An eye was diagnosed as having subclinical keratoconus if it was the fellow eye of a patient with keratoconus and showed the following features: (1) normal-appearing cornea at slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy; (2) inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes, detected on axial Placido disk-based videokeratographs (Keratron-Scout Optikon 2000 corneal topography), which were displayed using an absolute scale (1.5 dioptric steps); and (3) no history of contact lens wear, ocular surgery, or trauma. The control group was enrolled from patients with refractive errors of less than 3.0 D sphere and 1.0 D cylinder without other ocular pathology.

The Pentacam system is based on a 180-degree rotating Scheimpflug camera that can take 12 to 50 single captures to reconstruct the anterior chamber. In this study, anterior segment reconstructions were produced with 25 single captures. After completing a scan, the Pentacam software constructs the 3-dimensional image of the anterior segment and calculates CV in selected diameter.

Statistical analyses were performed with SPSS for Windows (version 17.0, SPPS, Inc.). All data were reported as means ± standard deviation. One-way analysis of variance was used to compare variables within groups. One-way analysis of variance with the least significant difference procedure was used to compare mean CV values. For each parameter, the following were calculated: area under the receiver operating characteristic (ROC) curve; standard error of the ROC; cutoff values for parameters, sensitivity and specificity level of the cutoff values.[22] A value of $P<0.05$ was considered statistically significant. A receiver operating characteristic (ROC), or simply ROC curve, is a graphical plot which illustrates the performance of a binary classifier system as its discrimination threshold is varied groups.

It is created by plotting the fraction of true positives out of the positives (TPR = true positive rate) vs. the fraction of false positives out of the negatives (FPR = false positive rate), at various threshold settings. TPR is also known as sensitivity, and FPR is one minus the specificity or true negative rate. Tukey's HSD test was used as post-hoc test to analyze differences among the groups.

Results

One eye of 94 patients (64 men, 30 women) with keratoconus, 36 patients (27 men, 9 women) with subclinical keratoconus, and 166 candidates for refractive surgery (112 men/54 women) with normal corneas were analyzed. Mean ages were 29.2±9.5, 28.2±5.4, and 27.2±8.1 years, respectively, in patients with keratoconus, subclinical keratoconus, and normal corneas. There were no difference among the groups with regard to age (p=0.172).

Mean CV in central 3 mm was 3.4±0.2 mm^3 in keratoconus, 3.6±0.2 mm^3 in subclinical keratoconus, and 3.8±0.3 mm^3 in normal eyes. Descriptive data about CV measurements in central 3, 5, 7, and 10 mm in three groups were shown in Table 1. The distribution of CV in central 3 mm in the three groups is summarized in Figure 1.

Comparison of mean CV in central 3 mm among the 3 groups with an ANOVA analysis showed that difference among all three groups were statistically significant (p=0.001). Post-hoc tests showed that the differences were statistically significant when comparing normal eyes with keratoconus (p=0.001) and subclinical keratoconus (p=0.001). In addition, the difference between keratoconus and subclinical keratoconus was statistically significant (p=0.001).

Comparison of CV in central 5, 7, and 10 mm among the 3 groups were all statistically significant - p=0.001, p=0.001, P=0.001, respectively. Post-hoc test results showed that there were statistically significant differences between both normal and keratoconus groups and normal and subclinical keratoconus groups in central 5mm (p=0.001, p=0.001), 7mm (p=0.001, p=0.001), and 10mm (p=0.001, p=0.001). There were statistically significant differences in central 5 mm (p=0.010), but insignificant difference in 7mm (p=0.140), and in 10mm (p=0.855) between keratoconus and subclinical keratoconus.

Figure 2 reports the distribution of CV in 3 mm in the three groups, to illustrate the overlap between normal corneas, and eyes with subclinical keratoconus and keratoconus.

Figure 3 compares results of the ROC curve analysis for keratoconus and normal corneas in central 3, 5, 7, and 10 mm. The ROC graph showed that CV measurements for central 3 mm had the highest area under curve value. The area under curve was 0.92 (95% confidence interval [CI]: 0.89-0.95). Based on the ROC curves, the optimal cutoff point to identify eyes with keratoconus was estimated to be 3.55 mm^3. This cutoff point was associated with a sensitivity of 82% and a specificity of 86%. CV for central 3 mm discriminated keratoconus from normal corneas highly successfully.

