

Retinal nerve fibre layer and ganglion cell complex thickness in patients with keratoconus



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Background: Keratoconus, a corneal ectasia, is associated with corneal thinning and altered optical media. Consequently, assessment of the visual field, optic nerve head and intraocular pressure measurements may be challenging in patients with keratoconus. Few studies have investigated posterior segment variables including the retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC) thickness in patients with keratoconus.

Aim: To investigate RNFL and GCC thickness in patients with keratoconus.

Methods: A comparative quantitative research design was used. The sample consisted of 56 participants (28 with mild, moderate or severe keratoconus, and 28 controls) who accessed the optometry clinic at the University of KwaZulu-Natal. There was an equal distribution of male ($n = 14$) and female ($n = 14$) participants in the keratoconus and control groups. Most participants were black ($n = 34$) or Indian ($n = 18$). Corneal power and refractive error were assessed with the Oculus Keratograph and subjective refraction respectively. The iVue-100 optical coherence topography device was used to measure RNFL and GCC thickness. Data were analysed by descriptive and inferential statistics.

Results: The mean global RNFL thickness was slightly higher in the control group than the keratoconus group for the right (106 μm vs. 99 μm) and left (103 μm vs. 98 μm) eyes but these differences were not significant ($p \geq 0.057$). For all RNFL quadrants, slightly lower mean RNFL measurements were found in the keratoconus group. The mean GCC thicknesses were marginally higher (3 μm – 6 μm) in the control group.

Conclusion: The RNFL and GCC thickness differences between patients with keratoconus and controls are not clinically significant. Therefore, abnormally reduced RNFL and GCC thickness measurements in patients with keratoconus warrant further investigation for other pathologies specifically glaucoma.

Introduction

Keratoconus is a bilateral asymmetrical non-inflammatory progressive corneal ectasia that affects one in every 2000 individuals in the general population.¹ This ectasia is associated with a conical shaped cornea, apical protrusion and corneal thinning.² Assessment of the visual field may be challenging in patients with keratoconus owing to corneal opacities, high refractive errors and/or higher order aberrations.³ Even though evaluation of optic disc photographs is a standard method to monitor optic nerve head changes in glaucoma suspects, this method may have limited usefulness in patients with keratoconus owing to poor-quality photographs and a relatively normal appearance of the optic nerve head.⁴ Moreover, patients with keratoconus usually present with myopia and low intraocular pressure (IOP) measurements.⁴ Even in the absence of keratoconus, IOP measurements may be underestimated in individuals with thinner corneas.^{1,5}

Glaucoma is an optic neuropathy that may result in irreversible blindness.¹ In a recent meta-analysis, Tham et al.⁶ estimated that the global prevalence of glaucoma will increase by 74% and affect approximately 112 million people by the year 2040. The assessment of IOP is used in the screening, diagnosing and monitoring of glaucoma, as IOP is a key modifiable factor linked to glaucoma.^{1,7,8} Since glaucoma is associated with myopia² and the evaluation of IOP as well as visual fields may be unreliable in patients with keratoconus, assessment of the retinal nerve fibre layer (RNFL) may be more useful to screen and monitor glaucoma in patients with keratoconus.³ Moreover, the RNFL is part of the ganglion cell complex (GCC) which is sensitive to early glaucomatous changes.⁹ Various quantitative and qualitative methods may be used to assess the RNFL including fundus photography with a red-free filter, confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography (OCT).¹⁰

Optical coherence tomography, first introduced in 1991,¹¹ is an imaging technique that uses low-coherence interferometry to create high-resolution cross-sectional images (tomograms) of biological tissues of interest.^{10,11} The technique of OCT is similar to ultrasonography except that it is a non-contact technique and uses reflected light waves to create the tomograms. Currently, OCT devices are being widely used for imaging in several biomedical fields (cardiology, urology, respiratory medicine, dermatology and developmental biology) as well as for anterior and posterior ocular segment imaging.^{12,13,14,15} To this extent, several studies have reported on the practical use of OCT devices for ocular diseases associated with the retina,^{15,16} cornea,^{17,18} anterior chamber angle^{19,20} as well as glaucoma.^{21,22} Moreover, studies have also reported that OCT devices are reliable for repeated measurements of RNFL thickness in individuals with keratoconus^{23,24} as well as individuals with normal corneas.^{25,26}

The influence of keratoconus on anterior ocular segment structures is well known wherein several studies have compared anterior segment variables in patients with keratoconus and healthy controls.^{27,28,29} However, not much is known about the influence of keratoconus on posterior ocular segment structures. Therefore, this study was conducted to investigate posterior segment variables, including the RNFL and GCC thickness, in patients with keratoconus.

