Received: 8 July 2022 | Accepted: 20 October 2022

DOI: 10.1111/opo.13066

ORIGINAL ARTICLE

OPO THE COLLEGE OF OPTOMETRISTS

Revisiting the oil droplet sign in keratoconus: Utility for early keratoconus diagnosis and screening

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Abstract

Purpose: An annular dark shadow (ADS) reflex has been observed while performing direct ophthalmoscopy on subjects with keratoconus. This study describes a method that may serve as a diagnostic technique for early keratoconus and may be used as a quantitative measure of severity.

Methods: Healthy keratoconic subjects and keratoconus suspects underwent corneal tomography and a full ocular examination. Keratoconus severity was graded based on Belin ABCD criteria. An iPhone camera was connected to a direct ophthalmoscope to take a picture of the eye. The height of the ASD was measured using the AutoCAD software. Differences between subject groups were evaluated by chi-squared and Mann–Whitney tests. Spearman correlation compared ocular parameters and the height of the ADS. A multiple stepwise linear regression was used to predict the height of the ADS based on clinical parameters.

Results: Fifty-eight subjects participated in this study: 37 healthy controls (37 eyes) and 21 keratoconics or keratoconus suspects (37 eyes). The ADS was present in all keratoconic and keratoconus-suspect eyes but in none of the controls. The height of the ADS was significantly correlated with keratoconus severity. Front corneal surface root mean square of higher order aberrations, sphere and anterior radius of curvature from the front apex curve are significant predictors of the height of the ADS.

Conclusions and relevance: The ADS may be a useful method to diagnose keratoconus and keratoconus-suspect cases and serve as a grading and follow-up method for tracking disease severity.

KEYWORDS
keratoconus, ophthalmoscopy, optics

INTRODUCTION

Keratoconus (KC) is a progressive disease that affects both eyes asymmetrically depending on the severity.[1–6] The aetiology is unknown but seems to be multifactorial, including genetic and environmental factors.[7–11]

The prevalence rate of KC in the United States has been reported as 1 in 2000.[12] In India, the prevalence rate was found to be 2300 per 100,000.[13] Recent epidemiological studies found a high prevalence of KC in the Middle East (>2%).[9,14–18] As a result, KC places a huge burden on both healthcare systems and individuals since it is the most common indication for corneal transplants in many parts of the world.[19,20] The disease often affects young people between 10 and 30 years of age, a time when good vision is crucial for normal development. Indeed, studies show that the visual-related quality of life for people with KC is poor and correlated with the vision in the worse eye.[21]

Corneal collagen cross-linking has been shown to stop the progression of the disease,[1,22] although it does not

improve vision in all cases. Thus, it is crucial to detect KC when patients are young and have a mild form before vision deteriorates.[23,24]

Keratoconus can be diagnosed via clinical signs and with advanced technology. It is characterised by stromal thinning that can be observed in the inferior-temporal cornea[6,25] and a cone shape which protrudes outwards.[6] In the early stages of the disease, an experienced clinician is often able to detect a scissoring reflex using retinoscopy.[26,27] As the disease progresses, the cornea becomes less touch-sensitive, and more clinical signs may become manifest, such as Rizzuti's sign (a nasal limbal light reflex), Fleischer's ring (iron deposits around the cone base) and Vogt's striae (vertical stress lines in the deep stroma).[6,25] These last two signs were found to be a marker of the disease at least at its intermediate stage.[28,29] In more advanced stages, Munson's sign (a V shape observed at the lower eyelid when the patient looks downwards) is seen, and in very severe cases, hydrops may occur.[30,31]

While these clinical signs enable the clinician to detect intermediate and advanced KC easily, the detection of early KC and forme fruste remains a challenge.[32] There is a global consensus among corneal disease experts that corneal tomography is the most sensitive method for early diagnosis of KC.[10] However, in many countries, tomographic instruments are not available due to affordability.

An annular dark shadow (ADS) reflex has been observed while performing direct ophthalmoscopy on patients with KC,[33–35] and is referred to as the oil drop sign.[33,36] The purpose of this study was to present results from a method that can quantify the ADS without pupil dilation in patients with KC and KC suspects, and to determine whether the ADS may serve as a diagnostic method for early KC and to quantify its severity.

Key points

- An annular dark shadow (ADS) has been observed while performing ophthalmoscopy on patients with keratoconus.
- This study presents a method that may be used to quantify the ADS in patients with keratoconus and keratoconus suspects.
- Visualising the ADS may be a good method to diagnose keratoconus and subclinical keratoconus cases, while assessing its height may serve as a grading and follow-up tool for disease severity.

METHODS

Subjects

This prospective study was approved by the Hadassah Academic College Ethics Committee and followed the tenets of the Declaration of Helsinki (protocol code 354). Healthy keratoconic and KC suspects between the ages of 18 and 60 years were eligible to participate. Subjects were recruited from the clinics and student body of Hadassah Academic College. All examinations took place at the Hadassah Academic College eye clinic. The methods were verbally explained to the participants, and they signed a statement of informed consent prior to their participation.