Figure 4 shows results of the ROC curve analysis to discriminate subclinical keratoconus and normal corneas with regard to CV measurements in central 3, 5, 7, and 10 mm. CV measurements in different diameters showed similar ROC curves. However, CV measurements in central 3 mm had the highest area under curve ratio in ROC graph. The area under curve was 0.76 (95% confidence interval [CI]: 0.67– 0.84) at this diameter. Based on the ROC curves, the optimal cutoff point to identify eyes with subclinical keratoconus was estimated to be 3.65 mm^3. This cutoff point was associated with a sensitivity of 61% and a specificity of 73%.

Discussion

The Oculus Pentacam is an anterior segment tomographer utilizing a rotating Scheimpflug camera. It offers a non-invasive method for assessment of topographic corneal thickness, corneal curvature, corneal volume, anterior chamber angle, and anterior chamber depth[23-28]. This study showed that CV measured with the Pentacam rotating Scheimpflug camera is lower in eyes with keratoconus or subclinical keratoconus than in normal corneas, and that CV measurements at central 3 mm is useful for discriminating these two conditions.

The clinical diagnosis of moderate to advanced keratoconus is facile because of the characteristic topographic pattern and the classical clinical signs.[1] On the other hand, diagnosing early keratoconus in patients with normal best spectacle-corrected

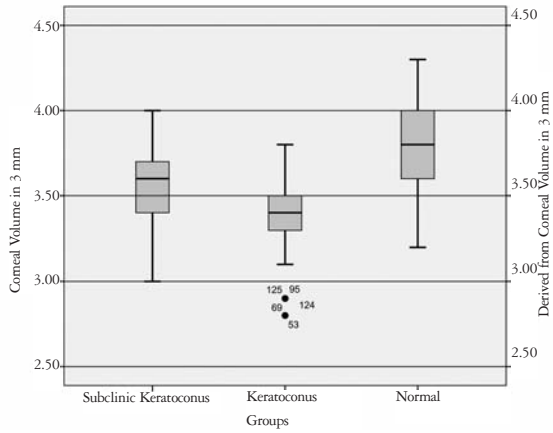

Figure 1. Distribution of corneal volume (mm^3) in central 3 mm in normal corneas, and in eyes with keratoconus and subclinical keratoconus

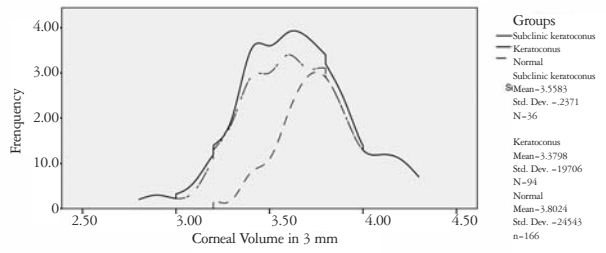

Figure 2. Distribution of corneal volume (mm^3) in central 3 mm in normal corneas, and in eyes with keratoconus and subclinical keratoconus

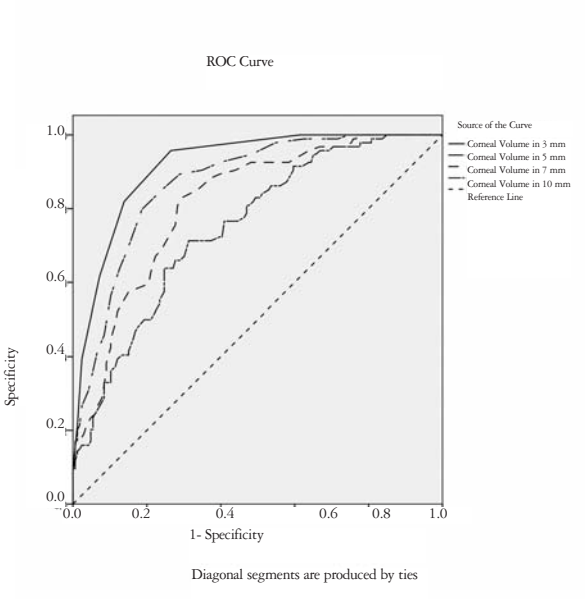

Figure 3. Receiver operator characteristic curves (ROC) for keratoconus versus normal corneas