Methodology

The study employed a comparative quantitative research design and was conducted at the Westville campus of the University of KwaZulu-Natal (UKZN). The study population comprised of patients accessing the UKZN optometry clinic. Keratoconus (mild, moderate or severe) and control participants were recruited using convenience and purposive sampling respectively. The control participants were race, age and gender matched to the participants with keratoconus. Study participants were aged between 18 years and 33 years to minimise the effect of age on RNFL thickness, as previous studies^{30,31} have reported a decrease in RNFL thickness with increasing age.

A complete ocular examination of both eyes, including case history, LogMAR distance visual acuity, refraction, slit lamp examination, ophthalmoscopy and IOP measurements, was conducted on all participants to assess their eligibility. Refractive error was determined by performing autorefractometry which was subsequently refined with subjective refraction. Subjective refraction was used to determine the spherical equivalent by adding the sphere power to half the negative cylinder power.³² The Oculus Keratograph, which is a reliable topographer,³³ was used to assess corneal power along the two principal meridians (K1 and K2). Participants with systemic and/or ocular diseases (other than keratoconus), history of ocular surgery and/or trauma, IOP > 21 mmHg, central corneal scarring and advanced keratoconus (K1 and/or K2 greater than 54 D with corneal scarring) were excluded.

Participants were diagnosed with keratoconus based on corneal topography and the presence of clinical signs,

associated with keratoconus, on slit lamp examination. The clinical signs of keratoconus included corneal thinning, Vogt striae, Fleischer's ring, corneal scarring and Munson's sign. The average corneal power along the two principal meridians (K1 and K2) were used to classify participants with keratoconus as either mild (< 48 D), moderate (48 D – 54 D) or severe (> 54 D). Participants with average corneal power > 54 D together with corneal scarring were classified as advanced keratoconus and excluded from the study.