Subjects were classified into two groups: KC and control. The KC group included both keratoconics and KC suspects. The diagnosis of KC was based on abnormal topography or tomography and at least one clinical sign.[6,10]

The early stages of KC are commonly referred to as subclinical or forme fruste KC and KC suspect, although there is a lack of unified criteria in the use of these terms.[37] In this study, subclinical KC was defined using the most common criteria according to a systematic review, that is suspicious topography, normal slit-lamp findings, visual acuity (VA) ~logMAR 0.0 (6/6) achievable with spectacle correction and manifest KC in the fellow eye.[38] Keratoconus-suspect eyes were defined as corneas with tomographic signs of KC but without evidence of clinical keratoconus in either eye.[32,39] However, due to the lack of unified criteria in the literature,[37] we combined these two groups to one subset, named keratoconus suspect.

Healthy control subjects had no limitations on spherical refractive errors but had corneal astigmatism <2.50 D. Since KC is an asymmetrical disease,[6] both eyes were included in the KC group,[40] while for healthy controls, only one eye (randomly assigned) was included in the analysis.

Exclusion criteria

Subjects who were diagnosed with any ocular pathology other than KC or underwent any eye surgery (except for cross-linking) were excluded. Other exclusion criteria included previous implantation of intracorneal ring segments or opacities such as cataracts or corneal opacities/scars. Additionally, KC subjects with hydrops that may affect the clarity of the ADS borders were not included. People with untreated systemic disease (e.g., diabetes or high blood pressure), epilepsy, pregnant women or subjects taking medication on a regular basis that could influence vision were also excluded.

Subjects who wore soft contact lenses were asked to remove them 60 min before the examination. Subjects who wore hard contact lenses were asked to remove their lenses the night before the examination. However, some patients with KC cannot function without contact lenses. In such cases, contact lens wear was not stopped, and the diagnosis of KC was based on previous medical records including their refraction results; VA was measured while wearing contact lenses and only after that determination were they asked to remove their lenses.

DESCRIPTION OF IMAGING PROCEDURE

An iPhone camera (iPhone XS MAX with 1242 × 2688 pixels, apple.com) was connected to a Welch Allyn direct ophthalmoscope (welchallyn.com). A specially designed apparatus was used to ensure that the images were taken at a fixed distance and angle from each eye (Figure 1). The subject was seated, and the height of the apparatus was adjusted so that the right triangle was positioned with its apex at the centre of the subject's eye. This results in the ophthalmoscope being positioned 50 cm horizontally and 18.2 cm above the patient's eye. The triangle was then rotated temporally, and the observer moved the ophthalmoscope to a new position 18.2 cm temporal to the subject's eye. The clinician observed the ophthalmoscope image via the iPhone and focussed on the cornea to capture the image. Each image was downloaded as a JPEG file and saved using an anonymous identification code.

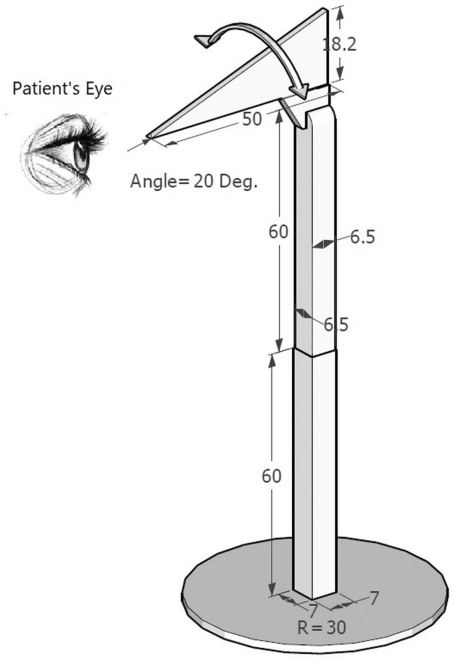

FIGURE 1 Measuring distance device. A special device was built to take the photographs at a fixed location from the subject (50 cm distance, 18.2 cm height, 20° rotation along the *x*-axis plane).

PROCEDURES

Subjects underwent an ocular examination including a health history questionnaire and monocular VA (Snellen chart) with habitual spectacles or contact lenses. Refractive error was assessed by subjective refraction and/or validated autorefraction (L80 Luneau, visionix.com).[41] Slit-lamp biomicroscopy and retinoscopy were used to evaluate clinical signs of KC. Corneal topography and tomography were performed three consecutive times in each eye (with the average value being calculated) using the Sirius system (Costruzioni Strumenti Oftalmici, csoitalia.it, Serial No. 12091654). An ophthalmologist specialising in cornea reviewed the results and classified each eye as KC or KC suspect.