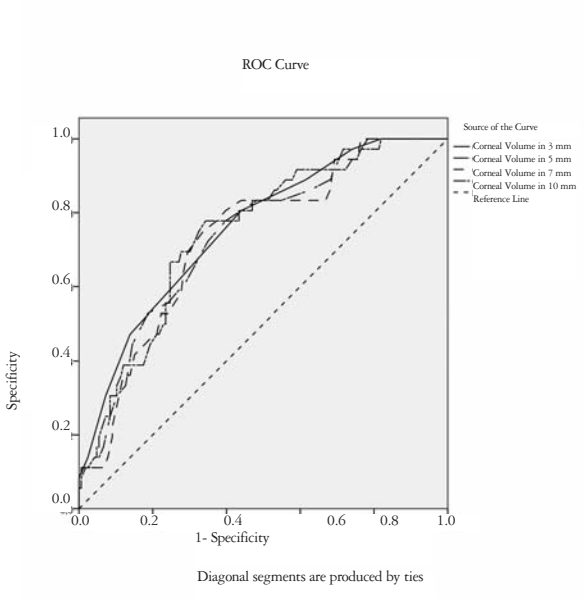

Figure 4. Receiver operator characteristic curves (ROC) for subclinical keratoconus versus normal corneas

Table 1. Corneal volume measurements in central 3 mm, 5mm, 7 mm and in 10 mm in patients with keratoconus, subclinical keratoconus, and normal corneas.(mm^3)

		n*	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Corneal Volume in 3 mm	Subclinic Keratoconus	36.00	3.56	0.24	0.04	3.48	3.64	3.00	4.00
	Keratoconus	94.00	3.38	0.20	0.02	3.34	3.42	2.80	3.80
	Normal	166.00	3.80	0.25	0.02	3.76	3.84	3.20	4.30
	Total	296.00	3.64	0.30	0.02	3.60	3.67	2.80	4.30
Corneal Volume in 5mm	Subclinic Keratoconus	36.00	10.51	0.64	0.11	10.29	10.73	8.80	11.70
	Keratoconus	94.00	10.14	0.58	0.06	10.02	10.25	8.30	11.50
	Normal	166.00	11.13	0.69	0.05	11.02	11.23	9.50	12.60
	Total	296.00	10.74	0.79	0.05	10.65	10.83	8.30	12.60
Corneal Volume in 7mm	Subclinic Keratoconus	36.00	22.73	1.30	0.22	22.29	23.16	19.30	25.10
	Keratoconus	94.00	22.21	1.29	0.13	21.95	22.48	17.80	25.20
	Normal	166.00	23.92	1.43	0.11	23.70	24.14	20.50	27.00
	Total	296.00	23.23	1.58	0.09	23.05	23.42	17.80	27.00
Corneal Volume in 10mm	Subclinic Keratoconus	36.00	55.72	3.11	0.52	54.67	56.77	48.00	62.60
	Keratoconus	94.00	55.34	3.80	0.39	54.57	56.12	42.30	62.90
	Normal	166.00	58.93	3.59	0.28	58.38	59.48	51.10	66.60
	Total	296.00	57.40	3.99	0.23	56.95	57.86	42.30	66.60

*number of patients

visual acuity and minimum or no clinical signs can be difficult.[20] This identification is especially important in preoperative screening for laser refractive surgery, because undetected corneal ectatic disorders can result in accelerated, progressive keratoectasia and unpredictable outcomes after LASIK and photorefractive keratectomy.[29,30]

Currently, Placido disk–based corneal topography is regarded as the most sensitive measurement for detecting ectatic corneal disorders such as keratoconus and pellucid marginal degeneration.[4,31] Topographic analysis reveals characteristic features of these diseases before biomicroscopic signs or symptoms. Normal, suspicious, and abnormal topography patterns of these diseases have been classified. Quantitative topographic indices, such as the Rabinowitz–McDonnell index,[13] keratoconus prediction index,[14] Z3 index,[32] central keratometry, inferior-superior (I-S), astigmatism, and skew percentage (KISA%) index,[15] have been developed to help diagnose keratoconus, and these indices are highly sensitive for keratoconus detection. However, topographic screening methods have shortcomings. First, satisfactory topography maps may not be available owing to corneal irregularity or tear film breakup. Second, topography may not detect all patients at risk for keratectasia. Randleman et al.[30] reported a meta-analysis in which 27% of 93 postrefractive surgery ectasia cases had normal preoperative topography, and 22% had an equivocal pattern (asymmetric bowtie). The asymmetric bowtie pattern is overrepresented in fellow eyes and relative eyes of keratoconus, but also occurs in normal eyes.[33] Third, it is difficult for these topography-based methods to distinguish keratoconus from contact lens–induced warpage,[34] subepithelial deposits or scarring, uneven tear film, lid artifact, or other causes of corneal distortion.[35] These causes of topographic distortion may cause a false-positive diagnosis of keratoconus or mask a true diagnosis of keratoconus.