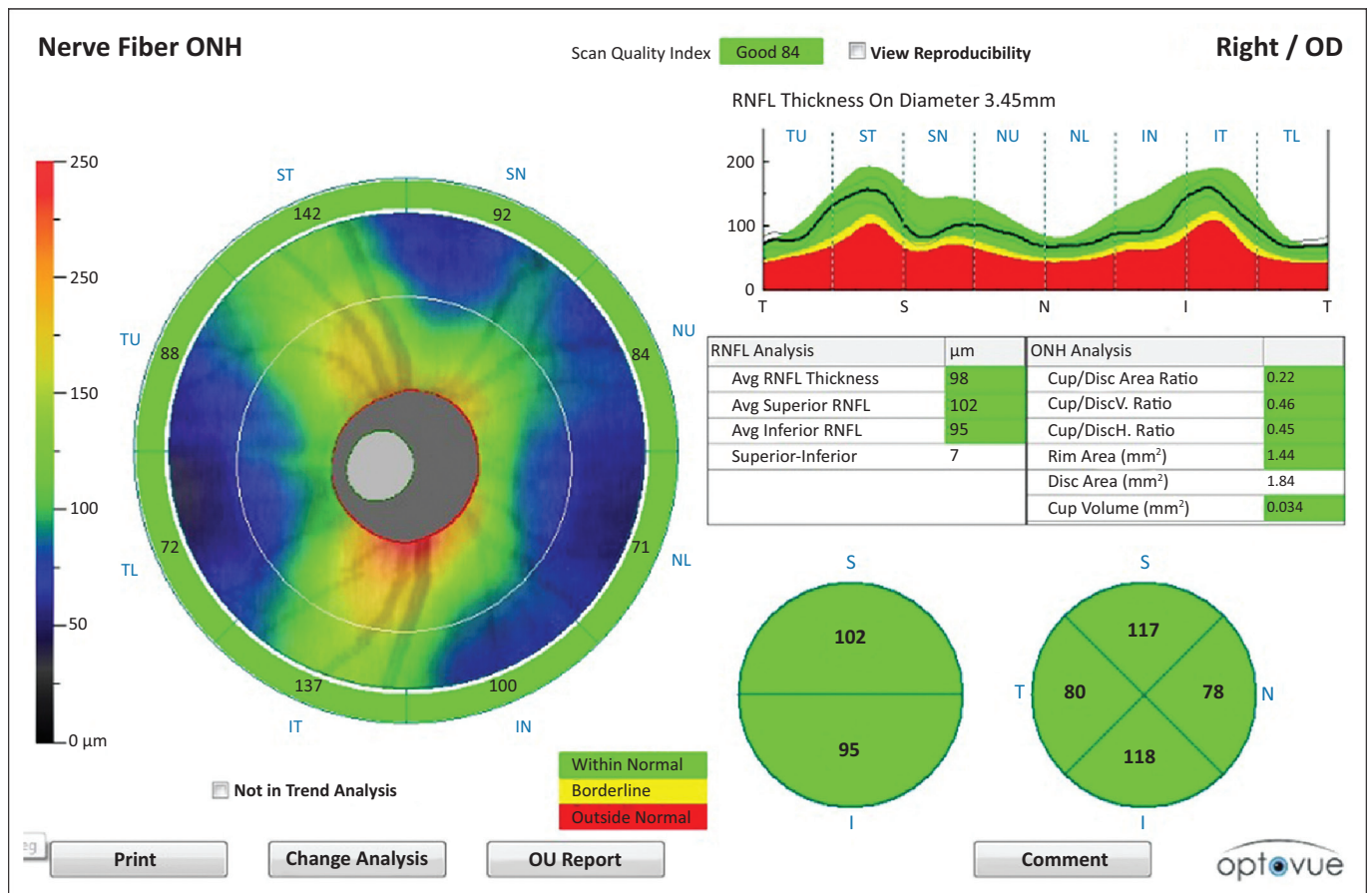
The Optovue iVue-100 OCT device was used to scan and measure the RNFL and GCC thicknesses for both eyes of all participants. This Fourier-domain OCT device is capable of operating at 26 000 A-scans per second with an axial resolution of 5 µm.³⁴ When scanning with the iVue-100 OCT device, participants were instructed to focus on the internal fixation target while the real-time image of the participant's eye and retina was monitored on the laptop screen. In accordance with the manufacturer's recommendations,³⁴ repeat scans were taken when the scan was labelled as 'poor' on the laptop screen or had a scan quality index < 27.

The RNFL thickness was assessed with the optic nerve head scanning protocol. This scanning protocol determines the global RNFL thickness and average thickness in the four quadrants (superior, inferior, nasal and temporal) along a 3.45 mm diameter circle when centred on the optic nerve head. The optic nerve head scanning protocol consists of 12 radial line scans of 459 A-scans each and 13 concentric rings of 429–969 A-scans centred on the optic nerve head. The optic nerve head scanning protocol displays the average global and quadrant RNFL thickness in an image display (Figure 1).

The GCC thickness was scanned and measured with the GCC scanning protocol, which consists of a single horizontal line scan and 15 vertical line scans. The horizontal and vertical line scans are 7 mm in length and consist of 934 A-scans each. The GCC scanning protocol displays the average total, superior and inferior GCC thickness in an image display (Figure 2).

For standardisation, the clinical equipment and environment (lighting, humidity and participant proximity to the air conditioning vent) were kept as constant as possible throughout the data collection period. Moreover, the subjective refraction, corneal power measurement and OCT scans were performed by one examiner each to ensure standardisation of the data collection procedures and prevent inter-examiner variability affecting measurements. Three consecutive measurements for corneal power, RNFL and GCC thickness were recorded and the averages computed.

Data were captured and analysed with the Statistical Package for Social Sciences (SPSS) version 24 using descriptive and inferential statistics. Data are presented as means ± standard deviations. The Shapiro–Wilk's test and graphical inspection of histograms were used to assess normality of the data. The independent sample *t*-test was used to compare RNFL and



Source: Modified screen shot of the output screen with the iVue-100 OCT

FIGURE 1: A retinal nerve fibre layer map showing the average global and quadrant retinal nerve fibre layer thicknesses.

GCC thickness between the keratoconus and control groups. A probability (p) value ≤ 0.05 was considered as statistically significant.