Keratoconus severity was assessed using the Sirius output, based on the ABCD grading, that is Anterior radius of curvature (ARC), Back surface radius of curvature (PRC), Corneal pachymetry at thinnest and Distance best-corrected vision.[42] For the A and B categories, the average anterior and posterior radius of curvature from the front/back apical areas (e.g., ARC front apex curve and PRC back apex curve), respectively, was used. For the C category, the thinnest corneal thickness (TCT) was used, while VA was used for the D category.

Another examiner, masked to the results of the clinical examination and classification (KC, KC suspect or control), was responsible for imaging the ADS. Images were taken three times using the apparatus described above. This examiner analysed each image on the iPhone and classified them as either having the ADS (see below) or not (Figure 2).

Images that include the ADS were analysed using the AutoCAD software (autodesk.com). The horizontal visible iris diameter, taken from the Sirius tomographer, was used to scale the image. The corneal diameter of the image was scaled to the actual corneal diameter of each subject's eye, so the measurements reflect the actual size of the black

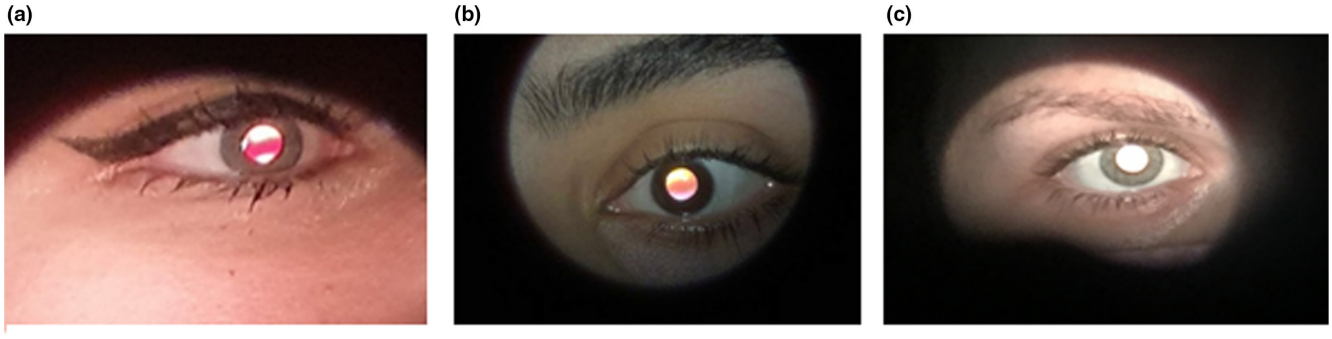

FIGURE 2 Images of the corneal plane. (a). The image of the annular dark shadow in a keratoconic eye. (b) The image of the annular dark shadow in a keratoconus suspect eye. (c) An image of a normal healthy eye

shadow in millimetres. Since the ADS often appears at an angle, we chose to measure its vertical height at the thickest point (Figure 3a, upper border at point 'C' to its lowest border at point 'D'). Measurements were recorded in millimetres (Figure 3b). The thickest point was determined by observation. When the thickest point was not clear, the height was measured at several different locations until the thickest point was determined. Each image was measured three times at the same point, and the average was used in subsequent analyses.

Statistical analysis

Normality was checked for each parameter of each group separately by means of the Anderson–Darling test. A chi-squared test was used to test differences between the sexes. The Mann–Whitney test was performed to assess clinical differences between the KC group and healthy controls. Spearman correlation was performed to test the association between ocular parameters and the height of the ADS. Statistics were calculated using SPSS Version 25 (ibm.com). A multiple stepwise linear regression was calculated to predict the height of the ADS based on the clinical parameters. $p \leq 0.05$ was considered statistically significant.

RESULTS

Fifty-eight subjects participated in this study: 37 were healthy controls (17 females, 37 eyes) and 21 had KC or were KC suspect (10 females, 37 eyes). The KC group included 10 subjects with bilateral KC (20 eyes), three subjects with KC in one eye and KC suspect in the fellow eye (six eyes), three subjects with bilateral KC suspect (six eyes), one subject with unilateral KC (one eye, the other eye had a corneal scar and was excluded) and four subjects with unilateral KC suspect (four eyes).

Table 1 summarises demographic data, visual acuity and refractive data for the KC and control groups. No significant differences between the groups were found for age ($p = 0.13$), sex ($p = 0.90$) and spherical refraction ($p = 0.35$).

