A novel tool for quantitative measurement of distortion in keratoconus

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BACKGROUND: Keratoconus is associated with thinning and anterior protrusion of the cornea resulting in the symptoms of blurry and distorted vision. The commonly used clinical vision tests such as visual acuity and contrast sensitivity may not reflect the symptoms experienced in keratoconus and there are no quantitative tools to measure visual distortion. In this study, we used a quantitative test based on vernier alignment and field matching techniques to quantify visual distortion in keratoconus and assess its relation to corneal structural changes.

METHODS: A total of 50 participants (25 keratoconus and 25 visually normal) completed the experiment where they aligned supra-threshold white target circles in opposite field in reference to guidelines and circles to complete a square structure monocularly. The task was repeated five times and the global distortion index (GDI) and global uncertainty index (GUI) were calculated as the mean and standard deviation respectively of local perceived misalignment of target circles over five trials.

RESULTS: Both GDI and GUI were higher in participants with keratoconus compared to controls ($p < 0.01$). Both parameters correlated with the best corrected visual acuity, maximum corneal curvature ($K_{max}$), topographical keratoconus classification (TKC) and central corneal thickness (CCT).

CONCLUSION: Our findings show that the quantitative measure of distortion could be a useful tool for behavioural assessment of progressive keratoconus.

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INTRODUCTION

Keratoconus is a progressive corneal condition characterised by anterior protrusion and thinning of the cornea. The aetiology of the condition is multifactorial with recent studies suggesting a role of inflammatory mechanisms [1, 2]. The estimated prevalence of keratoconus is reported to be 1 in 84 [3] to 1 in 375 [4] in young adults. The condition has a genetic heterogeneity and involves both autosomal dominant and autosomal recessive patterns [5]. The corneal structural changes lead to irregular astigmatism and myopia with the symptoms of blurry vision, increased sensitivity to glare, and distorted vision due to higher order aberrations [6–8]. The symptoms begin in adolescence or early adulthood and usually slowly progresses until mid-adulthood [8].

The commonly assessed structural measurements in keratoconus include corneal curvature, corneal topography, and corneal thickness using keratometer, corneal topographer, and ocular coherence tomogram (OCT) respectively. Visual acuity is the most commonly measured visual function outcome in the clinical setup. However, visual acuity is not a good predictor of symptoms experienced in keratoconus and vision related quality of life is reduced even in early stages of the disorder while good visual acuity may be maintained [9–12]. Contrast sensitivity meanwhile correlates both with higher order aberration [7, 13] and topographic indices [14]. However, clinically available contrast sensitivity charts may not be appropriate for the evaluation of moderate to advanced keratoconus [15]. Hence there is a lack of a perceptual visual measure that reflects symptoms experienced in keratoconus. Different parameters indicate keratoconus progression, and therefore need for intervention with methods such as collagen cross-linking. These include an increase in maximum corneal curvature by 1 D over a year [16], increase in astigmatism by 1–3 DC over 6 months, and reduction in central corneal thickness by 5% over 6 months [17]. Previous studies have demonstrated variable correlation of best-corrected visual acuity with these parameters, with contrast sensitivity again showing a better correlation [18, 19]. However, monitoring clinical progression requires specialist imaging equipment, and therefore regular visits to an eye care professional are required. Recently a new scoring system that includes clinical measures and the patient characteristics such as patient reported quality of vision, the Dutch Crosslinking for Keratoconus Score, is reported to be better at predicting when medical intervention may be needed [20]. A reliable perceptual measurement that better reflects patient’s visual status may further aid development of such scoring system. Such a measure could also potentially be used as a home-based test.

While visual distortion is one of the most common symptoms in keratoconus, there are currently limited methods to quantify such distortion and none as far as we are aware specifically designed...
for keratoconus. There have been approaches to quantify distortion using hyperacuity tasks in different ocular conditions [21–24]. Hyperacuity refers to the visual system’s ability to perform spatial tasks beyond the eye’s classical resolution limit with thresholds as low as 3 to 6 s of arc [25, 26]. Vernier alignment (vernier acuity), a classic hyperacuity task where participants discriminate difference in the relative spatial localisation of two or more visual stimuli such as lines or dots has been used in previous studies [27–29]. The use of such methods for conditions such as amblyopia [30] and age-related macular degeneration (AMD) [31] have demonstrated perceptual distortions exhibit a similar dissociation from visual acuity as clinical keratoconus indices. Thus, evaluating perceptual distortions may provide a more nuanced characterisation of visual function for ocular diseases.

In this study, we used a quantitative paradigm based on both vernier alignment and field matching techniques to quantify visual distortion experienced in keratoconus and assess its relation to corneal structural changes. Providing a means to reliably and systematically characterise the visual deficit in keratoconus enables future studies exploring the impact of established treatments upon these deficits.