Ethical considerations

The study (reference number BE415/16) was approved by the Biomedical Research and Ethics Committee at UKZN. Written informed consent was obtained from all participants after explaining the nature of the study and associated procedures. All ethical guidelines were adhered to during the study. After obtaining ethical approval, a pilot study was conducted to standardise the data collection procedure.

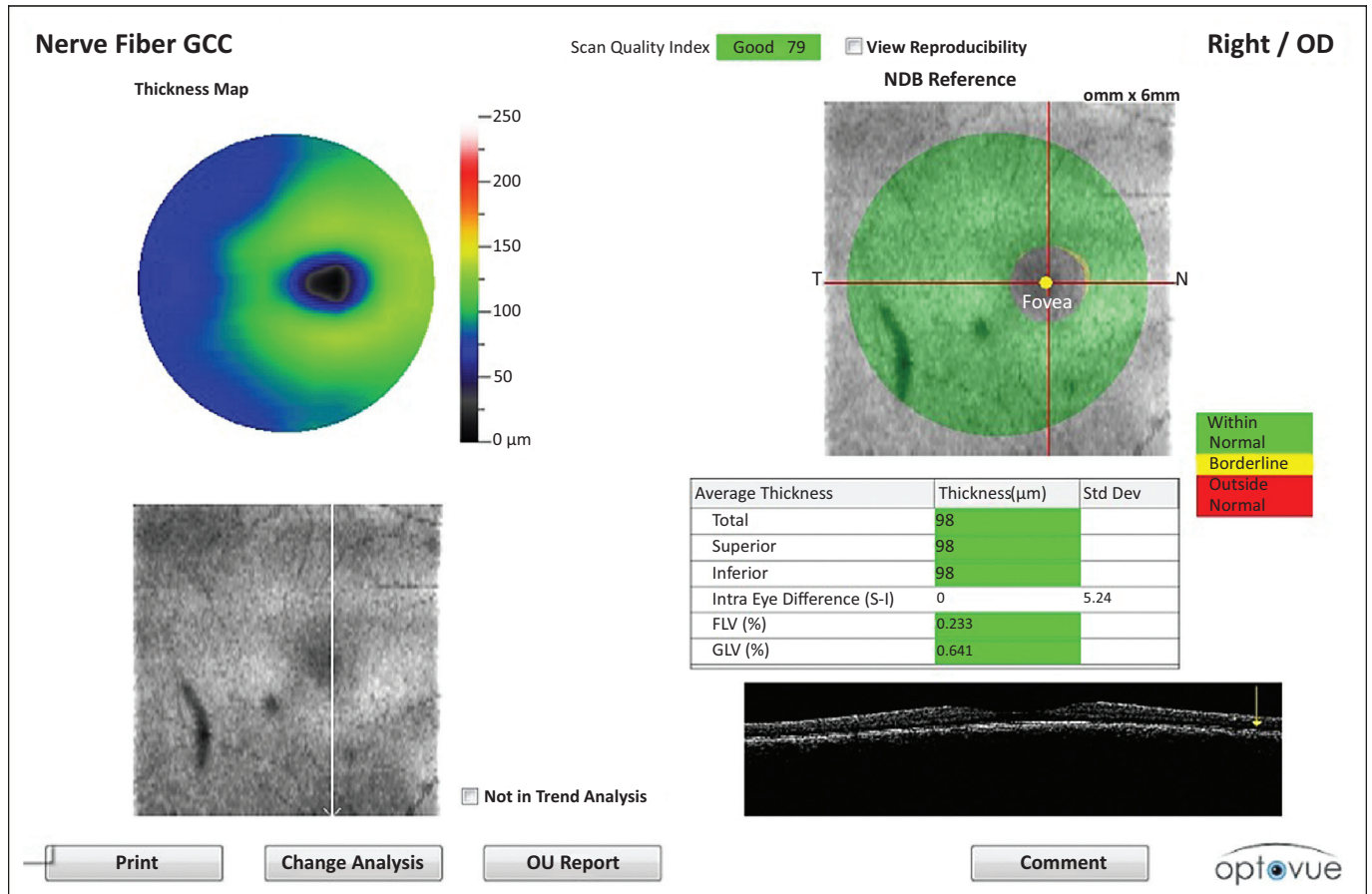
Results

The study sample consisted of 56 participants, which included 28 each in the keratoconus and control groups. There was an equal distribution of male ($n = 14$) and female ($n = 14$) participants within each group. The sample consisted of majority black people ($n = 34$) followed by Indian ($n = 18$) and mixed race ($n = 4$) participants. Ocular variables from 19 right eyes and 24 left eyes each from the keratoconus and control groups were used in the analysis for this study. Table 1 shows the demographic and ocular characteristics of the sample. There was no significant difference in mean age between the keratoconus (24.29 ± 5.02 years) and control (24.11 ± 4.67 years) groups ($p = 0.891$). However, participants in the keratoconus group were significantly more myopic