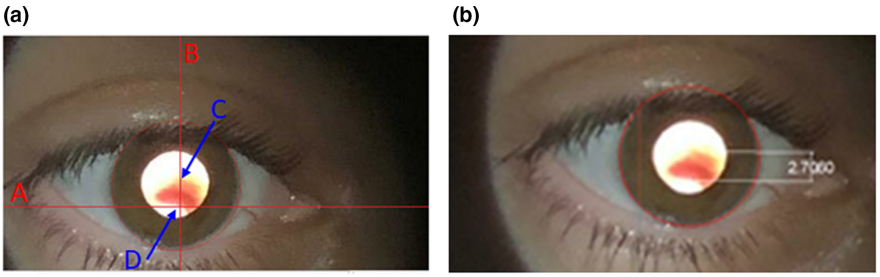

FIGURE 3 Measuring the height of the annular dark shadow using the AutoCAD software. (a) Red lines (A and B) are tools offered by the AutoCad software to identify the borders. In this image, they are at the lower border at point D. The upper border of the of the annular dark shadow is at point 'C'. (b) The height of the annular dark shadow is defined as the distance from point D to point C.

TABLE 1 Demographic data, mean visual acuity and refractive error for the keratoconus and control groups

	Healthy control group	Keratoconus group	Keratoconus suspects only	$p_{\text{Mann–Whitney}}$ keratoconus versus controls	$p_{\text{Mann–Whitney}}$ keratoconus suspect versus controls
N eyes	37	37	13	–	–
Mean age (years)	26.1 ± 7.9	28.1 ± 8.9	30.9 ± 11.8	0.13	0.14
Range	20–53	20–56	21–56		
Sex (male:female)	20:17	11:10	4:6	0.90[a]	–
Mean VA (decimal equivalent)	1.07 ± 0.11	0.88 ± 1.87	0.95 ± 0.10	<0.001	0.003
Range	0.80–1.21	0.20–1.00	0.70–1.00		
Mean sphere (D)	−1.05 ± 2.27	−1.55 ± 3.46	−1.40 ± 2.57	0.35	0.41
Range	−6.31 to +2.95	−14.5 to +3.50	−6.25 to +2.25		
Mean cylinder (D)	−0.51 ± 0.48	−3.22 ± 2.92	−1.16 ± 0.71	<0.001	0.001
Range	−2.03 to 0.00	−12.38 to-0.25	−2.50 to −0.25		
Mean SE (D)	−1.30 ± 2.23	−3.12 ± 4.0	−1.99 ± 2.66	0.012	0.34
Range	−6.47 to +2.54	−17.44 to +1.88	−6.82 to +1.50		

Abbreviations: D, dioptre; R, Spearman correlation results; SE, spherical equivalent; VA, visual acuity.

[a]Chi-squared test was performed to test the differences in sexes.

The keratoconus group had poorer VA ($p < 0.001$), higher cylindrical correction ($p < 0.001$) and higher spherical equivalent refractive error ($p = 0.01$). Furthermore, when comparing only the KC suspects vs. controls, we found that KC suspects had poorer VA ($p = 0.003$), higher cylindrical correction ($p = 0.001$) but similar spherical correction ($p = 0.41$) and spherical equivalent refractive error ($p = 0.34$).

The ADS was present in all KC and KC suspect eyes (mean height 2.24 ± 0.70 mm, range 0.87–3.39 mm, see Table S1 for raw data) but in none of the control eyes. There was a significant difference in height between KC and KC suspects (1.89 ± 0.60 mm vs. 2.88 ± 0.33 mm, $U = 284.5$, $p < 0.001$).

Using the Belin[42] classification of KC severity based on the ABCD parameters as described previously, a patient may be staged for each of the four parameters on an ordinal scale from one to five. A significant positive correlation was found between the height of the ADS and KC severity for parameters A ($r = 0.74$, $p < 0.001$), B ($r = 0.72$, $p < 0.001$), C ($r = 0.58$, $p < 0.001$) and D ($r = 0.34$, $p = 0.04$).

When examining the correlation between the height of the ADS and the four Belin ABCD parameters as continuous variables (see Table S1 for raw data), a significant positive correlation was found between the height of the ADS and VA ($r = 0.34$, $p = 0.04$, see also Figure 4), front apex curve ($r = 0.74$, $p < 0.001$, see also Figure 4), back apex curve ($r = 0.72$, $p < 0.001$, see also Figure 4) and TCT ($r = 0.58$, $p < 0.001$, see also Figure 4). Furthermore, other tomography parameters based on corneal curvature showed a positive correlation with the height of the ADS (cylinder [$r = 0.59$, $p < 0.001$], anterior keratometry [$r = 0.35$, $p = 0.03$]; and $r = 0.42$, $p = 0.01$ for anterior flat keratometry [K_1] and anterior steep keratometry [K_2], respectively) and posterior keratometry ($r = 0.35$, $p = 0.04$; and $r = 0.54$, $p = 0.001$ for posterior K_1 and K_2, respectively). This was also true for parameters based on corneal thickness (CCT [$r = 0.38$, $p = 0.02$] and front apex thickness [$r = 0.60$, $p < 0.001$]). By contrast, tomography parameters based on elevation[39] showed a negative correlation with the ADS symmetry index[39] of front corneal curvature (Sif, $r = -0.71$, $p < 0.001$), symmetry index of back corneal curvature (Sib, $r = -0.66$, $p < 0.001$), Baiocchi Calossi Versaci[39] front index (BCVf, $r = -0.79$, $p < 0.001$), Baiocchi Calossi Versaci back index (BCVb, $r = -0.70$, $p < 0.001$) and front and back corneal surface root mean square of higher-order aberrations[39] (RMSf, $r = -0.80$, $p < 0.001$; RMSb, $r = -0.74$, $p < 0.001$).