METHODS

Participants
A total of 25 participants (mean age = 29.84 ± 7.46 years, 15 females) with keratoconus at different disease stages and 25 normal controls (mean age = 22.12 ± 2.62 years, 17 females) were recruited for the study. All participants underwent measurements of the best-corrected monocular visual acuity (BCVA) with Bailey-Lovie log MAR chart after refraction with autorefractor (Topcon KR-8000PA) by an optometrist. The corneal assessment to ascertain keratoconus signs was carried out using Haag-Streit slit-lamp biomicroscope. The corneal mapping was conducted using a corneal topographer (Oculus Keratograph D-35582) and the central corneal thickness (CCT) was measured using anterior segment ocular coherence tomogram (Topcon 3D OCT-2000). A specialist established the keratoconus diagnosis based on the maximum corneal curvature ($K_{max}$) of ≥ 50.00D with topographic keratoconus classification (TKC) grading of >1.0 and the presence of classical keratoconus sign in either eye. The signs considered were Munson’s sign, Rizzuti’s sign, Vogt striae, and Fleischer ring, in addition to scissors reflex on retinoscopy. The clinical details of the keratoconus and control group are presented in Table 1.

Stimuli and procedure
The experimental stimulus was created and presented using MATLAB [32] software with Psychtoolbox extensions (Psychtoolbox 3.0) [33, 34] and presented on a computer screen with the resolution of 1920 × 1080 pixels. The task combined vernier alignment and field matching techniques. The stimuli consisted of eight circles (suprathreshold acuity and contrast) each subtending 0.37° at the viewing distance of 90 cm. The task for the observer was to align target circles with computer mouse click in relation to a reference line and circles presented against a 75% contrast grey background monocularly. At the start of the experiment a white central fixation (0.14°) throughout the task. Following this, two dots changed colour to orange (reference dots) and the task for the participant was to place the target circles at the mid-point and in alignment with these reference dots (Fig. 1e–g). The process continued until a square shape was completed by placing a total of seven target circles (Fig. 1h). Participants fixated on a central target (0.14°) throughout the task. There was no time limit for the completion of the task. If the participant reported having made an error with the dot placement (e.g., mis-click), the researcher removed the dot to allow another attempt.

Written informed consent was obtained from all participants once the nature of the experiment was explained. The experiment was completed monocularly with the patient’s best correction in place in a dark room, with the computer monitor being the only light source. The distance from the monitor was controlled using head and chin rest. The task was repeated five times and the global distortion index (GDI) and global uncertainty index (GUI) were calculated as the mean and standard deviation respectively of local perceived misalignment of target circles over five trials [30]. The distortion data for both keratoconus and normal controls did not follow a normal distribution (Shapiro-Wilk test, $p < 0.001$) hence nonparametric statistics were used for all analyses. The study followed the tenets of Helsinki declaration on human research participants and the research protocol was approved by the Campus Research Ethics Committee of the Faculty of Health, St. Augustine campus, the University of the West Indies.

RESULTS
The visual distortion measured as the global distortion index (GDI) was higher in keratoconus eyes ($n = 50, median (M) = 0.43°$) compared to the control eyes ($n = 50, M = 0.29°$), Mann-Whitney $U = 756, z = −3.41, p = 0.001$. Similarly, the global uncertainty index (GUI) was also higher in keratoconus eyes ($n = 50, M = 0.39°$) compared to the control eyes ($n = 50, M = 0.25°$), Mann-Whitney $U = 763, z = −3.36, p = 0.001$ (Fig. 2).

The relation between clinical parameters and distortion indices (GDI and GUI) were investigated using Spearman’s rank order correlation. These are shown for GDI in Fig. 3 and GUI in Fig. 4 for BCVA (Figs. 3a, 4a), maximum corneal curvature (Figs. 3b, 4b), central corneal thickness (Figs. 3c, 4c) and topographic keratoconus classification (TKC) scores (Figs. 3d, 4d). Among the clinical parameters, BCVA strongly correlated with maximum corneal curvature (Spearman’s rho ($\rho = 0.73, p < 0.001$) and moderately correlated with TKC scores ($\rho = 0.49, p < 0.001$) but not with central corneal thickness ($\rho = −0.27, p = 0.068$). Thus, poorer BCVA was associated with greater maximum corneal curvature and TKC scores. For the distortion indices, GDI was weakly correlated with BCVA ($\rho = 0.39, p = 0.005$), Fig. 3a), moderately correlated with maximum corneal curvature ($\rho = 0.55, p < 0.001$, Fig. 3b) and weakly correlated with TKC scores ($\rho = 0.32, p = 0.02$, Fig. 3d). A moderate negative correlation was also observed between GDI and central corneal thickness ($\rho = −0.43, p = 0.002$, Fig. 3c). Thus, higher GDI was associated with poorer BCVA, greater maximum corneal curvature and TKC scores, and lower central corneal thickness.