and had poorer best-corrected LogMAR distance visual acuity, steeper corneal powers (along the two principal meridians) as well as lower IOP measurements in both the right and left eyes ($p \leq 0.016$).

The means and standard deviations for global RNFL thickness and the RNFL thickness in each quadrant for both eyes in the keratoconus and control groups are presented in Table 2. In the right eye, the superior quadrant was thickest followed by the inferior, nasal and temporal quadrants in both the keratoconus and control groups. Although the temporal quadrant was thinnest in both groups for the left eye, the inferior quadrant recorded the highest value ($124 \mu\text{m}$) in the keratoconus group. For the control group, the superior and inferior quadrants were thickest and had an equal measurement of $132 \mu\text{m}$ (Table 2).

For both the right and left eyes, the mean thickness of the nasal quadrant was almost identical in the keratoconus and control groups (Table 2). With the exception of the nasal quadrant, the control group had higher mean RNFL thickness measurements than the keratoconus group for all quadrants. However, only the temporal quadrant in the right eye and superior quadrants in both eyes, with thickness differences of $7 \mu\text{m}$ and $13 \mu\text{m}$ respectively, were statistically significant ($p \leq 0.036$). In the inferior quadrant of both the right and left eyes, an insignificant thickness difference of $8 \mu\text{m}$ was noted between the control and keratoconus groups (Table 2).



Source: Modified screen shot of the output screen with the iVue-100 OCT

FIGURE 2: A ganglion cell complex map showing the average total, superior and inferior ganglion cell complex thicknesses.

TABLE 1: Means and standard deviations for age and ocular characteristics of the keratoconus ($n = 28$) and control ($n = 28$) groups.

Age and ocular characteristics	Keratoconus	Control	p^\dagger
Age (years)	24.29 ± 5.02	24.11 ± 4.67	0.891
Right eye spherical equivalent (D)	-5.87 ± 4.81	-0.73 ± 1.60	0.002‡
Left eye spherical equivalent (D)	-8.51 ± 12.39	-0.70 ± 1.35	0.016‡
Right eye visual acuity (LogMAR)	0.427 ± 0.28	-0.046 ± 0.11	< 0.001‡
Left eye visual acuity (LogMAR)	0.432 ± 0.24	-0.069 ± 0.13	< 0.001‡
Right eye corneal power: K1 (D)	49.52 ± 4.82	42.82 ± 1.03	< 0.001‡
Right eye corneal power: K2 (D)	52.72 ± 5.88	43.38 ± 1.31	< 0.001‡
Left eye corneal power: K1 (D)	50.65 ± 6.21	42.57 ± 1.35	< 0.001‡
Left eye corneal power: K2 (D)	55.27 ± 8.77	43.36 ± 1.59	< 0.001‡
Right eye IOP (mmHg)	12.20 ± 3.40	16.29 ± 2.15	< 0.001‡
Left eye IOP (mmHg)	11.35 ± 3.82	15.63 ± 2.30	< 0.001‡

IOP, intraocular pressure.

†, t -test; ‡, statistically significant.

In both eyes, the global RNFL thickness was 5 μm – 7 μm higher in the control group. However, these thickness differences were not statistically significant ($p > 0.05$). For the RNFL scans, the mean scan quality index was significantly higher in the control group for both the right (77 vs. 45, $p < 0.001$) and left (74 vs. 45, $p < 0.001$) eyes.

Figure 3 shows the mean GCC thickness for the keratoconus and control groups for the superior and inferior GCC areas of the right and left eyes. Overall, the mean GCC thickness was 3 μm – 6 μm higher in the control group with only the superior areas achieving statistical significance in both eyes

TABLE 2: Means and standard deviations for retinal nerve fibre layer thickness (μm) in the keratoconus and control groups stratified for the right and left eyes.