We reviewed subjects who had one eye with manifest KC and the other eye with subclinical KC (three subjects). In these cases, the ADS height was shorter in the KC eye than in the subclinical eye. For the 10 cases with bilateral KC, the height was shorter in the more severely affected eye for parameters A, B, C and in most cases for the D categories of the ABCD classification.[42] In three cases, there was poorer VA in one eye, while the ADS was shorter in the other eye.

Anterior corneal curvature, thickness, elevation and the posterior corneal curvature were derived from the Sirius device (Table 2). Mann–Whitney analysis showed that KC groups had steeper keratometry values ($p < 0.001$), thinner central corneal thickness (CCT, $p < 0.001$), thinner TCT ($p < 0.001$), steeper front and back apex curves ($p < 0.001$), larger symmetry index front (Sif) and back (Sib, $p < 0.001$), larger Baiocchi Calossi Versaci front (BCVf) and back indices (BCVb, $p < 0.001$) and larger front (RMSf) and back root mean square of higher-order aberrations (RMSb, $p < 0.001$, see Table 2).

Furthermore, when comparing only the KC suspects versus controls, similar results were found (see Table 2). Mann–Whitney analysis showed that KC suspects had steeper keratometry values ($p \leq 0.05$), thinner central corneal thickness (CCT, $p = 0.004$), thinner TCT ($p = 0.003$), steeper front and back apex curves ($p < 0.001$ and $p = 0.001$, respectively), larger symmetry index front (Sif) and back (Sib, $p < 0.001$ and $p = 0.001$ respectively), larger Baiocchi Calossi Versaci front (BCVf) and back indices (BCVb, $p < 0.001$ and $p = 0.001$ respectively) and larger front (RMSf) and back root mean square of higher-order aberrations (RMSb, $p < 0.001$, see Table 2).

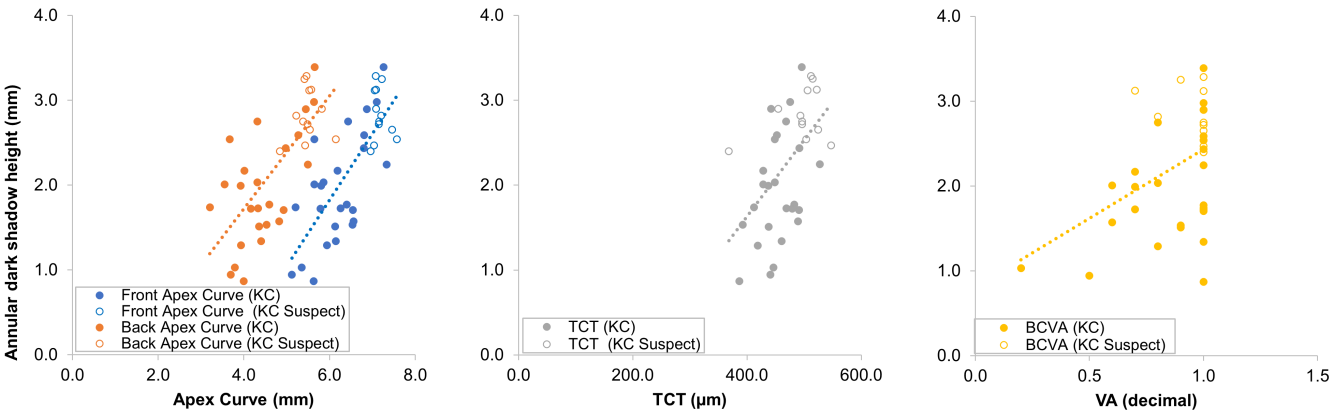

FIGURE 4 Correlation between the height of the annular dark shadow, corneal parameters and vision. Average of anterior and posterior radius of curvature of the apex areas (left figure), thinnest cornea thickness (middle figure) and best-corrected visual acuity (BCVA, right figure), relative to the annular dark shadow heights. Filled circles represent data of KC subjects; empty circles represent data of KC suspect subjects; dotted line represents the linear tradeline for all subjects (KC and KC suspect). KC, keratoconus; TCT, thinnest corneal thickness; VA, visual acuity