The global uncertainty index (GUI) also exhibited a weak positive correlation with BCVA ($\rho = 0.35, p = 0.01$, Fig. 4a), moderate correlation with maximum corneal curvature ($\rho = 0.53$, $p = 0.001$), moderately correlated with maximum corneal curvature ($\rho = 0.55, p = 0.001$), and weakly correlated with TKC scores ($\rho = 0.32, p = 0.02$, Fig. 4d).

Table 1. Clinical attributes of keratoconus and control participants.

| Clinical parameter | Keratoconus (n = 50 eyes) | Control (n = 50 eyes) |
|--------------------|--------------------------|----------------------|
| Best-corrected visual acuity, log MAR, mean (SD), mean Snellen | 0.21 (0.27), 6/9.6 | −0.09 (0.06), 6/4.8 |
| Refractive error (Sphere), dioptre sphere, mean (SD) | −2.52 (2.85) | −1.14 (1.61) |
| Refractive error (Cylindrical), dioptre cylinder, mean (SD) | −3.45 (2.10) | −0.77 (0.90) |
| Maximum corneal curvature, dioptre, mean (SD) | 54.48 (6.09) | 45.66 (1.58) |
| Mean corneal curvature, dioptre, mean (SD) | 47.03 (3.96) | 44.51 (1.41) |
| Central corneal thickness, micrometre (µm), mean (SD) | 495.34 (47.50) | 554.36 (25.71) |
and weak correlation with TKC scores ($\rho = 0.32$, $p = 0.02$, Fig. 4d). A moderate negative correlation was also observed between the GUI and the central corneal thickness (CCT) ($\rho = -0.44$, $p = 0.001$, Fig. 4c). Thus, higher GUI was associated with poorer BCVA, greater maximum corneal curvature and TKC scores, and lower central corneal thickness.

**DISCUSSION**

This study for the first time quantitatively evaluated visual distortion experienced in keratoconus. The results showed that visual distortion was higher in individuals with keratoconus compared to the normally sighted controls. The distortion indices also correlated with commonly measured clinical metrics of keratoconus such as $K_{max}$ and TKC.

The results demonstrate that measurements of visual distortion obtained with our paradigm differentiate individuals with keratoconus from those without. A similar paradigm based on vernier alignment has been used to measure perceptual distortion in amblyopia and AMD before [30, 31, 35, 36]. However these tests are lengthy to conduct in a clinical setting compared to the combined vernier alignment and field matching task used in the current study, which takes just a few minutes to complete. This renders our paradigm a more viable option for characterising visual distortions associated with keratoconus in clinical settings.

Both GDI and GUI increased with worsening visual acuity, albeit the correlation was weak. Using similar methods of distortion quantification, distortions were found to be higher in the amblyopic population compared to non-amblyopic controls [30, 35]. Amblyopic observers experience chronic distortion during development and may learn the spatial form of distorted optotypes. In contrast, AMD patients have an acquired deficit later in life and visual distortion (metamorphopsia) arises at the retinal level. Although research concerning the underlying basis of metamorphopsia in these patient groups continues to be limited, it has been suggested that the visual processing stream in such instances may be subject to top-down influences as a result of the slow progressing nature of the aetiologies, potentially resulting in...
some degree of visual adaptation to the degraded image quality and a resulting dissociation of perceived metamorphopsia from the visual acuity deficit [31]. Such influences may also explain why we found a higher GUI (index of stability of the visual percept) that correlated with certain clinical keratoconus indices.

In our sample, poorer BCVA was associated with greater maximum corneal curvature ($\rho = 0.73$) and TKC scores ($\rho = 0.49$) but was not significantly correlated with CCT ($\rho = -0.27$). Previous studies have shown that visual acuity shows a variable degree of correlation with the corneal structural measures and vision related quality of life in keratoconus [9–11, 37]. In comparison, contrast sensitivity has been found to correlate with corneal irregularities [37], higher order aberrations [13], and vision related quality of life [12]. However, proper measurement of contrast sensitivity is time
What this study adds

- This is the first quantitative study to assess distortion experienced in keratoconus.
- Distortion was higher in keratoconus compared to normal controls.
- Distortion measures correlated with clinical metrics of VA, Kmax and TKC.
- In future, the distortion test could be developed as a home-based tool to monitor keratoconus.

DATA AVAILABILITY

The datasets of the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS
MJ proposed the original research, developed the original methodology, conducted data analysis, and developed the first draft of the manuscript. KV contributed to methodology, collected data, conducted data analysis, and revised the manuscript. MP contributed to research and methodology development, data analysis, and revised the manuscript. NF contributed to research and methodology development and revised the manuscript. PB developed the original experiment, contributed to methodology, and revised the manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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