RNFL variable	Right eye		p^\dagger	Left eye		p^\dagger
	Keratoconus	Control		Keratoconus	Control	
Global	99 ± 10	106 ± 12	0.057	98 ± 9	103 ± 13	0.113
Superior	122 ± 15	135 ± 15	0.015‡	119 ± 12	132 ± 18	0.008‡
Inferior	121 ± 19	129 ± 16	0.143	124 ± 15	132 ± 16	0.089
Nasal	81 ± 13	80 ± 12	0.867	78 ± 11	78 ± 16	0.918
Temporal	72 ± 9	79 ± 9	0.036‡	72 ± 10	73 ± 9	0.649

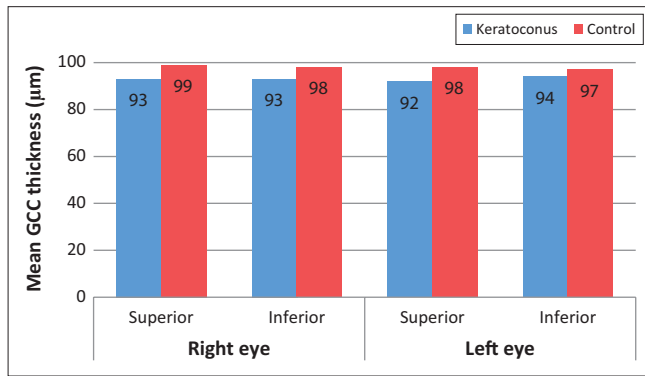
RNFL, retinal nerve fibre layer.

†, t -test; ‡, statistically significant.

($p \leq 0.029$). The total GCC thickness was also higher in the control group than in the keratoconus group for both the right (99 μm vs. 93 μm , $p = 0.029$) and left (97 μm vs. 93 μm , $p = 0.051$) eyes. For the GCC scans, the mean scan quality index was significantly higher in the control group for both the right (82 vs. 55, $p < 0.001$) and left (76 vs. 52, $p < 0.001$) eyes.

Discussion

In the present study, RNFL and GCC measurements were compared in a group of keratoconus and control participants accessing the UKZN optometry clinic. The results showed that both RNFL and GCC measurements were comparable between the keratoconus and control groups. The control participants had slightly higher global RNFL thickness measurements than the keratoconus participants (106 μm vs. 99 μm and 103 μm vs. 98 μm for the right and left eyes respectively), but these



GCC, ganglion cell complex.

FIGURE 3: Ganglion cell complex thicknesses for the superior and inferior ganglion cell complex areas in the keratoconus and control groups.

differences were not statistically significant ($p \geq 0.057$). This finding is in agreement with previous studies that have compared mean global RNFL thickness in individuals with keratoconus and controls.^{3,35} Cankaya et al.³ reported insignificantly thinner global RNFL thickness measurements in individuals with keratoconus than in age- and gender-matched controls (96.5 μm vs. 99.0 μm , $p = 0.43$). Bayhan et al.³⁵ reported a similar trend with thinner global RNFL thickness measurements in individuals with keratoconus compared with control participants (109.54 μm vs. 104.44 μm , $p = 0.265$). Despite also noting thicker global RNFL thickness measurements in healthy controls (94.7 μm) than individuals with keratoconus (≤ 90.7 μm), Uzunel et al.³⁶ reported that these thickness differences were statistically significant ($p < 0.001$). Unlike in the present study, Uzunel et al.³⁶ separated their participants with keratoconus ($n = 68$) into three grades, using the Amsler-Krumeich classification system, and analysed the different mean global RNFL measurements for each grade of keratoconus which may explain this difference.

We found that quantitative comparisons of the mean RNFL thickness in the four quadrants, between the two groups, showed a similar pattern to that of the global RNFL thickness. The mean RNFL measurements were marginally higher (1 μm – 13 μm) in the control group for all quadrants with the exception of only the nasal quadrant in the left eye where the same value (78 μm) was noted in the two groups. This finding is consistent with reports from previous studies,^{3,35} which also noted lower quadrant-specific mean RNFL thickness measurements in individuals with keratoconus when compared with healthy controls. For the superior quadrant, Bayhan et al.³⁵ reported a 13.6 μm statistically significant ($p = 0.045$) RNFL thickness difference between the keratoconus and control groups which is almost identical to the difference (13 μm , $p \leq 0.015$) noted for the superior quadrant of both eyes in the present study. Bayhan et al.³⁵ used a similar Optovue-based OCT device (RTVue-100) to measure the RNFL thickness and also included young adult participants (mean age ≤ 29.47 years) which may explain this similarity. In the present study, the mean RNFL thickness measurements for the nasal quadrants were almost identical in the two groups. This finding is in accordance with previous studies^{3,35}

which have reported less than 3 μm nasal quadrant RNFL thickness differences between individuals with keratoconus and healthy controls.