TABLE 2 Corneal parameters for keratoconus and control groups

	Control group	Keratoconus group	Keratoconus suspect only	$p_{\text{Mann-Whitney}}$ keratoconus versus controls	$p_{\text{Mann-Whitney}}$ keratoconus suspect versus controls
Anterior K_1 (mm)	7.93 ± 0.33	7.54 ± 0.44	7.73 ± 0.25	<0.001	0.04
Range	7.24 to 8.59	6.54 to 8.39	7.47 to 8.20		
Anterior K_2 (mm)	7.80 ± 0.30	7.18 ± 0.49	7.46 ± 0.29	<0.001	0.002
Range	7.21 to 8.37	6.03 to 7.88	7.11 to 7.88		
Average Anterior K (mm)	7.87 ± 0.31	7.36 ± 0.45	7.60 ± 0.25	<0.001	0.01
Range	7.22 to 8.48	6.38 to 8.09	7.31 to 8.03		
Posterior K_1 (mm)	6.78 ± 0.31	6.30 ± 0.69	6.59 ± 0.32	0.001	0.05
Range	6.11 to 7.47	4.70 to 7.52	5.99 to 7.14		
Posterior K_2 (mm)	6.38 ± 0.32	5.69 ± 0.65	6.10 ± 0.34	<0.001	0.008
Range	5.39 to 7.00	4.22 to 6.72	5.41 to 6.72		
Average Posterior K (mm)	6.58 ± 0.29	6.00 ± 0.66	6.34 ± 0.32	<0.001	0.03
Range	5.96 to 7.24	4.46 to 7.03	5.79 to 6.93		
TCT (μm)	529.40 ± 27.67	467.27 ± 42.04	494.96 ± 43.70	<0.001	0.003
Range	467.27 to 593.19	368.21 to 546.91	368.21 to 546.91		
CCT (μm)	533.18 ± 27.57	481.27 ± 40.43	5.09 ± 43.21	<0.001	0.004
Range	471.67 to 598.75	374.92 to 550.22	374.92 to 550.22		
ARC Front Apex Curve (mm)	7.55 ± 0.40	6.52 ± 0.69	7.18 ± 0.17	<0.001	<0.001
Range	6.24 to 8.14	5.12 to 7.57	6.96 to 7.57		
PRC Back Apex Curve (mm)	5.91 ± 0.62	4.78 ± 0.77	5.50 ± 0.30	<0.001	0.001
Range	3.23 to 6.68	3.21 to 6.15	4.80 to 6.15		
Front Apex Thickness (μm)	575.09 ± 54.87	489.30 ± 46.27	515.15 ± 53.38	<0.001	<0.002
Range	498.80 to 735.02	374.49 to 587.20	374.49 to 587.20		
Sif	0.04 ± 0.35	4.65 ± 3.80	1.47 ± 1.12	<0.001	<0.001
Range	−0.96 to 0.58	0.07 to 14.06	0.07 to 3.23		
Sib	0.02 ± 0.08	1.24 ± 0.91	0.42 ± 0.40	<0.001	0.001
Range	−0.13 to 0.20	−0.10 to 3.14	−0.10 to 0.98		
BCVf	0.14 ± 0.14	2.36 ± 1.82	0.82 ± 0.50	<0.001	<0.001
Range	0.00 to 0.47	0.13 to 6.09	0.13 to 1.86		
BCVb	0.12 ± 0.23	2.44 ± 1.89	0.85 ± 0.78	<0.001	0.001
Range	0.00 to 1.27	0.00 to 6.90	0.00 to 2.16		
RMSf	2.49 ± 1.06	11.50 ± 6.94	5.16 ± 2.58	<0.001	<0.001
Range	1.38 to 5.68	2.25 to 25.14	2.25 to 10.21		
RMSb	7.24 ± 3.61	23.17 ± 13.24	11.66 ± 4.69	<0.001	<0.001
Range	3.77 to 24.21	6.11 to 56.47	6.11 to 21.19		

Abbreviations: ARC, anterior radius of curvature; BCVb, Baiocchi Calossi Versaci back index; BCVf, Baiocchi Calossi Versaci front index; CCT, central corneal thickness; K_1, flat keratometry reading; K_2, steep keratometry reading; KC, keratoconus; KCS, keratoconus suspect; PRC, posterior radius of curvature; R, Spearman correlation results; RMSb, root mean square back of higher-order aberrations; RMSf, root mean square front of higher-order aberrations; SIb, symmetry index back; SIf, symmetry index front; TCT, thinnest corneal thickness; μm, micrometre.

$p<0.005$.