Corneal thinning is a key pathologic feature of keratoconus; therefore, a keratoconus diagnosis based on corneal thickness measurement may offer additional information not available on topography. Corneal thickness has been proposed to be a useful parameter for the clinical identification of keratoconus.[36,37] Studies using ultrasound[38,39] or slit-scanning technologies40 have found that the difference (or ratio) between the peripheral and the thinnest (or central) corneal thickness was significantly greater in eyes with keratoconus than in normal eyes. Corneal thickness measurements have some disadvantages. These measurements are taken from several points and they do not represent corneal three-dimensional structure. Instead, CV measurements are more appropriate to evaluate changes and variations in three-dimensional corneal structure.

Murata et al.[40] analyzed the anterior segment of refractive surgery candidates and studied the variability pattern in this population regarding CV, using the Pentacam. They reported that myopic patients had less mean CV compared to hyperopic patients. They found that mean CV values of the myopia group were: 3.87±0.23 mm^3 at 3 mm, 11.31±0.67 mm^3 at 5 mm, and 24.30±1.43 mm^3 at 7 mm. In the hyperopia group, mean CV were: 4.01±0.20mm^3 at 3 mm, 11.73±0.58 mm^3 at 5 mm, and 25.09±1.21 mm^3 at 7 mm. In our study, we measured mean CV as 3.8±0.2 mm^3 at 3 mm, 11.13±0.69 mm^3 at 5 mm, and 23.92±1.43 mm^3 at 7 mm in normal eyes. There was a close similarity between our CV measurements and Murata et al's reported values. This parallelism supports the reliability of our measurements.

Ambrosió et al.[21] reported that CV measurements in eyes with mild to moderate keratoconus were significantly lower than those in a group of normal eyes. In addition, Emre et al.[35] reported that there was a progressive decrease in CV with the progression of the disease. The mean CV in the severe keratoconus group was smaller than that in the mild keratoconus and control group. These two studies indicate a positive prospect for CV measurements in subclinical keratoconus diagnosis.

In our study the ROC graph showed that CV measurements for central 3 mm had the highest area under curve value. The area under curve was 0.92 (95% confidence interval [CI]: 0.89-0.95). Area under curve values for other diameters were lower. Thus, CV measurements in central 3 mm diameter were better to discriminate keratoconus and normal corneas. Based on the ROC curves, the optimal cutoff point to identify eyes with keratoconus was estimated to be 3.55 mm^3. This cutoff point was associated with a sensitivity of 82% and a specificity of 86%. It was seen that CV for central 3 mm highly discriminated keratoconus from normal corneas. Although CV measurements yielded satisfactory sensitivity and specificity ratios to discriminate keratoconus from normal, results were less satisfactory for subclinical keratoconus diagnosis. The area under curve was 0.76 (95% confidence interval [CI]: 0.67– 0.84) at this diameter in discrimination of subclinical keratoconus from normal corneas. Based on the ROC curves, the optimal cutoff point to identify eyes with keratoconus was estimated to be 3.65 mm^3. This cutoff point was associated with a sensitivity of 61% and a specificity of 74%. These results show that using CV measurements in central 3 mm to diagnose subclinical keratoconus has a low sensitivity.

Ambrósio et al.[21] evaluated whether the corneal thickness spatial profile and CV distribution differentiate keratoconic corneas from normal corneas. They reported that indices generated from corneal thickness measurements over the entire cornea and calculations of volume can identify mild to moderate keratoconus, but their study did not include subclinical keratoconus cases. Sanctis et al.[42] studied sensitivity and specificity of posterior elevation in discriminating keratoconus and subclinical keratoconus from normal corneas. They reported that the posterior elevation was less effective in discriminating subclinical keratoconus than it was in discriminating keratoconus. The cutoff point of 29 microns had 68% sensitivity and 90.8% specificity. Their reported sensitivity level is close to our sensitivity level. It appears that both posterior elevation and CV measurements are not enough alone to make subclinical keratoconus diagnosis effectively.

As a conclusion, it may be stated that CV measurements can help keratoconus diagnosis but several other parameters such as location of the thinnest point and distance of the central (geometric) point to the thinnest point, could also be extracted from corneal tomography examination to reach more sensitive methods to discriminate subclinical keratoconus.

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