In our study, the mean GCC thickness was slightly thinner in the keratoconus group than in the control group. For the superior GCC area in both eyes, the thickness difference between the two groups was identical (6 μm , $p \leq 0.029$). This finding is in agreement with Bayhan et al.³⁵ who also noted a small yet significant superior GCC thickness difference between individuals with keratoconus and healthy controls (4.6 μm , $p = 0.018$). Moreover, the study by Bayhan et al.³⁵ also reported an insignificant 4 μm thickness difference for the inferior GCC area which is consistent with the results (3 μm – 5 μm , $p > 0.05$) found in the present study. For the total GCC, the two groups showed thickness differences of 4 μm and 6 μm for the right and left eyes respectively, which is in agreement with a previous study that reported a 5.78 μm thickness difference.³⁵

Overall, the mean global RNFL thickness, RNFL thickness in each quadrant and GCC thicknesses were slightly lower in the keratoconus group than in the control group. The extent of these thickness differences ranged from 1 μm to 13 μm . Previous studies have reported that thicker RNFL measurements are not associated with visual field anomalies.^{37,38,39} Consequently, it is speculated that substantial retinal ganglion cell loss and associated RNFL thinning is necessary before a functional visual field loss is detected.^{39,40,41,42} A recent study⁴² reported that at least 8.4% of global RNFL thinning is needed to detect functional loss when evaluated with visual field assessments. A previous study,⁴¹ which measured RNFL thickness in 72 normal and 40 glaucomatous participants, reported that a 17% decrease in global RNFL thickness is necessary to detect a functional visual field loss. Moreover, these researchers⁴¹ highlighted 75.3 μm as the 'tipping point' value at which visual field loss can be detected clinically. In the present study, the mean global RNFL thickness values for both the keratoconus and control groups were higher than 75.3 μm . In addition, the global RNFL thickness difference between the two groups is equivalent to only 6% and can therefore be regarded as clinically insignificant as they are lower than the values associated with functional losses.^{41,42}

The exact reason for the marginal differences in RNFL and GCC thickness between the keratoconus and control groups is unknown. However, it may be related to corneal geometric and biomechanical variables including central corneal thickness (CCT) and corneal hysteresis (CH) respectively. It is well known that keratoconus is associated with central corneal thinning and reduced CCT measurements.²⁷ The Ocular Hypertension Treatment Study (OHTS) noted that thinner CCT measurements are a risk factor for the development of primary open-angle glaucoma.⁴³ Moreover, previous studies have reported that eyes with thinner CCT measurements have larger^{44,45} and deeper optic cups.⁴⁵

Corneal hysteresis describes the viscoelastic characteristic of the cornea⁴ and has been shown to vary in eyes with different ocular diseases. Research studies have consistently reported that individuals with glaucoma have significantly lower CH measurements than healthy controls.^{44,46} However, contradictory findings have been reported for CH measurements in individuals with keratoconus. Some studies have reported that mean CH measurements are significantly lower in individuals with keratoconus than normal individuals.^{28,47} However, Cohen and Myers⁴ reported that individuals with keratoconus, who either had glaucoma or were glaucoma suspects, had similar mean CH measurements to healthy controls. Shah et al.⁴⁸ also noted that mean CH measurements were similar and had considerable overlap between healthy controls and individuals with mild keratoconus. There is no correlation between CH and RNFL or GCC thickness.^{46,49} Moreover, Insull et al.⁴⁴ suggested that CH does not affect the optic disc size as it is not related to the optic disc area. It is possible that the lack of association between CH and RNFL, GCC as well as optic disc size may account for the similar RNFL and GCC thicknesses noted between the two groups in this study. Thus, we speculate that the CH measurements in the two groups were relatively similar which may explain the lack of clinically significant thickness differences between the two groups. This explanation is reasonable considering that even though there were obvious CCT differences between participants in the keratoconus and control groups, none of the participants in these groups had glaucoma and/or were suspected of having glaucoma. However, we suggest that future studies compare CH measurements among healthy controls, individuals with keratoconus as well as individuals with keratoconus and concurrent glaucoma to validate this speculation.