A stepwise multiple regression was conducted to evaluate whether different clinical parameters (VA, spherical equivalent, sphere, anterior K_1, anterior K_2, posterior K_1, posterior K_2, thinnest corneal thickness, central corneal thickness, ARC front apex curve, PRC back apex curve, front apex thickness, symmetry index front (Sif), symmetry index back (Sib), Baiocchi Calossi Versaci front index (BCVf), Baiocchi Calossi Versaci back index (BCVb), root mean square front of higher-order aberrations (RMSf), root mean square back of higher-order aberrations (RMSb)) were able to predict the height of the ADS. It was observed that RMSf, sphere and ARC appeared as significant predictors (F [3, 33] = 9.07, $p < 0.005$, $R^2 = 0.80$, adjusted $R^2 = 0.78$). The analysis showed that RMSf ($\beta = -0.41$, t [36] = −2.45, $p = 0.02$),

sphere ($\beta = -0.40$, t [36] $= -4.70$, $p < 0.001$) and ARC front apex curve ($\beta = 0.53$, t [36] $= -3.01$, $p = 0.005$) did predict the height of the ADS significantly.

DISCUSSION

This study shows the potential usefulness of a method for the diagnosis of KC and KC suspects using a direct ophthalmoscope combined with a digital camera to capture the ADS or 'oil drop' image. The ADS was present in all KC and KC suspect eyes but in none of the controls. The ADS can be used as a quantitative measure of KC severity since a significant correlation was found between the height of the ADS and the severity of the disease. Thus, as the disease progresses, the ADS becomes thinner.

Early detection of KC, especially before vision deteriorates, is important since treatment with collagen cross-linking may stop the progression of the disease.[22] While it is relatively straightforward to diagnose KC, it is challenging to diagnose early KC and KC suspects. Intermediate and advanced cases can be diagnosed based on classic clinical signs, using slit-lamp examination and retinoscopy.[28,29,43] However, these signs may not be present in the early stage of KC nor in KC suspects.[22] Corneal tomography is the most sensitive method for early diagnosis and monitoring the progression of KC.[10] A recent systematic review found subclinical KC and KC suspects were most often diagnosed based on corneal topography signs and slit-lamp examination.[37] However, these instruments are not always affordable and thus may not be available in all clinical settings, especially in developing countries. Consequently, patients may not be diagnosed before vision deteriorates, which may increase the impact of keratoconus, and represents a significant health concern for both patients and healthcare systems.[44]

Recent epidemiological studies found a high prevalence of KC, especially in the Middle East.[8,9] As a result, KC places a huge burden on healthcare systems and on individuals since it is the most common indication for corneal transplants in many parts of the world.[19,20] The disease affects young people between 10 and 30 years of age, at which time good vision is crucial for normal development. Indeed, studies show that the visual-related quality of life for people with KC is poor and correlates with the vision in the worse eye.[21]

The present study found that the ADS can help in the diagnosis of KC. The system presented in this study can be used as an affordable, accessible and portable tool for detecting keratoconus even in its early stages. This method is appropriate for community use and can allow extensive screening in areas without good access to eye care. Thus, it may be used via telemedicine in areas where a clinician (optometrist or ophthalmologist) is not present, but a technician can be trained to use the instrument with the image being transmitted to a specialist for classification. In addition, the observed correlation between the severity of the disease and the height of the ADS suggests that it may be of value in the follow-up of KC subjects and suspects and to document the development of the disease. Further research is required to test this association further.

The ADS quantified in the current study is likely the same phenomena reported in earlier studies. For example, in 1859, the British surgeon William Bowman described a technique to detect the conical cornea using an ophthalmoscope.[34] Foster and Yamamoto[35] mentioned a dark shadow reflex seen with the ophthalmoscope as one of several clinical signs to detect KC. Pathmanathan et al.[33] also described an ophthalmoscopic sign of early KC. They mentioned that if the eye is viewed at a distance of about 1 m through a direct ophthalmoscope, then a dark central disc or an annular shadow could be seen disturbing the normal red reflex. They claimed that this sign can be as sensitive as corneal topography in the detection of corneal asymmetry.[33] Nartey[36] added that this appearance is known as the 'oil drop sign', because of the disruption of the red reflex by a circular, dark or reddish-brown central shadow which looks like an oil drop. The CLEK Study Group also mentioned that the presence or absence of an irregular corneal surface may be identified by an irregularity in the red reflex observed with the direct ophthalmoscope.[30,45]

The ADS seen by the ophthalmoscope has been used as an inclusion criterion for detecting KC in several previous studies.[30,33–36,45] However, none tested the technique as a screening method for detecting KC, relative to KC severity or in comparison with corneal tomography.[10,37] In addition, the current study is the only investigation to find a correlation between the height of the ADS and the severity of KC. These results illustrate that the ADS may enable long-term follow-up, even in areas where there is poor access to health care. We noted three cases of bilateral KC, where VA was worse in one eye, yet the ADS was thinner. This unexpected finding may be due to cone location that is inferior to the visual axis and the pupil margins seen in the tomography maps.

The method presented in this study may be a superior screening tool for early KC than retinoscopy. Keratoconus often produces irregular astigmatism, resulting in a scissoring retinal reflex using the retinoscope.[3,6] A recent study comparing retinoscopy and tomography found a sensitivity of 98% and specificity of 78%.[27] However, since the scissoring reflex cannot be quantified, it cannot be correlated with the severity of KC. By contrast, the ADS measured here was present in all KC suspects and all subjects with early KC. Furthermore, the thickness of the ADS can be determined and correlated with disease severity, making it a better option than retinoscopy.