In our study, the mean global RNFL for the control group which consisted of normal healthy participants was ~ 105 μm . This value is comparable to mean RNFL thickness values (range 105.5 μm – 107.7 μm), also measured with OCT devices, reported in studies involving healthy Indian,^{50,51} Korean^{52,53} and Turkish⁵⁴ populations. Despite also using a Fourier-domain OCT device to measure the RNFL thickness, Cankaya et al.³ reported a slightly lower global RNFL thickness value (99 μm) which may be attributed to the inclusion of slightly older participants (mean age 31.5 years) and a larger sample size ($n = 74$) in their control group. Nevertheless, such comparisons across studies should be interpreted with caution as RNFL thickness varies with several ocular and demographic factors.^{51,55}

Few studies have measured RNFL thickness in individuals with keratoconus and these studies have reported conflicting results. The mean global RNFL thickness in the keratoconus group (~ 99 μm) in the present study is comparable to the mean value (97 μm) reported by Cankaya et al.³ in individuals with keratoconus. In contrast, Bayhan et al.³⁵ reported a higher mean global RNFL thickness (104.44 μm). It is likely that differences in the study methodologies specifically related to the different OCT devices used to measure RNFL thickness are accountable for the variations observed. To this

extent, researchers have cautioned against comparing RNFL thickness values across studies as variations have been observed even when the RNFL is measured on the same individuals with different OCT devices.^{26,56}

It was found that, as expected, the keratoconus group was significantly more myopic and had steeper corneal power measurements as has been reported previously.^{28,29} In OCT devices, the scan quality index/signal strength associated with a scan is an indication of the quality of the scan. Thus, the scan quality index may influence the validity of the measurements obtained with the OCT devices.^{57,58} In the present study, the mean scan quality indices for the RNFL and GCC scans were higher than the minimum value (27) recommended by the manufacturer in both the keratoconus and control groups. However, the mean scan quality indices were significantly lower in the keratoconus group as has been noted in previous studies.^{59,60} The scan quality index may be affected by refractive changes.^{60,61} Consequently, the higher spherical equivalent refractive error associated with the keratoconus group is the likely explanation for this finding. Moreover, patients with keratoconus have reduced clarity of the optical media which may have also contributed to the lower scan quality indices noted in this group.⁴

Strengths of the present study include the use of standardised data collection measurement protocols for the subjective refraction, corneal power measurement and OCT scans. Moreover, the study used a high-resolution Fourier-domain OCT device to record several OCT measurements for each eye. Limitations of this study included the exclusion of participants with advanced keratoconus owing to reduced optical media and a relatively small sample size even though the keratoconus and control groups were matched for demographic characteristics. Therefore, it is recommended that future studies include a larger sample size and participants with different stages of keratoconus to investigate RNFL and GCC measurements in the different stages of keratoconus. In addition, the influence of keratoconus on retinal thickness measurements for all layers should be investigated, as this study only focused on the RNFL and GCC thicknesses.

Conclusion

The results of this study are important and may help in diagnosing and monitoring glaucoma in individuals with keratoconus. Evaluation of the GCC is important as it has good sensitivity in differentiating between healthy and glaucomatous eyes which may be a consequence of GCC changes occurring early in glaucoma.^{62,63} Thus, it is proposed that evaluation of the GCC in addition to the RNFL may be more important especially in individuals with keratoconus where other clinical tests (tonometry, optic nerve head assessment and visual fields) necessary for evaluation of glaucoma may be unreliable. The study concludes that keratoconus is associated with RNFL and GCC thickness changes that are not clinically significant. Therefore, abnormally reduced RNFL and GCC thickness in patients

with keratoconus warrants further investigation for retinal and optic nerve head pathologies specifically glaucoma.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

D.S. was the study leader. N.G. and N.R. provided feedback on the study design. P.C., N.M., M.M., K.M.E., D.S. and N.W. performed the data collection. N.R. and N.G. wrote the manuscript.

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