The source of the ADS measured in this study is not clear, nor is the reason why its height changes as the disease progresses. There are various possible factors that may explain this phenomenon. Light enters the eye through the pupil, hits the retina and is reflected back through the pupil producing a red reflex seen with the ophthalmoscope. Any disturbance of the light in the optical path will appear

as a dark shadow.[46] In patients with KC, the disturbance could come from the anterior cornea or the stroma. The present study showed that anterior corneal parameters were the only ones that predicted the height of the ADS in the multiple regression model. Thus, this suggests that the source of the ADS may be due to changes in the anterior cornea. Alternatively, the distortion may be created by uneven distribution of collagen in the stroma and separation of collagen bundles in the Bowman layer.[47] These changes may affect the retro-illumination creating an ADS. Another possible explanation for the occurrence of the dark shadow is based on the wave theory of light, considering that the junction of the two areas with different local curvatures (cone and surrounding area) may act as a scattering source with the capability of cancelling part of the backscattered light in specific portions of the pupillary area, thereby creating the appearance of more transparent areas.[48] Alternatively, light scattering may be the source of the ADS. The refraction of scattered light by the different ocular elements distributed over a wide angle may be significantly different in the area of the cone than the rest of the cornea, thus creating an area within which no light is scattered. This would generate the appearance of a dark band.[48] However, the phenomena described in densitometry appear different from the ADS and therefore may not explain it. Future studies should be performed to confirm which explanation is the most appropriate for this phenomenon, or alternatively if several of them can be combined simultaneously.

There are several limitations to this study. The detection of the ADS with the ophthalmoscope is based on operator-dependent skill and may be missed. However, the examiner in this study was an expert in this technique. Further investigations should compare interoperator results using the method described here and include operators with less experience. The current study is limited in that it did not assess intersession repeatability. Future research could follow the same patients longitudinally to assess changes in the height of the ADS and how they correlate with KC severity. Another limitation is the number of participants who were KC suspects. Since the height of the ADS is largest at onset and gradually decreases as KC progresses, there may be a threshold for the ADS to form. This threshold may be detected in a longitudinal study that follows subjects at risk of developing KC, such as first-degree relative of KC subjects.[11]

Most patients with KC have high astigmatism, which may also be the source of the ADS. To exclude this possibility that the ADS was a result of high astigmatism, we tested several subjects with high astigmatism and looked for the ADS. In four subjects (five eyes, three females) with high astigmatism (mean refractive astigmatism −2.90 ± 0.95D, range −4.00 to −2.00D; mean corneal astigmatism 2.91 ± 0.45D, range 2.34 to 3.39D), the ADS was not present. These participants with high astigmatism were studied as a proof of concept, and their findings suggest that the ADS is not a result of the high astigmatism found in patients with KC. Further studies should focus on a quantitative analysis of a large number of eyes with high astigmatism, but without KC.

The results of the present study show that the ADS may be a good method to diagnose KC and subclinical KC cases and serve as a grading method for its severity. In addition, it can serve as a follow-up tool to track the severity of the condition. Further studies examining the use of this method in a large population could add valuable information regarding the prevalence of KC in areas with limited access to public health.

AUTHOR CONTRIBUTIONS

Arige Gideon Abou Said: Conceptualization (lead); data curation (equal); formal analysis (supporting); investigation (lead); methodology (equal); project administration (equal); supervision (lead); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **David Pablo PiÑero:** Formal analysis (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Einat Shneor:** Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); project administration (equal); resources (lead); supervision (supporting); visualization (equal); writing – original draft (lead); writing – review and editing (lead).

ACKNOWLEDGEMENTS

We would like to thank Prof. Joseph Peri Frucht for helping in the recruitment and clinical evaluation of keratoconus subjects and to Mr. Yair Raiz for statistical support. We would like to thank Sireen Said-Ahmed, Zahra Nashashibi, Haneen Sumaira, Oroob Barakeh, Elisheva Michaels, Jehad Abu-Taa and Ibrahim Naffar for collecting and organising the data. We would like to thank Mr. Gideon Zahi for support with the AutoCAD software.

CONFLICT OF INTEREST

E.S. and A.G.A.S. from Hadassah Academic College have filed a provisional patent on 'Products, Systems, and Methods for Diagnosing Keratoconus with an Ophthalmic Device' (Application number 63/180246 and Confirmation number 4151). All authors certify that they have no other affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gideon Abou Said A, Piñero DP, Shneor E. Revisiting the oil droplet sign in keratoconus: Utility for early keratoconus diagnosis and screening. *Ophthalmic Physiol Opt*. 2022;00:1–10. https://doi.org/10.1111/opo.13066